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Enantioselective [2+2] Photocycloadditions and Their Applications in Total Synthesis

Saner Poplata

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Vorsitzende: Prof. Dr. Tanja Gulder

Prüfer der Dissertation:
1. Prof. Dr. Thorsten Bach
2. apl. Prof. Dr. Wolfgang Eisenreich

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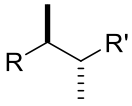
In this thesis, the relative configuration of racemates is represented by straight lines (bold or hashed). The absolute configuration of enantiomerically pure or enriched compounds is represented by wedge-shaped lines (bold or hashed).

racemate 

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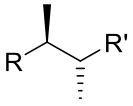
enantiomerically enriched 

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Für meine Familie

Per aspera ad astra.

(Seneca)

Zusammenfassung

Die [2+2] Photocycloaddition ist einer der wichtigsten photochemischen Transformationen und wurde als Schlüsselschritt in zahlreichen Totalsynthesen von Naturstoffen seit den frühen 1960er Jahren eingesetzt. Im frühen 21ten Jahrhundert, kamen erste Berichte hinsichtlich katalytischer, enantioselektiver Varianten der [2+2] Photocycloaddition zum Vorschein. Bisher jedoch, verblieb die enantioselektive [2+2] Photocycloaddition von einfachen cyclischen Enonen unentdeckt. In unserer Studie haben wir zunächst die Reaktionsbedingungen für die enantioselektive, intramolekulare [2+2] Photocycloaddition von einfachen cyclischen Enonen optimiert. Als bester Katalysator für diese Substratklasse wurde ein Prolin-basiertes Oxazaborolidin, welches sich aus einem 2,3-Dimethylphenyl substituierten Prolinol und einer 2,4,6-Trifluorophenylboronsäure zusammensetzt, identifiziert. Die Umsetzung von zehn geeigneten Substraten führte zu Photocycloadditionsprodukten mit Ausbeuten bis zu 86% und Enantiomerenüberschüssen bis 96% *ee*. Um die Anwendbarkeit unserer Methode in Totalsynthesen zu demonstrieren, wurden neue Syntheserouten für die Naturstoffe Italicen und Isoitalicen entwickelt. Die diastereoselektiven Formalsynthesen von Italicen und Isoitalicen erwiesen sich als erfolglos, da die parallele kinetische Racematspaltung des Bestrahlungsvorläufers keine hohen Enantiomerenüberschüsse der Schlüsselintermediate erzielte. Darauffolgend haben wir die Reaktionsbedingungen in der enantioselektiven intermolekularen [2+2] Photocycloaddition von Cyclopentenon- und Cyclohexenon-Derivaten eingesetzt. Wir erhielten 30 Photoadditionsprodukte mit hohen Ausbeuten bis zu 93% und hohen Enantiomerenüberschüssen bis zu 96% *ee*. Ausgewählte Photoadditionsprodukte dienten als Ausgangsstoffe für enantioselektive Formalsynthesen von Caryophyllen, Isocaryophyllen, Quadron, Sterpuren, Grandisol und Cerapicol. Der synthetische Nutzen unserer entwickelten Methode wurde durch die erste enantioselektive Totalsynthese von (–)-Grandisol präsentiert. In weiteren Studien, versuchten wir diese Methode auf die enantioselektive c*is*-t*rans* Isomerisierung von Cyclooctenon zu erweitern. Unsere Methode erwies sich jedoch als ungeeignet für diese Transformationen.

Abstract

The [2+2] photocycloaddition is one of the most important photochemical transformations and has been employed as the key step in a plethora of total syntheses of natural products since the early 1960s. In the early 21st century, first reports began to emerge concerning catalytic enantioselective variants of the [2+2] photocycloaddition. So far, however, the enantioselective intermolecular [2+2] photocycloaddition of simple cyclic enones remained elusive. In our study, we initially optimized the reaction conditions for the enantioselective intramolecular [2+2] photocycloaddition of simple cyclic enones. As the most proficient catalyst for this substrate class, a proline-based oxazaborolidine was identified which is comprised of a 2,3-dimethylphenyl substituted prolinol and a 2,4,6-trifluoroboronic acid. The conversion of ten suitable substrates led to photocycloaddition products in yields up to 86% and enantiomeric excesses up to 96% *ee*. In order to demonstrate the applicability of our method in total syntheses, new synthetic routes were developed for the natural products italicene and isoitalicene. The diastereoselective formal syntheses of italicene and isoitalicene proved to be unsuccessful, as the parallel kinetic resolution of the irradiation precursor did not produce high enantiomeric excesses in the key intermediates. Subsequently, we employed these reaction conditions in the enantioselective intermolecular [2+2] photocycloaddition of cyclopentenone- and cyclohexenone derivatives. We obtained 30 photocycloaddition products in high yields up to 93% and high enantiomeric excesses up to 96% *ee*. Selected photocycloaddition products served as starting material for enantioselective formal syntheses of caryophyllene, isocaryophyllene, quadrone, sterpurene, grandisol and cerapicol. The synthetic utility of our developed method was showcased in the first enantioselective total synthesis of (–)-grandisol. In subsequent studies, we attempted to extend this method to the enantioselective c*is*-t*rans* isomerization of cyclooctenone. Our method, however, proved to be unsuitable for these transformations.

1. Introduction

1.1 The Discovery and Development of the [2+2] Photocycloaddition

The most powerful light source known to mankind is the sun, but it was not until the late 18th century when for the first time scientists were able to harness its energy for chemical reactions.[1] Almost one hundred years later, in 1877, *Liebermann* made an observation in his studies on thymoquinone that led to a major breakthrough in photochemistry. He observed the formation of an insoluble compound which he identified to be a polymer of thymoquinone. A series of experiments led to the conclusion that light was responsible for this chemical transformation.[2,3] It was not until 1967, when by NMR-spectroscopy[4] and crystallography[5] the structure of the photodimer of thymoquinone **1** was unambiguously assigned. This is the first example of a [2+2] photodimerization product. Further studies on solid state photochemistry in the late 19th and early 20th century by *Bertram*[6], *Riiber*[7] and *Ciamician*[8] led to the discovery of photodimerizations of cinnamic acid to the naturally occurring α-truxillic acid **2**. In 1908, *Ciamician* reported the first photoadduct obtained in solution by an intramolecular [2+2] photocycloaddition of (+)-carvone and proposed **3** as the structure which was confirmed in 1957.[9,10] These milestones in photochemistry paved the way for numerous studies on [2+2] photodimerizations and intramolecular [2+2] photocycloadditions which predominantly were carried out until the 1960s.[11,12]

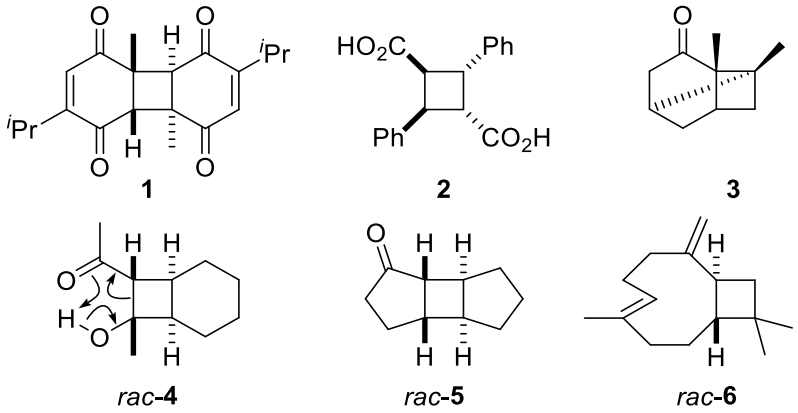


Figure 1. A collection of [2+2] photocycloaddition products that represent milestones in the field of photochemistry.

In 1962, *de Mayo* reported a photoreaction of acetylacetone in cyclohexene which included one of the first observations of an intermolecular [2+2] photocycloaddition between two different reaction partners.[13] The intermediate photoadduct *rac*-**4** underwent a retro-aldol reaction to a 1,5-diketone, this sequence is also known as the *de Mayo* reaction. Almost concurrently, *Eaton*

reported photoadduct *rac*-**5** resulting from an intermolecular [2+2] photocycloaddition between cyclopentenone and cyclopentene. It was one of the first isolated photoadducts at that time.[14] Shortly after, in 1963, *Corey* employed this newly found reaction as the key step in his total synthesis of *rac*-caryophyllene (*rac*-**6**) and its isomer *rac*-isocaryophyllene.[15,16] This was the first time the [2+2] photocycloaddition was employed in the total synthesis of a natural product. Ever since this discovery, the [2+2] photocycloaddition has continuously evolved into what is now a powerful tool for the total synthesis of natural products.[17-20] Considering the synthetic importance of this reaction, the development of stereoselective variants has been extensively explored in recent decades.[21-23] Consequently, the objective of this thesis was to develop an enantioselective [2+2] photocycloaddition method for simple cyclic enones which act as starting materials for the total syntheses of numerous natural products such as *rac*-caryophyllene (*rac*-**6**).

1.2 Mechanism of the [2+2] Photocycloaddition

Cyclic α,β-unsaturated ketones, i.e. enones, have been extensively employed in [2+2] photocycloaddition reactions due to their relevance in organic synthesis.[24,25] This substrate class can be directly excited by irradiation with a wavelength above $\lambda > 300$ nm and furthermore, possesses photochemical properties which ensure high yielding reactions. The course of a photochemical reaction is complex and involves multiple steps to the final product (Figure 2). First, the substrate being in its singlet ground-state (S_0) absorbs a photon of an appropriate energy, i.e. wavelength, leading to an excitation to the singlet state S_1. Simplistically, the excitation process consists of the electron from the HOMO overcoming the HOMO-LUMO energy gap to the LUMO. Being in the excited singlet state S_1, the substrate can follow two different reaction pathways: Firstly, it can decay to the singlet ground state S_0 through spontaneous emission of light (fluorescence) or a non-emissive internal conversion (IC). Secondly, it can undergo an intersystem crossing (ISC) where its spin multiplicity is changed from singlet to triplet, thus affording the substrate in a T_1 state, typically of ππ* character. Since the ISC proceeds efficiently in enone substrates, photoreactions are commonly carried out via direct excitation.[26-28] Similar to the reaction pathways originating from the S_1 hypersurface, the substrate can decay from T_1 to S_0 by an emissive (phosphorescence) or non-emissive ISC pathway. Due to the long lived and diradical nature of the triplet excited state T_1 of enones, an excess of olefin can quench this state forming a 1,4-diradical while remaining on the triplet hypersurface.[23,29-36] After an ISC to the singlet state S_0, the 1,4-diradical can either cyclize to the product or it can undergo a cycloreversion effectively regenerating starting material. Depending on the temperature and the solvent, cyclic enones in general efficiently harness the absorbed light for subsequent photochemical reactions with high quantum yields Φ (0.1-0.9).[37]

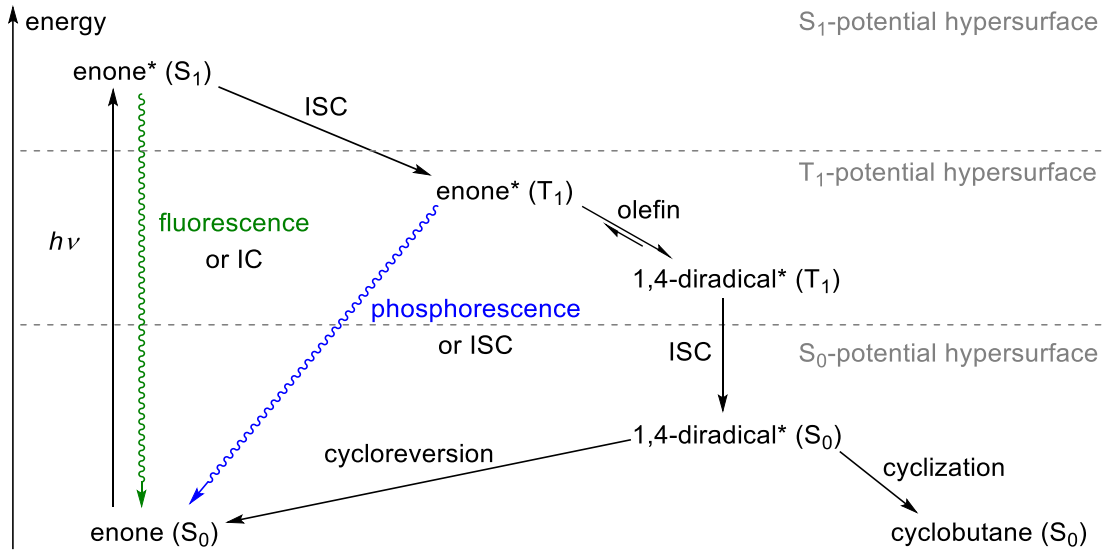


Figure 2. Schematic reaction course of a [2+2] photocycloaddition upon direct excitation of the substrate.

Although direct excitation of enones leads to efficient product formation, it has been reported that for catalytic enantioselective reactions, sensitization is recommended. Catalysts bearing derivatives of xanthone[38] and thioxanthone[39] have been successfully employed in catalytic enantioselective [2+2] photocycloaddition reactions. Classically, sensitizers are employed for photoprecursors that physically cannot undergo ISC. These substrates usually are simple olefins which exhibit a large energy gap between the singlet and the triplet hypersurfaces. Photosensitizers, however, can efficiently undergo ISC. This can be attributed to the small energy gap between S_1 and T_1. Crucially, due to this small energy gap, S_1(sens) can be lower than S_1(subs) while at the same time, T_1(sens) is higher in energy than T_1(subs). Consequently, at longer wavelength, it is possible to suppress photoexcitation of the substrate, while simultaneously accessing T_1(subs) via triplet-triplet energy transfer (TTET) from the photoexcited sensitizer T_1(sens) (Figure 3). This energy transfer proceeds via the *Dexter* mechanism which involves a mutual electron-electron exchange between sensitizer and substrate under retention of the spin multiplicity.[40] For the TTET to occur, a close spatial proximity of the substrate and the sensitizer is crucial.

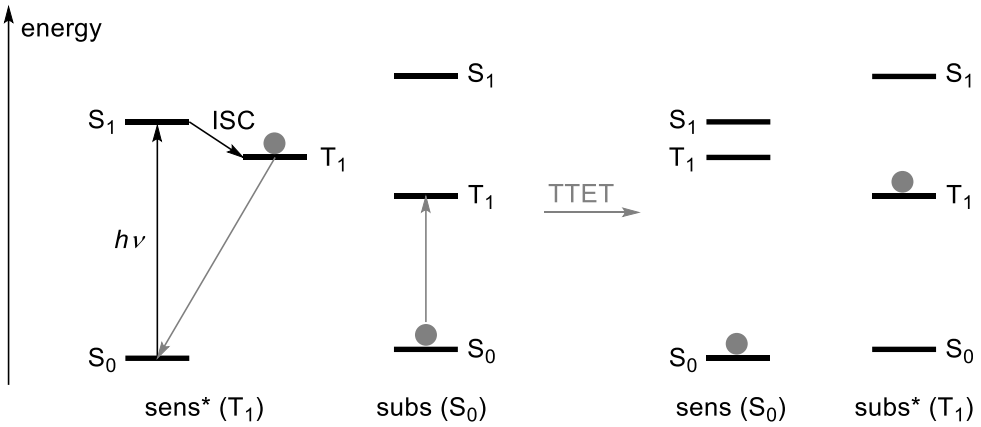
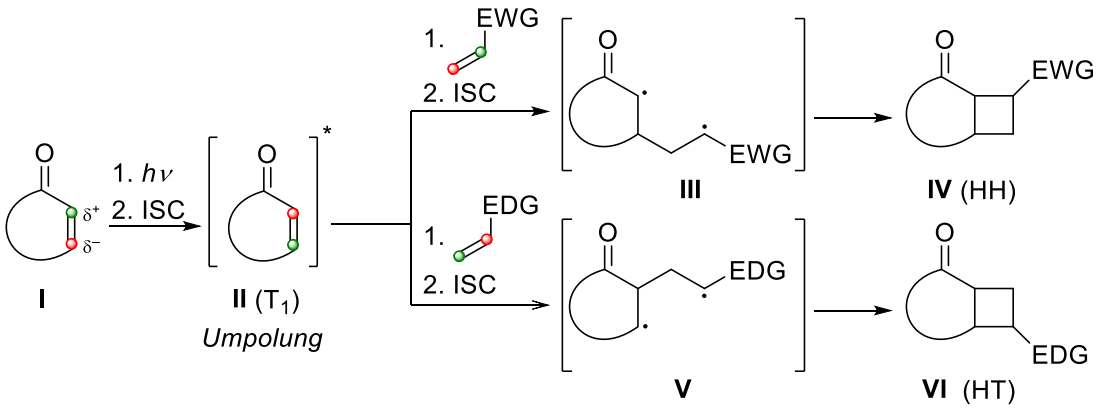


Figure 3. Mechanism of the triplet-triplet energy transfer (TTET), i.e. sensitization.

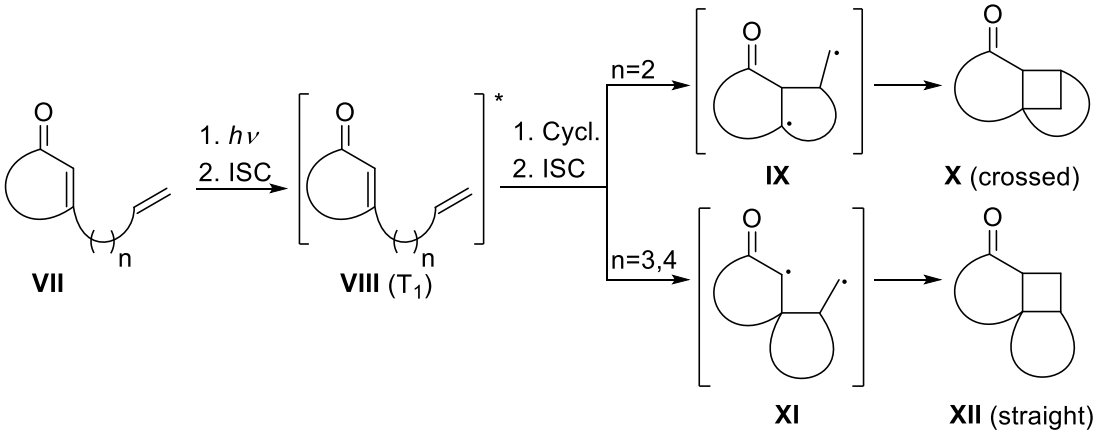
The regioselectivity in intermolecular [2+2] photocycloaddition reactions is influenced by the umpolung of the enone **I** upon excitation (Scheme 1).[41,42] This is due to the excited enone **II** having an inverted electron distribution. Consequently, the α-carbon is electrophilic (marked in red) and the β-carbon is nucleophilic (marked in green) in enone **II**. In the presence of excess olefin, the long lived triplet state T_1 of **II** can be quenched. This can occur by a radical addition into electron poor alkenes. A consecutive ISC leads to 1,4-diradical **III** yielding head-to-head (HH) product **IV**. Conversely, electron rich alkenes lead to 1,4-diradical **V** which cyclizes to the head-to-tail (HT) product **VI**.[43] On the triplet hypersurface, 1,4-diradicals **III** and **V** can undergo cleavage to the corresponding alkene and enone **II**.[44]



Scheme 1. Regioselectivity in intermolecular [2+2] photocycloadditions of cyclic enones.

In the intramolecular [2+2] photocycloaddition the electronic nature of excited enone **VIII** does not influence the regioselectivity. Here, the *Rule of Five* postulated by *Hammond* and *Srinivasan* influences the course of the 1,4-diradical formation (Scheme 2).[36,45] This is consistent with *Baldwin's rules*, in which the formation of the less stable 1,4-diradical occurs due to the fast 5-*exo*-trig reaction.[46] The thermodynamically favored 6-*endo*-trig reaction is slower and therefore does not occur. If the side-chain in **VII** is two atoms long, 1,4-diradical

IX is formed, leading to the crossed product **X**. If the chain is longer, an initial bond formation between β-carbon atom and alkene provides 1,4-diradical **XI** which cyclizes to the straight photoproduct **XII**.



Scheme 2. Regioselectivity in intramolecular [2+2] photocycloadditions of cyclic enones.

In 1995, *Weedon* experimentally proved the existence of 1,4-diradicals in intermolecular (analogously to **III** and **V**) as well as intramolecular (analogously to **IX** and **XI**) [2+2] photocycloaddition by trapping the radical intermediates with hydrogen selenide. Consequently, the *Rule of Five* was substantiated.[47-49]

1.3 Enantioselective [2+2] Photocycloaddition

In the early 1980s, first synthetically relevant stereoselective [2+2] photocycloadditions in solution were achieved by implementing chiral auxiliaries in the reacting enones.[50] Diastereoselectivity was induced by sterically blocking one diastereotopic face of the enone, thus forcing the cycloaddition to occur on the opposite diastereotopic face. Synthetically relevant enantioselective variants of the [2+2] photocycloadditions in solution were developed more than twenty years later.[22] Enantioselective catalysis of photochemical reactions is particularly challenging due to the capricious nature of the highly energetic and short lived photoexcited intermediates.[51] Therefore, conceptually novel methods had to be developed to influence the absolute stereochemistry of enantioselective photochemical reactions.[52,53]

1.3.1 Chiral Auxiliaries and Templates as Stochiometric Reagents

The implementation of chiral auxiliaries in [2+2] photocycloadditions in solution was first reported in 1982 by *Tolbert*.[54] Methyl (–)-bornyl fumarate (**7**) was employed as a chiral olefin which reacted with *trans*-stilbene in a diastereoselective [2+2] photocycloaddition. The auxiliary was cleaved under acidic conditions and re-esterification with methanol furnished

dimethyl μ-truxinate (**8**) in 20% yield and 90% *ee* (Figure 4). Subsequent mechanistic studies revealed that a charge-transfer complex of diester **7** and *trans*-stilbene was formed which can be excited at a longer wavelength of 366 nm.[55]

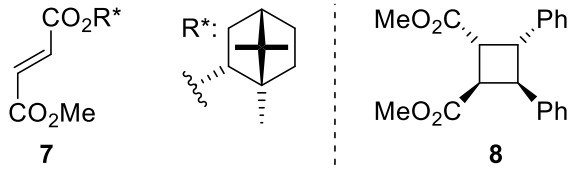
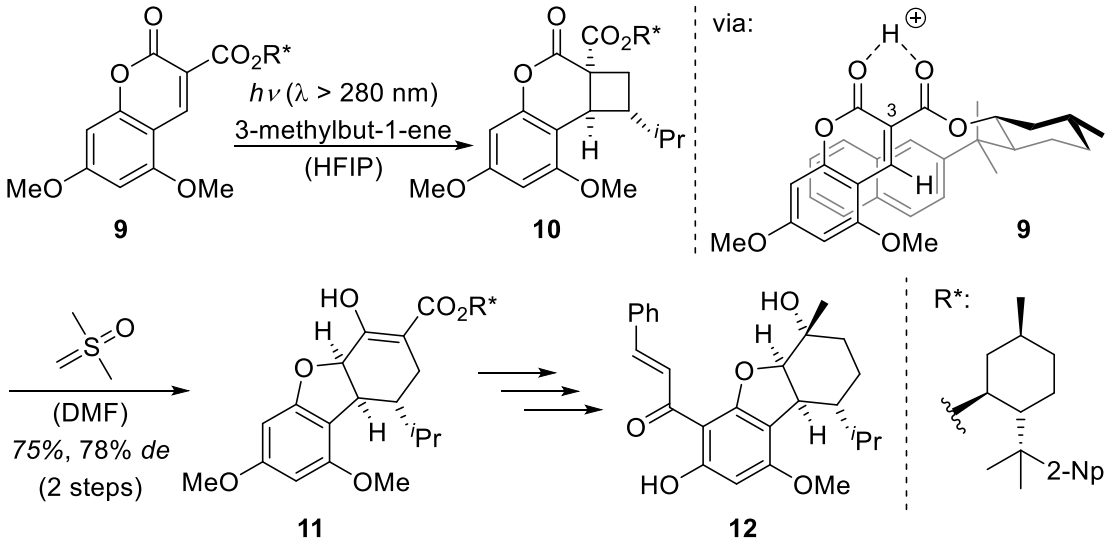


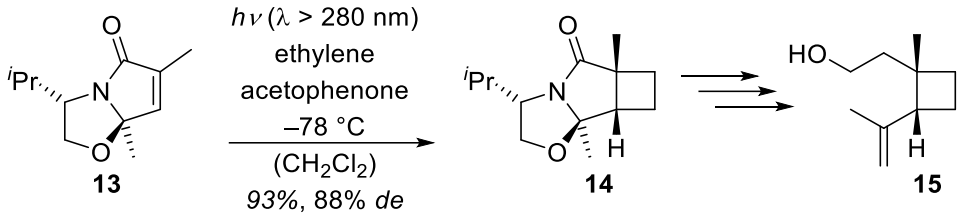
Figure 4. Structures of irradiation precursor **7** and dimethyl μ-truxinate (**8**).[54]

In the following years, acyclic chiral esters of cyclic enones were further developed and provided high diastereoselectivities even with simple olefins such as ethylene.[56-60] This well-developed principle was employed in a an asymmetric total synthesis of (–)-linderol A (**12**) by *Ohta* (Scheme 3).[61] Coumarin **9** was dissolved in hexafluoro-*iso*-propanol (HFIP) which is slightly acidic and it is proposed that upon protonation, the two carbonyl groups are conformationally locked. One diastereotopic face of the enone is therefore blocked by the naphthyl moiety. Consequently, the photocycloaddition with the olefin is forced to occur on the the *si* face of the carbon atom in the 3-position. The generated photoadduct **10** was treated with dimethylsulfoxonium methylide which attacked the lactone carbonyl carbon atom. This induced a rearrangement and following the release of dimethyl sulfoxide, the desired product **11** was furnished in 75% yield and 78% *de* over two steps. Including a separation of the diastereomeric mixture **11** on chiral HPLC, (–)-linderol A (**12**) was obtained in an overall yield of 23% over a total of 13 steps.



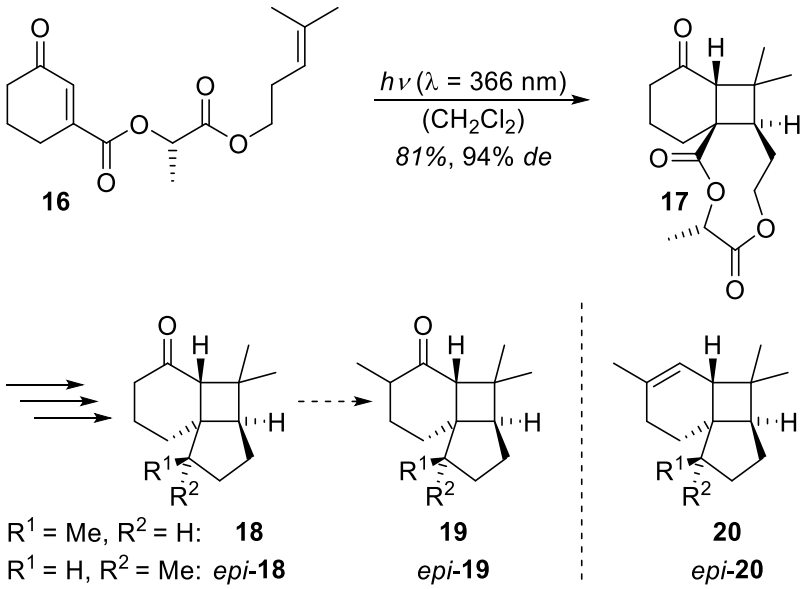
Scheme 3. Diastereoselective [2+2] photocycloaddition of coumarin **9** with 3-methylbut-1-ene.[61]

If the chiral auxiliary is incorporated into the irradiation precursor in such a manner that it becomes conformationally locked, the subsequent photocycloadditions proceed with high levels of stereoselectivity.[62-65] *Meyers* demonstrated the synthetic utility of such auxiliaries in his asymmetric total synthesis of (–)-grandisol (**15**) (Scheme 4).[66] Bicyclic lactam **13**, derived from L-valine, was irradiated in ethylene-saturated dichloromethane at –78 °C in the presence of the photosensitizer acetophenone. The photoadduct **14** was furnished in 93% yield in 88% *de* and after cleavage of the auxiliary in methanolic hydrosulfuric acid, further synthetic steps provided (–)-grandisol (**15**).



Scheme 4. Diastereoselective [2+2] photocycloaddition of cyclic enone **13** with ethylene.[66]

Chiral linkers which connect two reactions partners have also been shown to be effective in transferring their chiral information to the desired photoproducts.[67-70] In 2001, *Piva* reported an asymmetric approach towards italicene (**20**) and isoitalicene (*epi*-**20**) using an (*S*)-lactic acid based chiral linker as an auxiliary (Scheme 5).[71] This approach proved to be particularly effective for enone **16**, providing photoadduct **17** in 81% yield in excellent diastereomeric excess (94% *de*). Although the cleavage of the linker was relatively straightforward, the cyclization to the five-membered rings in ketones **18** and *epi*-**18** proved to be significantly challenging. A formal synthesis of either of the natural products italicene (**20**) and isoitalicene (*epi*-**20**), however, was not completed as it was stated that the α-methylation to ketones **19** and *epi*-**19** had not been possible.



Scheme 5. Diastereoselective intramolecular [2+2] photocycloaddition of enone **16**.

While chiral auxiliaries are able to induce high diastereoselectivities, the covalent bonding to the substrate requires additional synthetic steps to incorporate and cleave the chirality inducing component. Alternatively, a non-covalent bonding of suitable substrates to chiral complexing agents, also referred to as templates, can be achieved, for example by hydrogen bonding. Thus, an asymmetric reaction course can be induced without changing the molecular structure of the substrate. There is a plethora of reports on various templates employed in solution, however, no significant enantioselectivities were achieved and thus the synthetic utility for the total synthesis of natural products is still limited.[72] In 2000, our group first reported template **22**,[73] the synthesis of which is based on *Kemp*'s triacid,[74] which can coordinate quinolone derivatives such as **21** in host-guest complexes **21**·**22**.[75,76] Template **22** acts as both a hydrogen bonding donor and acceptor. It can bidentately bind to lactams which in turn conformationally locks the host-guest complex and thus results in good enantioface differentiation. When employed in stochiometric amounts, template **22** and its enantiomer *ent*-**22** enabled enantioselective intra- and intermolecular [2+2] photocycloadditions of quinolone[75-77] and isoquinolone[78,79] substrates with high yields and excellent enantioselectivities up to 99% *ee*.

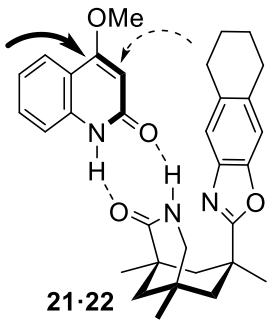
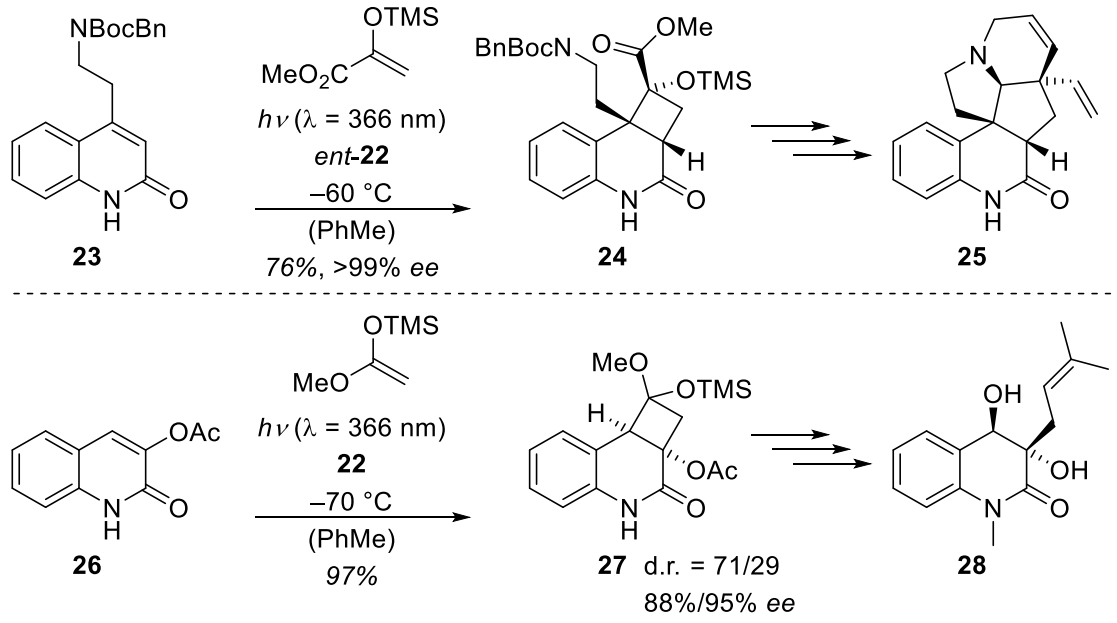


Figure 5. Example for a host-guest complex **21**·**22** shielding one enantiotopic face of the enone (dashed arrow) and forcing photochemical reactions from the opposite face (bold arrow).[76]

Furthermore, templates **22** and *ent*-**22** were applied in enantioselective total syntheses of the natural products (+)-meloscine (**25**) and (–)-pinolinone (**28**) (Scheme 6).[80,81] The enantioselective [2+2] photocycloaddition furnished photoadduct **24** in high yield of 76% in >99% *ee*. Further conversion including a ring expansion of **24** furnished (+)-meloscine (**25**). The implementation of a [2+2] photocycloaddition as the key step had dramatically increased the overall yield. This new route was also considerably more concise in comparison to a total synthesis reported by *Overman*, which includes a thermal reaction as the key step.[82,83]

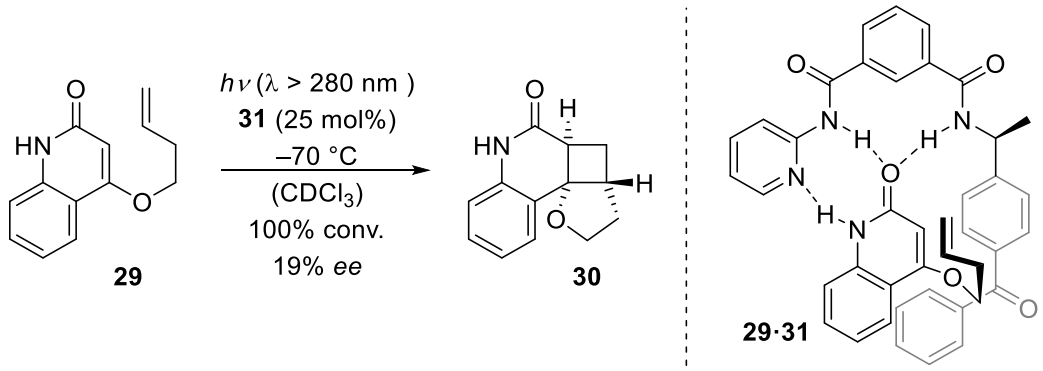


Scheme 6. The template mediated intermolecular enantioselective [2+2] photocycloaddition as the key step for the total syntheses of (+)-meloscine (**25**) (upper sequence) and (–)-pinolinone (**28**) (lower sequence).[80,81]

The same concept was applied to an asymmetric synthetic route to (–)-pinolinone (**28**). An enantioselective photocycloaddition as the key step yielded a diastereomeric mixture of **27**. Here, the major diastereomer was isolated in 88% *ee* and the minor in 95% *ee*. This study represents the first literature-known total synthesis of (–)-pinolinone (**28**) which unambiguously assigned its absolute configuration.

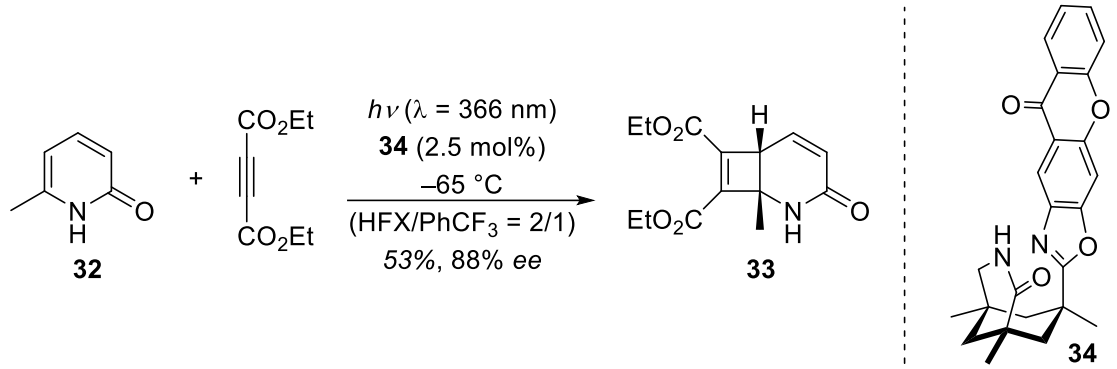
1.3.2 Catalysis with Hydrogen Bonding Templates

In parallel with ongoing work of our group,[84] *Krische* reported in 2003 chiral template **31** which combines a hydrogen bonding site for lactams with a sensitizer (Scheme 7).[85] It was shown that omitting the pyridine moiety as a hydrogen bonding site in **31** results in a racemic reaction. Furthermore, the sensitizer moiety benzophenone (marked in grey) acts as a steric shield impeding reactions on the *re* and thus accelerating those from the *si* face. However, yields were not given and the enantioselectivity was low (19% *ee*). This can be attributed to a probable racemic background reaction as the reaction was carried out at a wavelength of $\lambda > 280$ nm which can potentially photoexcite the non-coordinated substrate. Another explanation might be the lack of rigidity in the structure of template **31**.



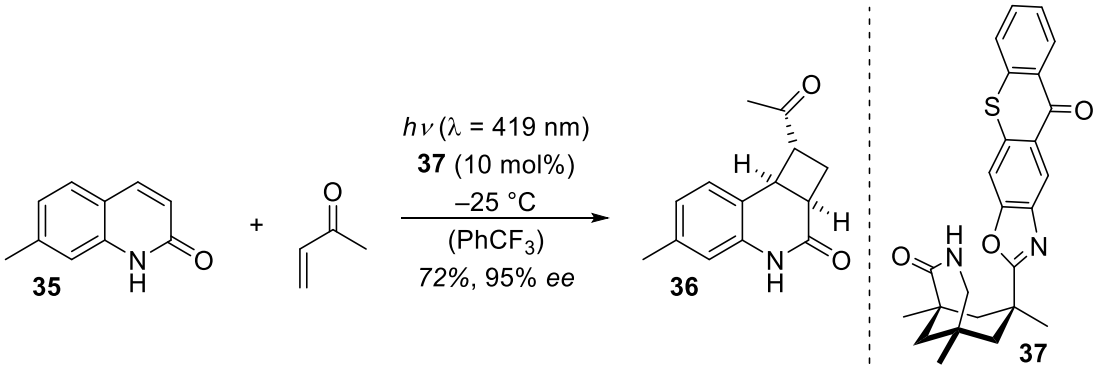
Scheme 7. First catalytic enantioselective [2+2] photocycloaddition with template **31** as catalyst.[85]

In our group advantage was taken by the rigid structure of template **34** and the chemically inert shield was changed to a sensitizer moiety based on xanthone.[38] The new template *ent*-**34** was successfully employed in highly enantioselective intramolecular [2+2] photocycloadditions of quinolone substrates. Compared to the benzophenone moiety in **31**, the xanthone in **34** represents a tetracycle which can only rotate about the single bond connecting itself to the template and thereby not affecting the shielding effect. Applied in the intermolecular [2+2] photocycloaddition of 2-pyridones with alkynes, template **34** could provide photoadducts in up to 92% *ee* with a catalyst loading of only 2.5-5.0 mol% (Scheme 8).[86] Employing an apolar solvent mixture of 2:1 hexafluoro-*m*-xylene (HFX) and trifluorotoluene resulted in a freezing point depression below –65 °C. At this temperature, it was proposed that more stable hydrogen bonds could be formed which resulted in high enantioselectivities.



Scheme 8. Enantioselective intermolecular [2+2] photocycloaddition of 2-pyridones using template **34**.[86]

In recent years, visible-light mediated photochemical reactions have attracted much attention in the scientific community leading to numerous photochemical reactions employing visible light as an environmental energy source for chemical reactions.[87,88] In this context, template **37** bearing a thioxanthone moiety as a sensitizer was developed in our group.[39] The enantioselective intramolecular [2+2] photocycloaddition of various quinolone substrates proceeded with high enantioselectivities up to 94% *ee*. Thioxanthone absorbs visible light and concurrently has the appropriate triplet energy for a sensitization of various quinolone substrates. Additionally, quinolone substrates do not absorb visible light and therefore cannot undergo a racemic background reaction under these reaction conditions. The enantioselective intermolecular [2+2] photocycloaddition of quinolones with alkenes was also achieved (Scheme 9).[89] Twelve combinations of quinolones and alkenes led to high enantioselectivities (80-95% *ee*). Alkenes with electron withdrawing groups in conjugation with the double bond were tolerated in this catalytic reaction. With an apparatus for solar irradiation it was shown that even sunlight can be used as the light source.



Scheme 9. Enantioselective intermolecular [2+2] photocycloaddition of quinolones with alkenes using template **37** with visible light.[89]

Another hydrogen bonding template is the thiourea-based catalyst **38**, reported by *Sibi* and *Sivaguru*, which efficiently coordinates to coumarin **39** (Figure 6).[90,91] The key aspect of this

catalyst is the acidic hydroxy group which activates the chromophore of coumarin **39**. This enables selective excitation of the bound substrate and thus induces high enantioselectivity. It is known that photocycloadditions with coumarins are enhanced by the presence of Lewis acids.[92] Without the trifluoromethyl groups in the BINOL moiety, the enantioselectivity was severely diminished, presumably due to a less acidic hydroxy group. High enantioselectivities up to 94% *ee* were obtained with catalytic amounts of **38** (10 mol%). Our group subsequently developed chiral thiourea **40** which was employed in 50 mol% together with 10 mol% thioxanthone as an external sensitizer in the enantioselective [2+2] photocycloaddition of dihydropyridone **41** with visible light (Figure 6).[93] The C_2-symmetrical catalyst **40** could simultaneously coordinate to two substrates **41** at their respective ketone carbonyl groups. It is assumed that thioxanthone not only acts as a sensitizer but also enhances the enantioselectivity by acting as a shield during the sensitization process and therefore impeding the attack of the olefin from the *re* face. However, the substrate scope was limited and the highest enantioselectivity was obtained from substrate **41** in 75% *ee* and in excellent yield.

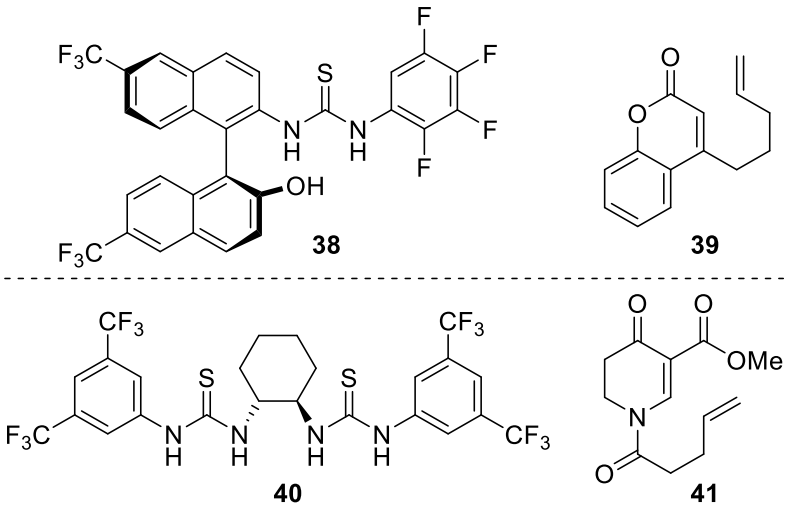
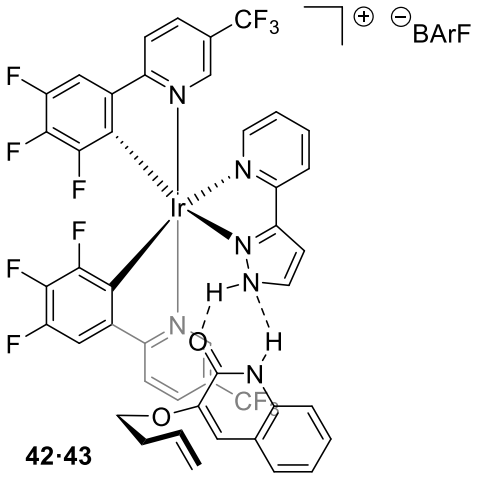


Figure 6. Chiral thiourea-derived catalysts **38**[90] and **40**[93] which are employed in enantioselective [2+2] photocycloadditions.

In a recent study by *Yoon*, a chiral iridium complex **43** functioned as both a sensitizer and hydrogen bonding template in the enantioselective conversion of quinolone **42** with visible light (Figure 7).[94] The pyrazole moiety concurrently functions as a hydrogen donor and acceptor with a strong coordination constant towards quinolone substrates. The remaining ligands were shown to dramatically influence the binding constant in the complex **42·43**. Enantioselectivity is induced by a simultaneous shielding caused by the pyridyl group (marked in grey) as well as a sensitization process involving a π-π interaction between the ligand and the substrate **42**. With a catalyst loading of only 1 mol% the substrates were converted in high enantioselectivities up to 91% *ee*. Furthermore, a major advantage of this catalytic system is the simple derivatization of iridium complex **43** which can potentially ensure an expeditious optimization of the catalyst for new quinolone and other hydrogen bonding substrates.



42·43

Figure 7. Host-guest interaction between iridium complex **43** and quinolone **42**.[94]

1.3.3 Catalysis with Chiral Lewis Acids

The impact of Lewis acids on the reaction course of a [2+2] photodimerization of coumarins was first reported in 1983 by *Lewis*.[95] A second study revealed that Lewis acids can enable intermolecular [2+2] photocycloadditions between coumarins and alkenes.[92] This pioneering work demonstrated that a coordination of a Lewis acid onto the carbonyl group of coumarin increases the singlet state S_1 lifetime and enhances an ISC to the triplet state T_1 resulting in accelerated subsequent photoreactions. Further studies confirmed that Lewis acid coordination can both, dramatically influence the photophysical properties[96-98] of α,β-unsaturated ketones as well as change the regioselectivity[99] of a [2+2] photodimerization. In recent years, the development of enantioselective photocatalysis using chromophore activation as the key principle dramatically increased.[100] Accordingly, there are three major activation modes which can enable an enantioselective catalysis in [2+2] photocycloadditions and other photochemical reactions (Figure 8). Activation mode a) describes a Lewis acid induced bathochromic shift which changes the wavelength at which the substrate can be effectively photoexcited. This mode is typically apparent in α,β-unsaturated esters or amides, in which both, a bathochromic shift and a change of the reaction course ($S_1 < T_1$) is induced. Activation mode b) induces a bathochromic shift of the ππ* absorption band leading to a strong overlap with the nπ* transition. The nπ* transition is commonly apparent in α,β-unsaturated ketones. Consequently, the increased extinction coefficient ε' at a constant wavelength (dashed line) enables a selective excitation of the catalyst-substrate complex. Finally, activation mode c) induces a lowering of the triplet energy of a substrate which enables a selective sensitization of a Lewis acid-substrate complex.

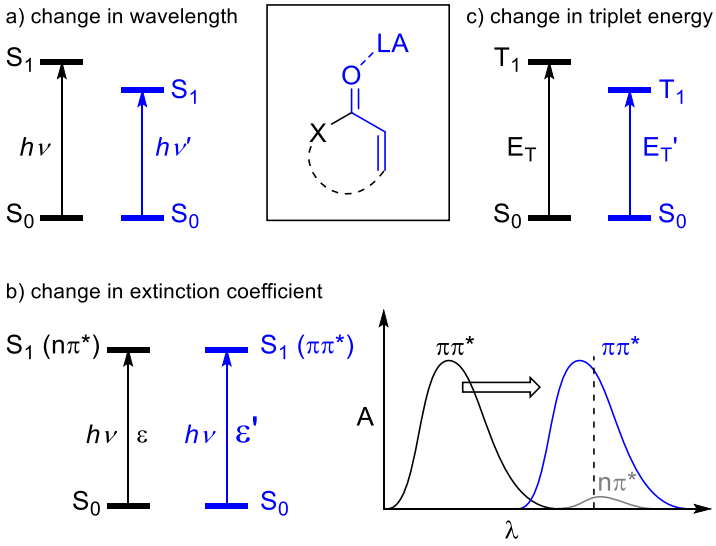
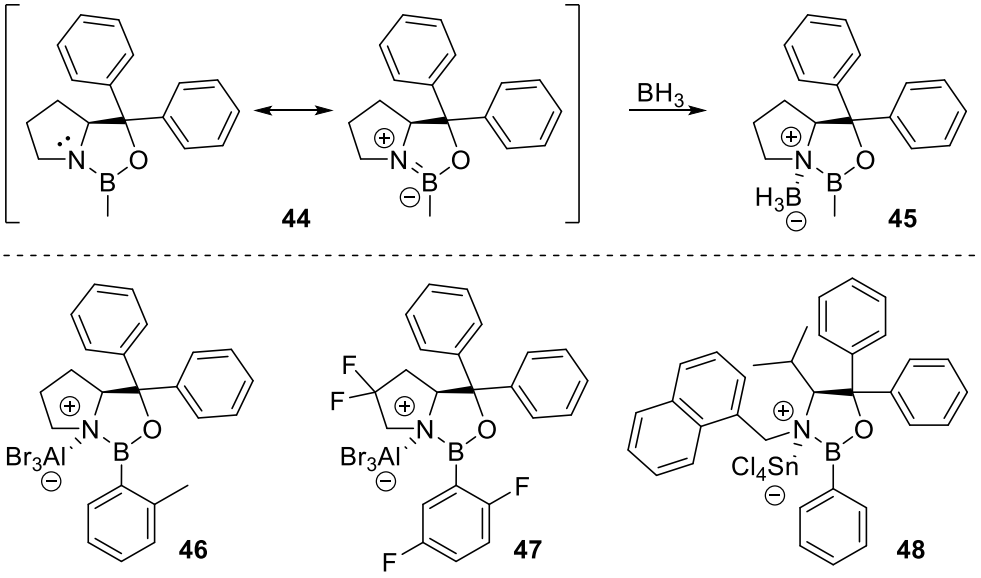


Figure 8. Three activation modes of an α,β-unsaturated ketone or ester/amide chromophore.

1.3.3.1 Oxazaborolidines as Catalysts

In the early 1980s the group of *Itsuno* discovered a chiral reducing reagent consisting of diphenyl valinol and borane which reduces secondary ketones in high enantioselectivities.[101-105] *Corey*, *Bakshi* and *Shibata* recognized the potential for the synthetic utility of this reducing complex and carried out further investigations. In 1987, they reported the structure of an oxazaborolidine **44** which was moisture tolerant, storable and hence applicable to a variety of synthetic organic reactions (Scheme 10).[106,107] It is now known as the *Corey-Bakshi-Shibata* catalyst (CBS catalyst) and in combination with borane the resulting catalyst **45** can be employed in the enantioselective reductions of ketones. The structure of **45** was confirmed by crystal structure analysis.[108]



Scheme 10. Various oxazaborolidine catalysts based on L-proline and L-valine.

In the following years, new oxazaborolidine derivatives, e.g. **46**, **47** and **48**, were reported. These were employed in *Diels-Alder* reactions involving α,β-unsaturated carbonyl compounds providing excellent yields and enantioselectivities.[109-113] The Lewis acids coordinating on the nitrogen atom prevent a resonance stabilization (see **44**) and therefore enhance the Lewis acidity of the boron atom. This principle is also known as combined Lewis acid catalysis and has been successfully applied to various Lewis and Brønsted acid based chiral catalysts.[114]

Inspired by the reports by *Lewis* (see above),[92,95] our group set out to investigate whether chiral Lewis acids could be implemented in enantioselective [2+2] photocycloaddition of coumarin derivatives. An extensive screening of various chiral Lewis acids was carried out by *Guo*.[115] Oxazaborolidine **49** was identified as the most proficient catalyst with respect to high enantioselectivities in the [2+2] photocycloaddition of coumarin **39** (Figure 9).[116] Further

studies by *Brimioulle* expanded the substrate scope and further substantiated the putative complexation model **39·49'**.[117] The interaction between coumarin **39** and catalyst **49'** is postulated to consist of a Lewis acid-Lewis base interaction between the boron atom of **49'** and the oxygen atom of **39** as well as a hydrogen bonding between the oxygen atom of **49'** and the α-hydrogen atom of **39**. This bidentate binding mode ensures good enantioface differentiation in which the *re* face is shielded by the aryl group (marked in grey). Furthermore, it was revealed that upon coordination of a Lewis acid the singlet state lifetime is enhanced in the bathochromically shifted UV absorption of **39** and that the catalyzed reaction proceeds on the triplet hypersurface [activation mode a)].

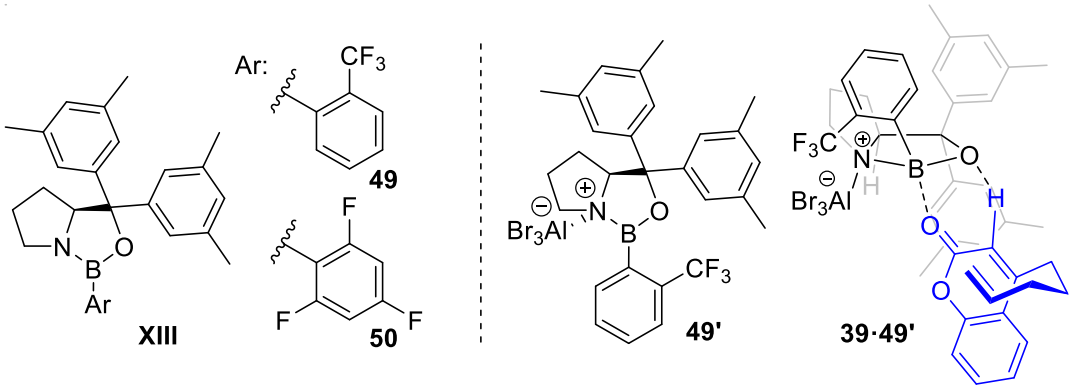
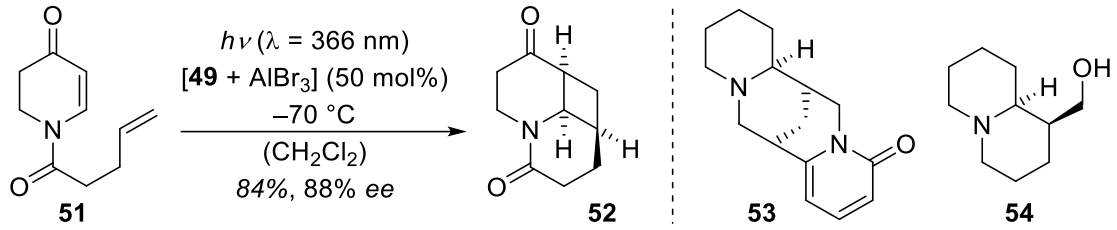


Figure 9. Oxazaborolidines **49** and **50** developed in our group (left). Aluminum bromide activated oxazaborolidine **49'** and its complex with coumarin derivative **39·49'** (right).

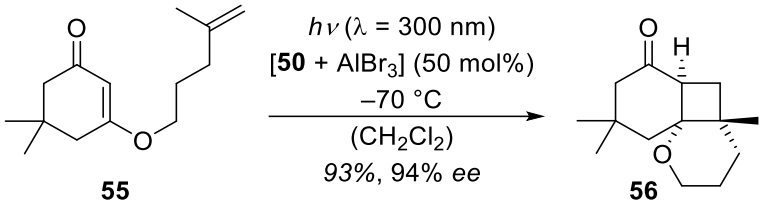
In search for new substrates for enantioselective intramolecular [2+2] photocycloadditions *Brimioulle* discovered that α,β-unsaturated ketones show a strong bathochromic shift of the ππ* absorption band and at the same time a disappearance of the nπ* absorption band in the UV Vis spectrum [activation mode b)].[118] Consequently, the racemic background reaction was inhibited by the stronger absorption of the Lewis acid-substrate complex. Although the reaction time was significantly increased, dihydropyridones could be converted with high yields and high enantioselectivities (Scheme 11).[119] Furthermore, one of the photoadducts acted as a starting point in an enantioselective formal synthesis of (+)-thermopsine (**53**) and a total synthesis of (+)-lupinine (**54**). Additional mechanistic studies revealed the different reaction courses on which coumarin substrates and dihydropyridones proceed.[120] When coordinated to a Lewis acid, coumarins change their reaction course from the singlet to the triplet hypersurface. Overall this results in a reaction acceleration and therefore enantioselectivity is induced. Dihydropyridones, however, remain on the triplet hypersurface but dramatically decrease in reaction rate. The enantioselectivity is achieved by a stronger absorption of the Lewis acid-substrate complex at longer wavelengths. Theoretical studies by *Wang* and *Dolg* revealed

that the mechanism of the enantioselective [2+2] photocycloaddition is mainly influenced by an enhanced spin-orbit coupling from the heavy atoms (bromine) in catalyst **49'** resulting in higher ISC rates.[121,122]



Scheme 11. Enantioselective [2+2] photocycloaddition of dihydropyridone **51** (right). Structures of (+)-thermopsine (**53**) and (+)-lupinine (**54**).[119]

Changing the aryl substituent on the boron atom from 2-trifluoromethylphenyl to 2,4,6-trifluorophenyl furnished new catalyst **50** which could enantioselectively convert alkenyloxy substituted enones (Scheme 12).[123] The bathochromic shift was considerably less pronounced in comparison to dihydropyridones, therefore shorter excitation wavelengths were necessary. This study uncovered a strong correlation between the photon flux and the enantioselectivity which varied for each substrate. Photoadducts were obtained in high yields and enantiomeric excesses up to 94% *ee*. Additionally, it was possible to further convert the photoadducts in a *de Mayo* reaction by addition of hydrochloric acid yielding complex tricyclic structures.

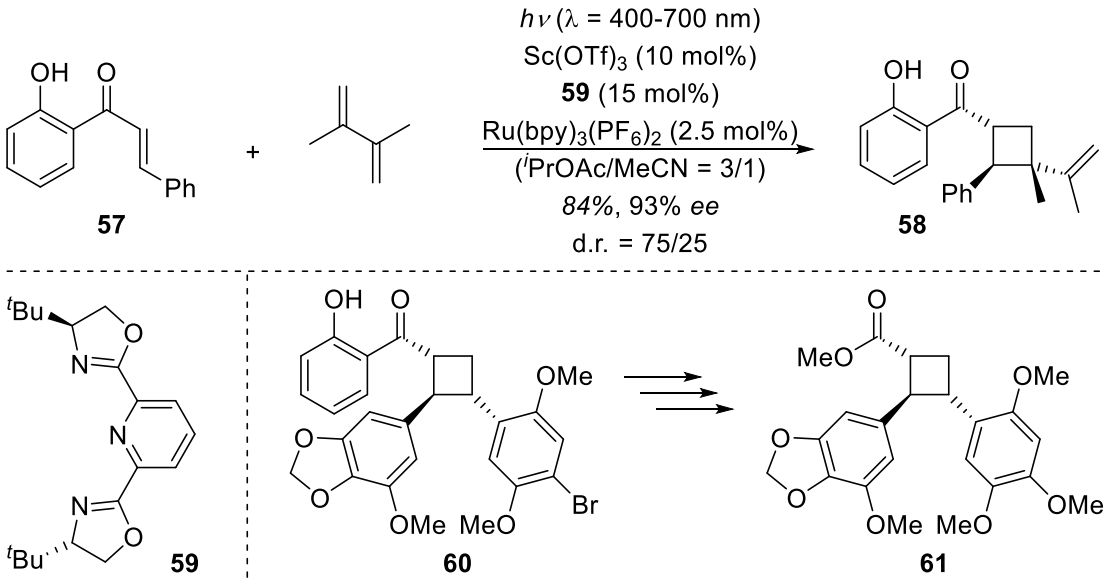


Scheme 12. Enantioselective [2+2] photocycloaddition of enone **55** with new catalyst **50**.[123]

This method proved to be successful in the enantioselective conversion of cyclic enones and has been implemented in the enantioselective total syntheses of natural products. As alluded to earlier, simple cyclic enones are ideal precursors for natural product target compounds which can be accessed by a synthetic route involving a [2+2] photocycloaddition as the key step.[19] Further developments of catalyst **50** for synthetically relevant irradiation precursors are therefore of tremendous interest. Consequently, studies towards this end are the main focus of this thesis.

1.3.3.2 Metal Complexes as Catalysts

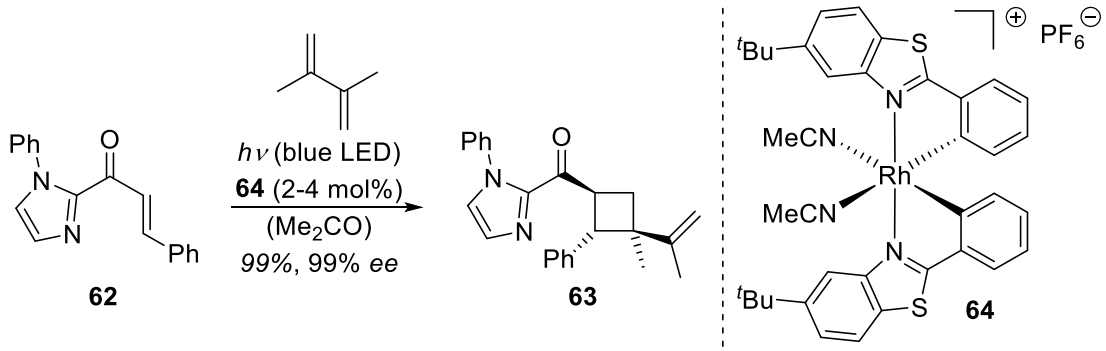
The application of chiral Lewis acids in enantioselective [2+2] photocycloadditions attracted significant attention among the scientific community. *Yoon* reported a combination of a chiral Lewis acid europium complex and a photoredox catalyst $Ru(bpy)_3Cl_2$.[124] This dual catalysis converted acyclic aryl substituted enones with simple acyclic enones in a radical cascade mechanism leading to cyclobutanes with high yields and excellent enantiomeric excesses with visible light. The advantage of this system is that only Lewis acid coordinated substrates are reduced by the photocatalyst, thus preventing a racemic background reaction. However, it is not a classical [2+2] photocycloaddition, but a photoelectron transfer (PET) catalyzed reaction.[125] In a later study, scandium(III) triflate in combination with pybox ligand **59** induced high enantioselectivities in intermolecular [2+2] photocycloadditions of chalcone derivatives with dienes (Scheme 13).[126] Here, photocatalyst $Ru(bpy)_3(PF_6)_2$ acts as a triplet sensitizer which selectively sensitizes Lewis acid coordinated chalcones [activation mode c)]. Due to the lack of a background reaction and good enantioface differentiation excellent enantioselecitivities were obtained. The method was further extended to styrenes enabling an enantioselective total synthesis of (+)-norlignan (**61**) from photoadduct **60** (Scheme 13).[127]



Scheme 13. Enantioselective [2+2] photocycloaddition of chalcone **57** with 2,3-dimethylbuta-1,3-diene. Strucure of the natural product (+)-norlignan (**61**).

A reaction design, reported by *Meggers*, involves a chiral iridium complex **64** which upon coordination of substrate **62** absorbs blue light (420-490 nm) and induces high enantioselectivities (Scheme 14).[128] The imidazole based auxiliary in enone **62** is responsible for an effective coordination to **64** in which the acetonitrile ligands easily dissociate and vacate

a coordination site. The formed substrate-catalyst complex can be selectively excited with visible light to its S_1 state. This rapidly undergoes an ISC to the T_1 state from which the reaction proceeds [activation method b)]. Excellent yields and enantioselectivities were obtained. Using this method, it was shown in a further study that also benzofuran and benzothiophene derivatives were enantioselectively converted to [2+2] photoadducts in excellent enantiomeric excesses.[129]

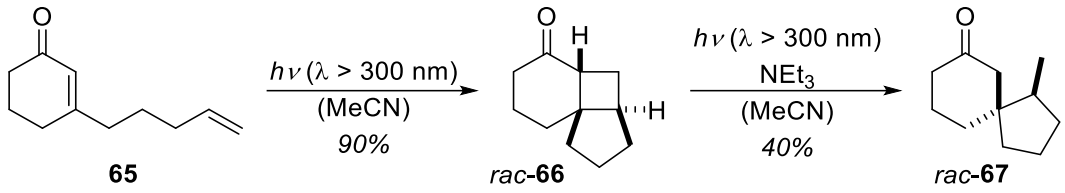


Scheme 14. Enantioselective [2+2] photocycloaddition of enone **62** with 2,3-dimethylbuta-1,3-diene.[128]

2. Intramolecular [2+2] Photocycloadditions of Cyclic Enones

2.1 Literature Background and Project Aims

The intramolecular [2+2] photocycloaddition of cyclic enones with alkene side chains has been extensively investigated with respect to diastereoselectivity and regioselectivity.[33,130-132] It represents a powerful tool to obtain tricyclic carbon scaffolds in a single synthetic step. In a study reported by *Mattay*, all-carbon irradiation precursor **65** was transformed to the tricyclic photoadduct *rac*-**66** in 90% yield (Scheme 15).[133] Subsequently, *rac*-**66** underwent a reductive ring opening to spiro compound *rac*-**67** via a photoelectron transfer, with triethylamine acting as the reductant. The same cleavage of the cyclobutane ring was reported by *Kakiuchi*.[134] In their study, a reductive cleavage by samarium(II) iodide furnished *rac*-**67** in 99% yield.



Scheme 15. Intramolecular [2+2] photocycloaddition of **65** and subsequent reductive cleavage of the formed cyclobutane ring.[133]

The carbon scaffolds represented by *rac*-**20** and *rac*-**68** occur in numerous natural products (Figure 10). In 1984, *Weyerstahl* reported the isolation of the sesquiterpene hydrocarbons (–)-italicene (**20**) and (+)-isoitalicene (*epi*-**20**).[135,136] An intramolecular [2+2] photocycloaddition was employed as the key step in the racemic total synthesis of *rac*-**20**. In a sequence involving a reduction of the ketone and elimination using *Burgess* reagent,[137] the natural products *rac*-**20** and *rac*-*epi*-**20** could be generated. There are several reports of either formal syntheses of *rac*-italicene (*rac*-**20**) and *rac*-isoitalicene (*rac*-*epi*-**20**) or constructions of the corresponding carbon scaffolds.[138-141] These syntheses include thermal reactions as key steps. Consequently, the reaction sequences towards the tricyclic core structure are longer. The first diastereoselective formal synthesis towards (–)-italicene (**20**) and (+)-isoitalicene (*epi*-**20**) was reported by *Piva* in 2001.[71] Starting from an intermediate product analogously to *rac*-**19**, the natural product *rac*-acorenone (*rac*-**68**) was synthesized by *Oppolzer*.[142] A more concise formal synthesis of *rac*-**68** was reported by *Kakiuchi*.[134] The key structure of *rac*-acorenone (*rac*-**68**) is present in numerous natural products.[143-146]

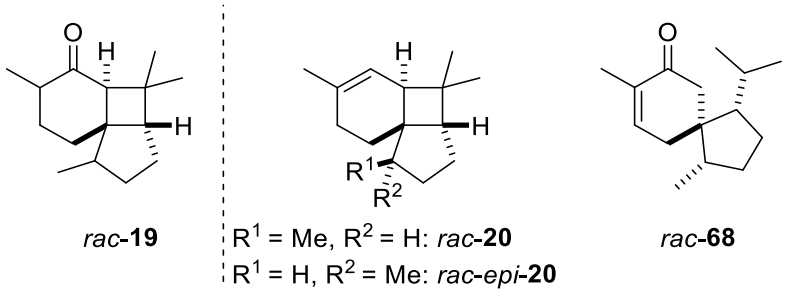
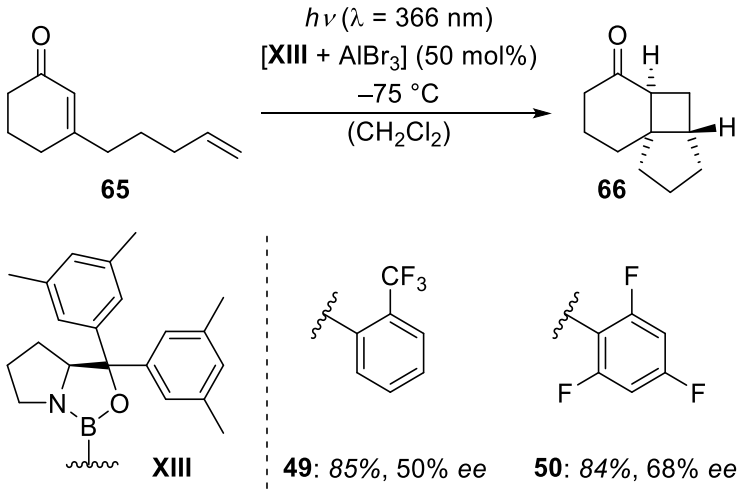


Figure 10. Structures of natural products *rac*-italicene (*rac*-**20**), *rac*-isoitalicene (*rac*-**20**) and *rac*-acorenone (*rac*-**68**).[135,142]

Preliminary experiments towards an enantioselective intramolecular [2+2] photocycloaddition of enone **65** were previously carried out in our group by *Brimioulle*.[118] Catalysts **49** and **50**, which proved to be the optimal catalysts for the enantioselective intramolecular [2+2] photocycloaddition of dihydropyridones[119] **51** and alkenyloxy-substituted enones[123] **55**, were employed (Scheme 16).



Scheme 16. Preliminary results of the enantioselective intramolecular [2+2] photocycloaddition of enone **65**.[118]

Catalyst **49** provided **66** in 85% yield and 50% *ee*. Catalyst **50** also furnished photoadduct **66** in 84% yield and 68% *ee*. The chromophores of the previously studied irradiation precursors significantly differ from substrate **65**. The α,β-unsaturated ketones of dihydropyridones **51** and enones **55** are in direct conjugation with nitrogen- and oxygen atoms, respectively. This has a significant impact on the bathochromic shift and the Lewis basicity of the carbonyl oxygen atom. Furthermore, this demonstrates that the previously developed catalysts **49** and **50** are not universally applicable. Hence, a new catalyst had to be identified for substrate **65**.

Considering the synthetic relevance of the all-carbon scaffolds *rac*-**20** and *rac*-**68**, the aim of this project was to establish a set of optimal reaction conditions for an enantioselective intramolecular [2+2] photocycloaddition of substrate **65**. The enantiomeric excess had to be

above 80% with high chemical yields. A diastereoselective synthesis of the natural products italicene (**20**) and isoitalicene (*epi*-**20**) was then to be carried out in order to showcase the synthetic utility of our method.

2.2 UV/Vis Measurements

As a starting point in our investigations, the absorption properties of the irradiation precursor **65** were investigated. UV/Vis spectra were measured in dichloromethane at two different concentrations (500 µM and 50 mM) (Figure 11). The absorption band of the ππ* transition shows a maximum at λ_{max} = 234 nm with ε = 17008 $M^{-1}cm^{-1}$. It tails into higher wavelengths until λ = 275 nm where the absorption band of the nπ* transition emerges. The weak absorption band of the nπ* transition became visible in a more concentrated sample (50 mM) at λ_{max} = 324 nm with ε = 47 $M^{-1}cm^{-1}$.

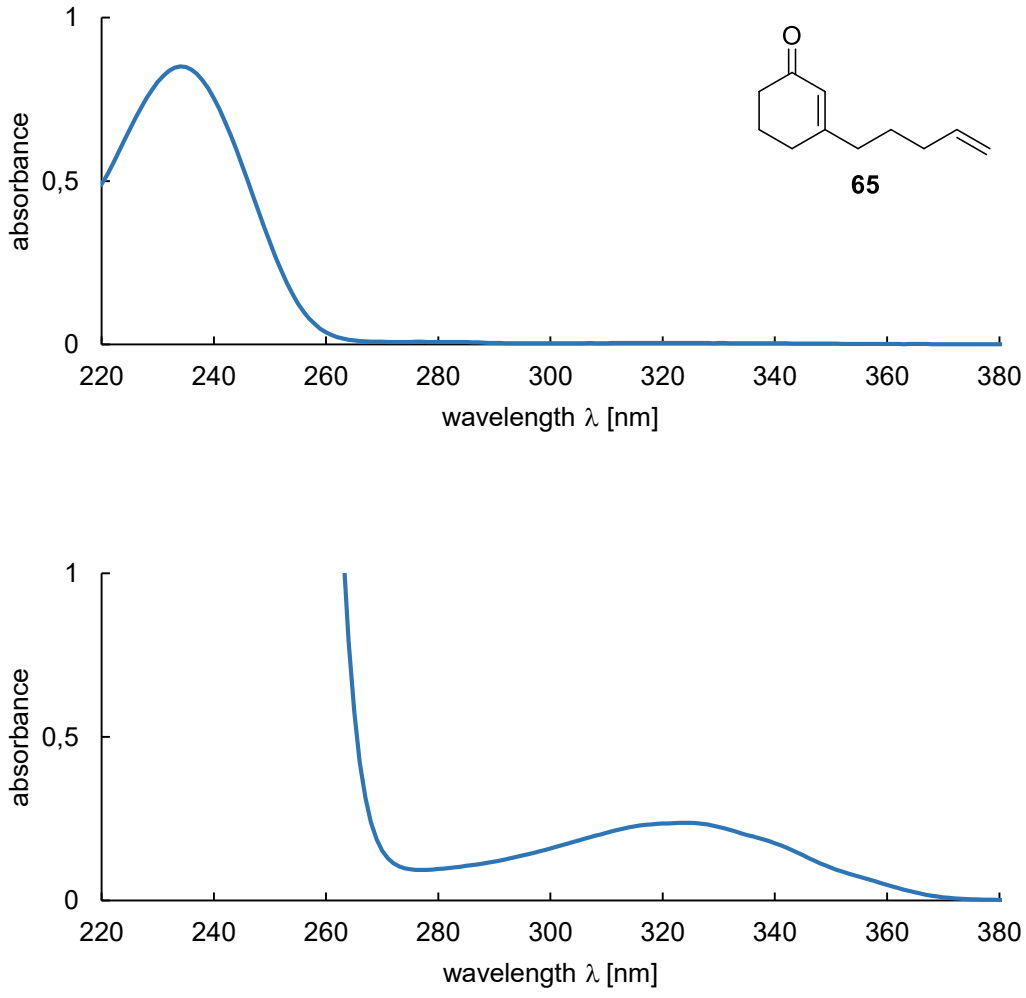


Figure 11. UV/Vis-spectra of enone **65** in dichloromethane depicting the absorption band of the ππ* transition (c = 500 µM, upper spectrum) and of the nπ* transition (c = 50 mM, lower spectrum).

A racemic reaction appeared to be feasible at irradiation wavelengths $\lambda = 254$ nm, 300 nm, 350 nm and 366 nm. The longer the wavelength, the milder the reaction conditions generally become, albeit reaction times tend to increase. However, less by-products would be formed. Using shorter wavelengths would result in fast reactions. This difference in reaction rate is related to the difference in extinction coefficients at the two absorption maxima of the ππ* and the nπ* transition.

In order to observe the impact of a Lewis acid on the chromophore, substrate **65** was treated with each 20 equiv of $EtAlCl_2$ and BCl_3 in dichloromethane at a concentration of 500 μM (Figure 12). An excess of the respective Lewis acid ensures complete complexation of the substrate **65**. The maximum of the ππ* transition absorption band of complex **65**·$EtAlCl_2$ was observed at $\lambda_{max} = 281$ nm with $\varepsilon = 13746\ M^{-1}cm^{-1}$ with a tailing down to $\lambda = 330$ nm. The absorption maximum is bathochromically shifted with a difference of $\Delta\lambda_{max} = 47$ nm compared to uncomplexed **65**. Complex **65**·BCl_3 exhibits an absorption maximum at $\lambda_{max} = 288$ nm with $\varepsilon = 17832\ M^{-1}cm^{-1}$. The absorption band shows a stronger bathochromic shift of $\Delta\lambda_{max} = 54$ nm and similarly tails down to $\lambda = 330$ nm. Both complexes **65**·LA show stronger absorptions at $\lambda = 324$ nm than the nπ* transition of **65**. Neither of the complexes **65**·LA show a weak absorption band of an nπ* transition. Due to the coordination of the free electron pair orbital n, an nπ* transition is inhibited.

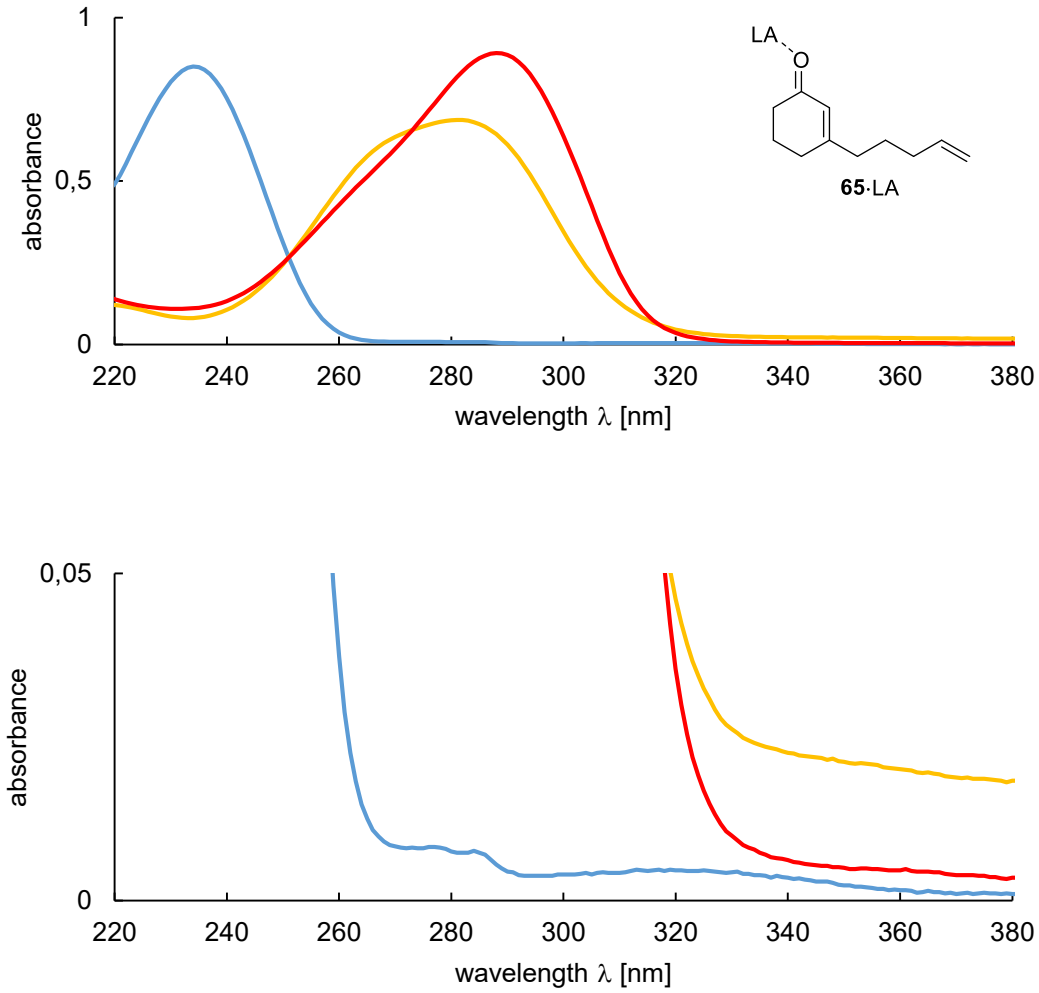
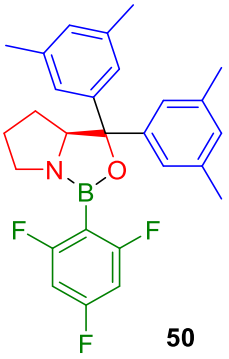


Figure 12. UV/Vis-spectra of enone **65** in the absence of a Lewis acid (blue) and in the presence of 20 equiv $EtAlCl_2$ (orange) and and 20 equiv BCl_3 (red). The lower figure shows a magnification of the upper spectrum. The measurements were carried out in dichloromethane (c = 500 μM).

The strong bathochromic shifts effected by both Lewis acids indicate the feasibility of an enantioselective chiral Lewis acid catalyzed reaction. The preliminary results of *Brimioulle* confirmed this hypothesis.[118]

2.3 Synthesis of the Oxazaborolidine Catalysts

An extensive screening of various chiral Lewis acids for the enantioselective intramolecular [2+2] photocycloaddition of coumarins **39** was carried out in our group by *Guo*.[115] It was found that only oxazaborolidine based catalysts were able to induce significant levels of enantioselectivity. Consequently, catalysts which structurally differ from the oxazaborolidine catalyst-type were not investigated. We identified three moieties which were straightforward to vary within oxazaborolidine catalyst **50** (Figure 13). The main two parts consist of the proline-derived amino alcohol bearing two additional aryl groups. The boronic acid is the last component involved in the synthesis of the catalyst. In our group it was observed by *Guo* and *Brimioulle* that the aryl groups forming the prolinol backbone of the catalysts have a more significant impact on the enantioselectivity than the boronic acids. However, only the 3,5-dimethylsubstituted aryl group proved to be best suited for photochemical reactions. The variation of the boronic acid component is the simplest and quickest method in order to find a suitable oxazaborolidine catalyst for a new substrate. Boronic acids are abundantly commercially available and in one synthetic step with a prolinol, a new catalyst can be generated. In our case, however, the previously established prolinol did not yield desirable results. Consequently, we investigated a series of new oxazaborolidines with different amino acids and backbone aryl groups.

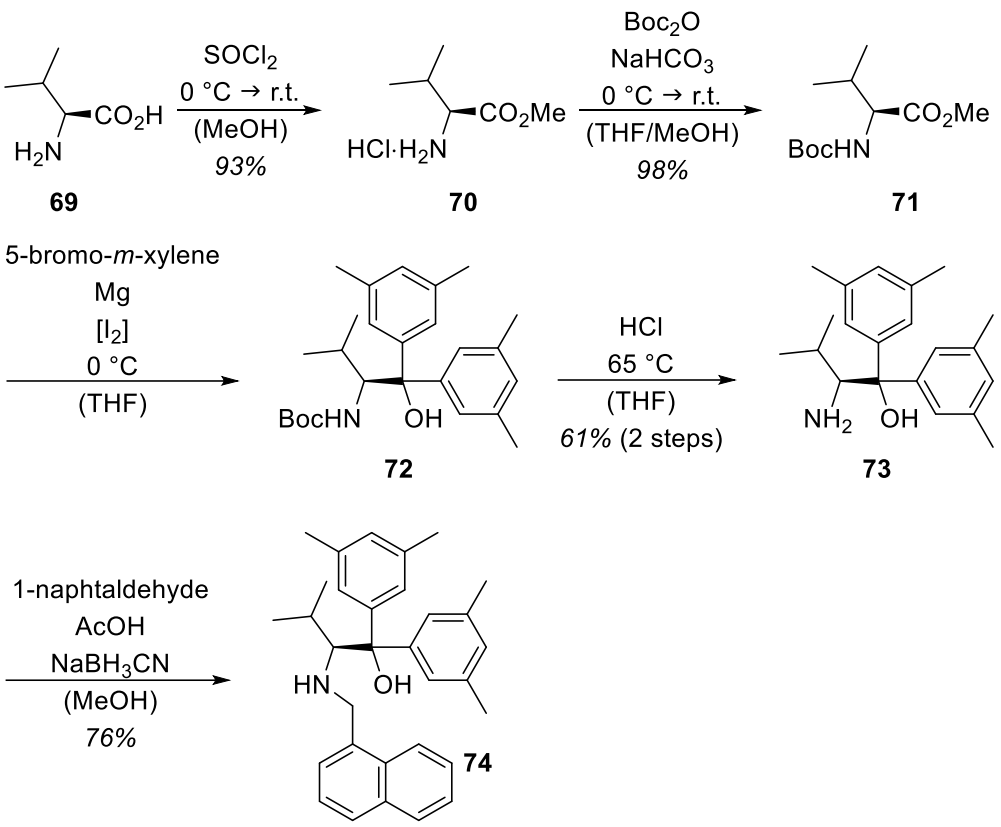


50

Figure 13. Three variables in the oxazaborolidine catalyst (here **50**): amino acid (red), aryl groups of the backbone (blue) and the boronic acid (green).

In 2005, *Yamamoto* reported a non-moisture sensitive valine-based oxazaborolidine.[112] It was used for various regioselective and asymmetric *Diels-Alder* reactions resulting in excellent yields and enantiomeric excesses.[113,147,148] Because the 3,5-dimethyl-substituted aryl group proved to be the most proficient aryl substituent for asymmetric photoreactions, the originally reported valine-based catalyst was structurally varied to incorporate the 3,5-dimethylphenyl motif. The synthesis of the catalyst precursor **74** started from L-valine (**69**) following

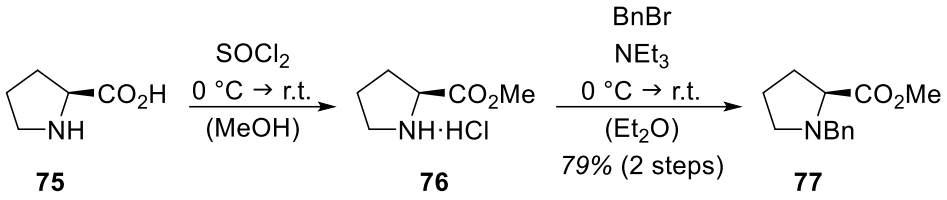
literature-known procedures (Scheme 17). Conversion of **69** with thionyl chloride in methanol provided valine methyl ester hydrochloride **70** in 93% yield.[149] An *N*-Boc protection of the free amine furnished Boc-protected valine methyl ester **71** in 98% yield.[150] A *Grignard* addition with 5-bromo-*m*-xylene led to Boc-protected valinol **72** which was consecutively deprotected using a hydrochloric acid solution in tetrahydrofuran. Valinol **73** was isolated in 61% yield over two steps.[151] The last step involved a reductive amination with 1-naphtaldehyde yielding 76% of the catalyst precursor **74**.[112]



Scheme 17. Synthesis of catalyst precursor **74** starting from L-valine (**69**).

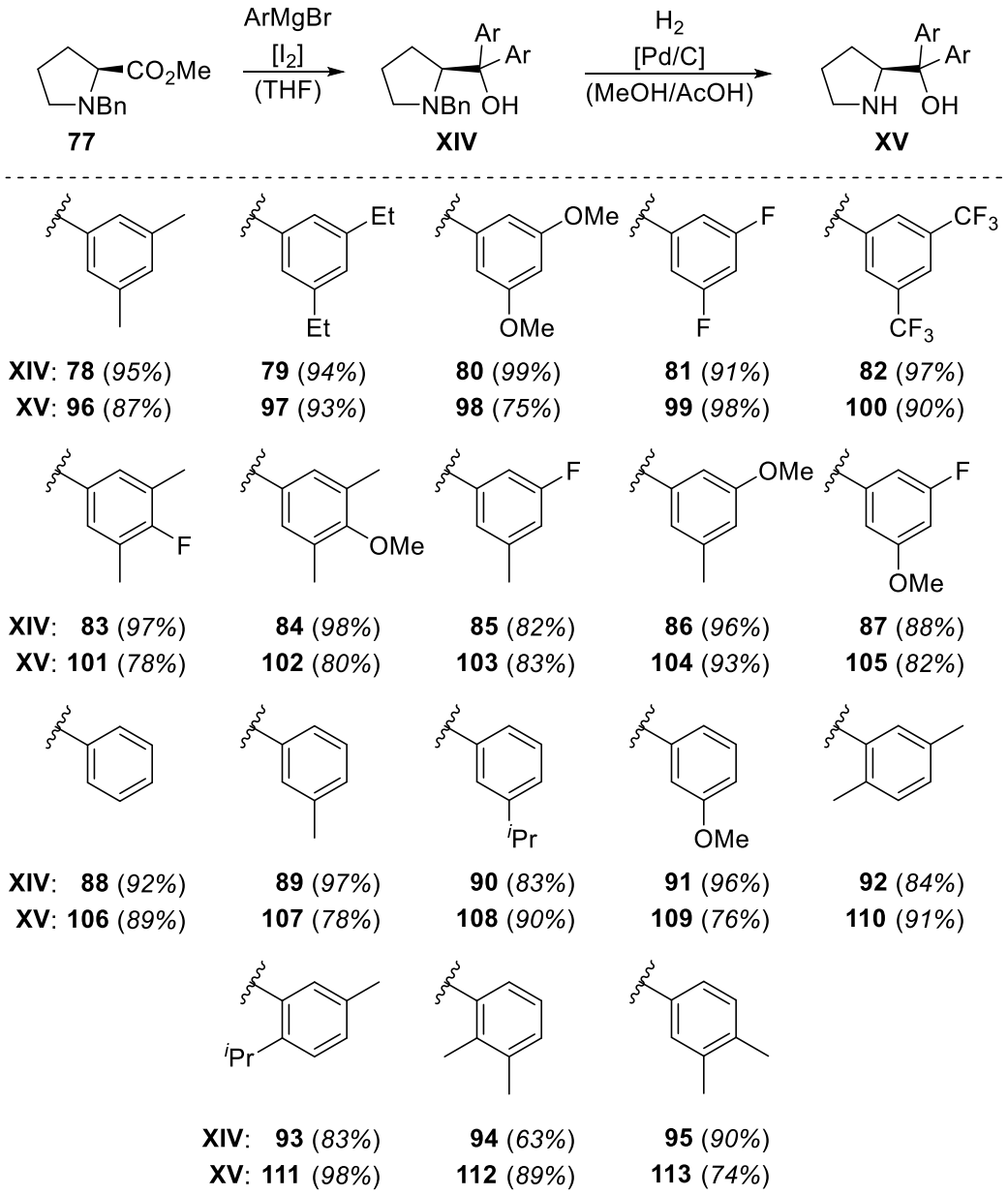
The previously synthesized proline-based catalyst precursors predominantly incorporated symmetrical aryl groups in the backbone.[115,118] It was considered to synthesize prolinols with aryl groups that were symmetrically 3,5-disubstituted (**96**-**100**), unsymmetrically 3,5-disubstituted (**103**-**105**, **107**-**109**), having a *para*-substituent (**101**, **102**, **113**) and having an *ortho*-substituent (**110**-**112**). In analogy to a literature-known procedure by *Gilmour*, catalyst precursors **XV** were synthesized starting from naturally occurring L-proline (**75**).[152] Treatment with thionyl chloride in methanol provided the proline methyl ester hydrochloride **76**. A benzyl protection furnished benzyl proline methyl ester **77** in 79% yield over two steps (Scheme 18). The protocol for the benzylation deviated from the literature-known one. In the literature procedure, toluene was used as the solvent and the reaction was carried out at reflux. Under

these reaction conditions, however, we observed a significant amount of benzyl ester products. Presumably, they are formed either by ester hydrolysis and subsequent benzylation or transesterification with in situ formed benzyl alcohol. A change in solvent to diethyl ether using mild conditions at room temperature completely inhibited this side reaction.



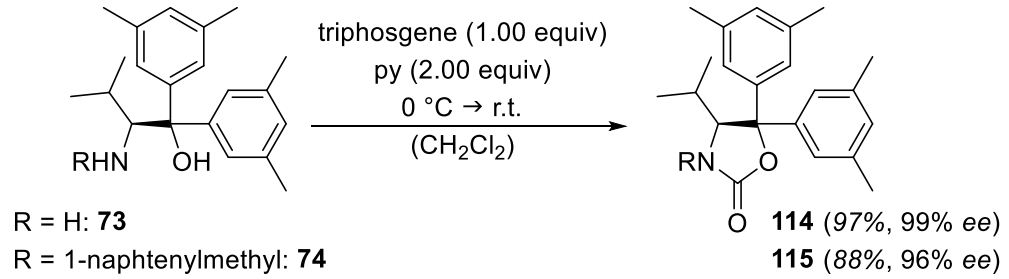
Scheme 18. Synthesis of benzyl-protected proline methyl ester **77**.

A *Grignard* addition with various aryl bromides provided benzyl protected prolinols **XIV** in high yields up to 99%. The benzyl group was deprotected by hydrogenolysis with catalytic palladium on carbon. The free prolinols **XV** were obtained in high yields up to 98% (Scheme 19). The *Grignard* additions of *ortho*-substituted aryl magnesium bromides (for **92**-**94**) required higher reaction temperatures of 100 °C. Presumably this is due to the increased steric hinderance of the organometallic reagent. Di-*ortho*-substituted aryl magnesium bromides did not add into the ester group with no conversion being observed. Benzyl protected prolinols **XIV** were promptly deprotected due to the tertiary amine being oxidized over time. Oxidized amines were observed in several samples in high-resolution ESI MS spectra. The purification of the free prolinols **XV** was challenging due to their basicity and high polarity.



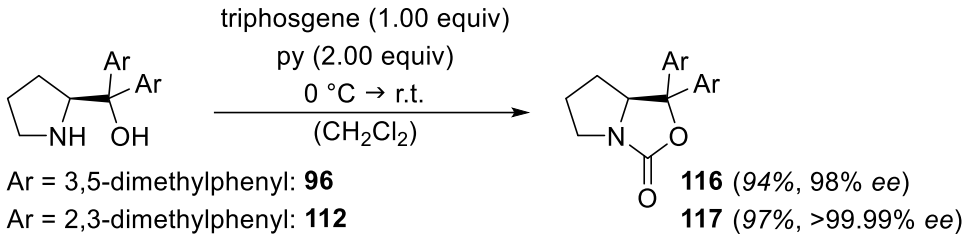
Scheme 19. Synthesis and scope of prolinols **XV**.

Since in a catalytic enantioselective reaction the chiral information of the catalyst is transferred to the substrate, high catalyst enantiopurity is of paramount importance. To examine the enantiopurity of the catalyst precursors, a cyclization to oxazolidinones was carried out to allow for the enantiomers to be separable on a chiral stationary phase by analytical HPLC. In analogy to a procedure reported by *Palomo*, the cyclization of the catalyst precursors was carried out with triphosgene and the enantiomeric excess was determined by chiral HPLC.[153] The oxazolidinone **114** was isolated in 97% yield with 99% *ee*, whereas **115** had a decreased enantiomeric excess of 96% (Scheme 20). This loss of enantiopurity can be traced back to the reductive amination step. Here, the imine intermediate may have induced a partial racemization of **74**.



Scheme 20. Cyclization of **73** and **74** to the oxazolidinones **114** and **115**.

The cyclized prolinols **116** and **117** were obtained in high yields up to 97% and high enantiomeric excesses up to >99.99%. The loss of enantiopurity for **96** (98% *ee*) is reasonably low. It has been previously described that a reduction of the enantiomeric excess can occur in the *Grignard* reaction when an excess of the organometallic species is present.[118] Therefore, a very slow addition of the *Grignard* reagent to the proline ester **77** impeded such a racemization.

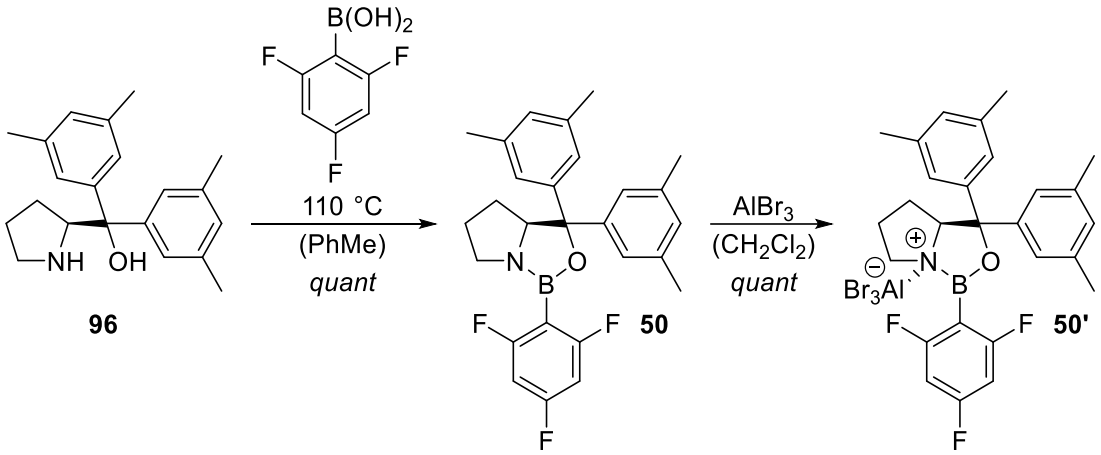


Scheme 21. Cyclization of **96** and **112** to the oxazolidinone **116** and **117**.

The synthesis of the oxazaborolidine catalysts was carried out following a literature-known procedure reported by our group (Scheme 22).[123] Here, prolinol **96** is discussed as an example. In a condensation reaction with 2,4,6-trifluorophenylboronic acid using a *Dean-Stark* apparatus the oxazaborolidine **50** was quantitatively formed. The resulting oxazaborolidine **50** was then activated with an appropriate Lewis acid (in this case aluminum bromide) immediately before the photochemical reaction. This method was applied to all proline- and valine-based catalysts.

Due to their extreme moisture sensitivity, oxazaborolidines required handling under dry conditions in the glovebox in order to prepare samples for full characterization. For NMR analysis, dry deuterated benzene proved to be the most suitable solvent providing clean NMR spectra. We were able to fully assign all proton and carbon signals (see chapter 6.3.3.1) for oxazaborolidines **50** and **207** (see chapter 2.5.9). Characteristic signals for oxazaborolidines were observed with ^{11}B and ^{19}F NMR spectroscopy. The boron atoms of **50** and **207** exhibit characteristic signals at 30.2 ppm and 29.7 ppm, respectively. This is in accordance to literature-known and analogous oxazaborolidines (e.g. **47** without aluminum bromide activation)[111] where the signals corresponding to the boron atoms appear at approximately

30 ppm. In oxazaborolidine **49**, however, the boron atom has a slightly downfield shifted signal at 35.4 ppm.[117,118] This is likely due to the aryl group at the boron atom bearing a trifluoromethyl group instead of a fluorine atom. Due to clear spectra, the ^{19}F signals of the fluorine atoms in **50** and **207** provide a good evaluation of the oxazaborolidine purity. Their signals appear at approximately –100 ppm which is consistent with a report by *Corey*.[111] Despite having fully characterized both oxazaborolidines **50** and **207**, we were not able to record spectra of the respective aluminum bromide activated catalysts **50'** and **207'**. They are very unstable at room temperature and decompose rapidly. However, there are reports in which spectra of aluminum bromide[111] and trifluoromethanesulfonimide[154] activated oxazaborolidines were recorded. The ^{1}H NMR signals show partial downfield shifts of the respective original oxazaborolidine as well as a strong broadening of the signals. Therefore, an assignment of these signals remained elusive.



Scheme 22. Synthesis of catalyst **50** and its activation with aluminum bromide to **50'**.

Preceding work on enantioselective [2+2] photocycloadditions in our group by *Brimioulle* revealed that it was optimal to synthesize the oxazaborolidines for each reaction individually.[118] Storage of the respective oxazaborolidines resulted in partial decomposition over time and thus the results with respect to yield and enantioselectivity in the catalytic photochemical reactions varied. Furthermore, the Lewis acid activated form is temperature sensitive and therefore must be handled at temperatures below –20 °C.

2.4 Synthesis of the Irradiation Precursors

From a retrosynthetic point of view, test substrate **65** consists of an enone moiety **118** (blue) and an alkene moiety **119** (red) (Figure 14). They can be separately derivatized and then in a *Grignard* reaction combined to generate a library of irradiation precursors. Syntheses of alkene side chains, vinylogous esters and irradiation precursors are discussed below.

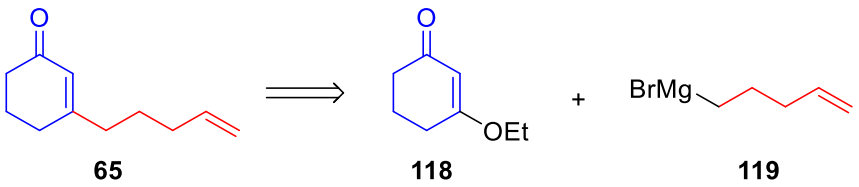
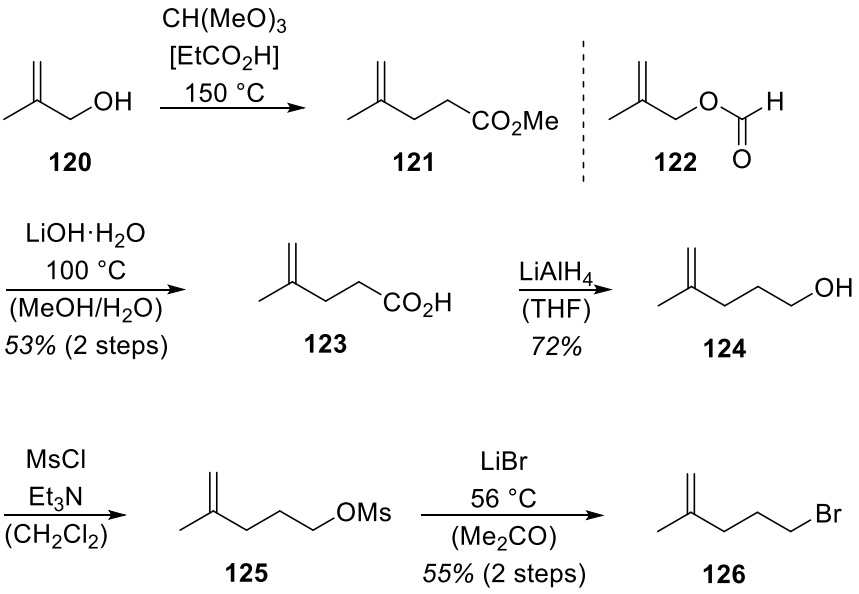


Figure 14. Retrosynthesis of the test substrate **65** into its enone moiety **118** (blue) and the alkene side chain **119** (red).

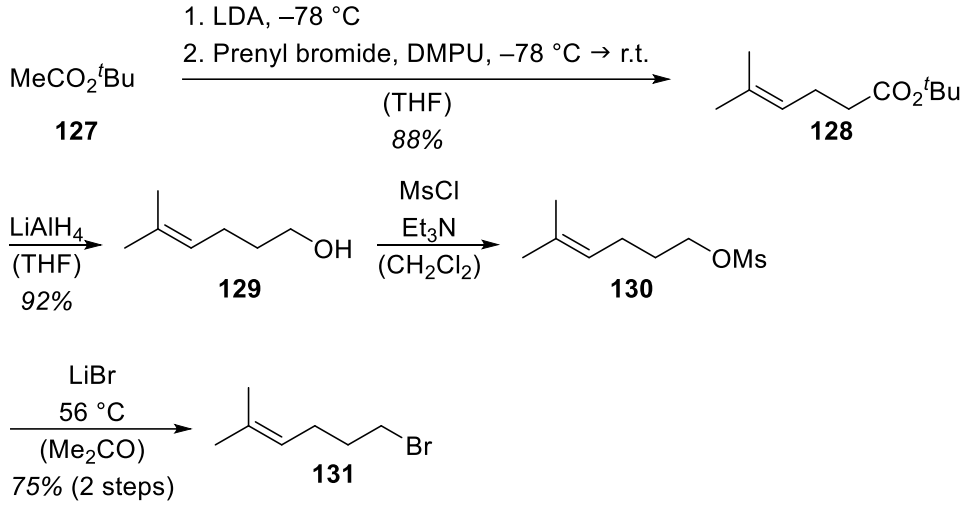
Alkenyl bromide **126** was synthesized over five steps in an overall yield of 21% starting from allyl alcohol **120** (Scheme 23). A *Johnson-Claisen* rearrangement of allyl alcohol **120** furnished methyl ester **121** following a modified procedure by *Floreancig*.[155] Ester **121** was obtained alongside acylated alcohol **122**. This mixture was submitted to saponification conditions enabling a separation of the product mixture yielding acid **123** in 53% over two steps. In accordance to a modified procedure by *Choi*, reduction with lithium aluminum hydride provided alcohol **124** in 72% yield.[156] In analogy to a protocol by *Gaertner*, alcohol **124** was first mesylated (**125**) and subsequently brominated in a nucleophilic substitution (S_N2) furnishing alkenyl bromide **126** in 55% yield over two steps.[157]



Scheme 23. Synthesis of alkenyl bromide **126** starting from allyl alcohol **120**.

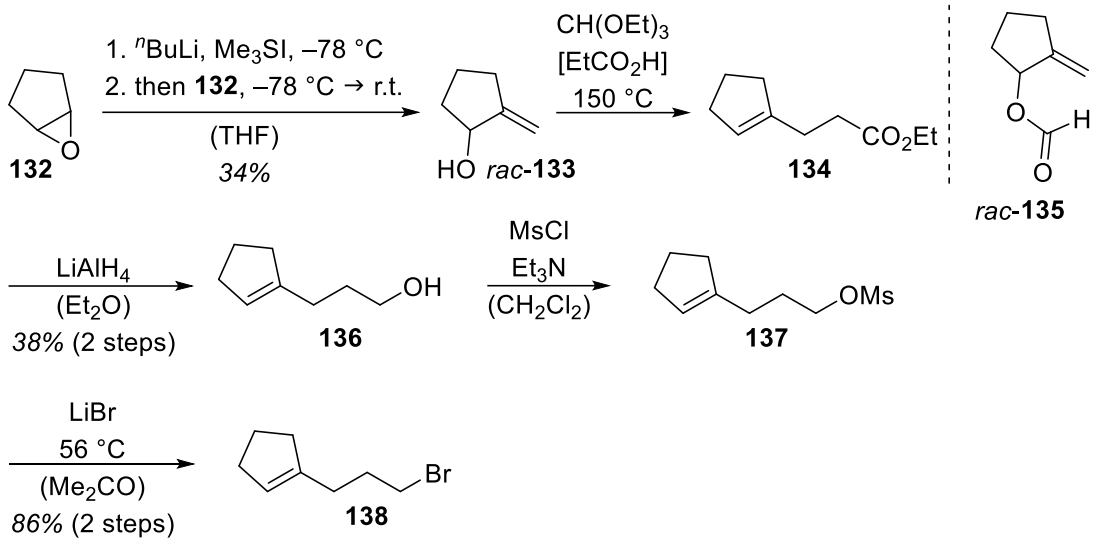
Starting from ester **127**, the terminally dimethyl substituted alkenyl bromide **131** was obtained in an overall yield of 61% over four steps (Scheme 24). Following a protocol reported by *Thomas*, ester **127** was first deprotonated with lithium diisopropyl amide (LDA) at –75 °C and the generated enolate was subsequently treated with the electrophile prenyl bromide furnishing alkenyl ester **128** in 88% yield.[158] Reduction of the ester with lithium aluminum hydride

provided alcohol **129** in 92% yield.[156] Mesylation and subsequent treatment with lithium bromide furnished alkenyl bromide **131** in 75% yield over two steps.[157]



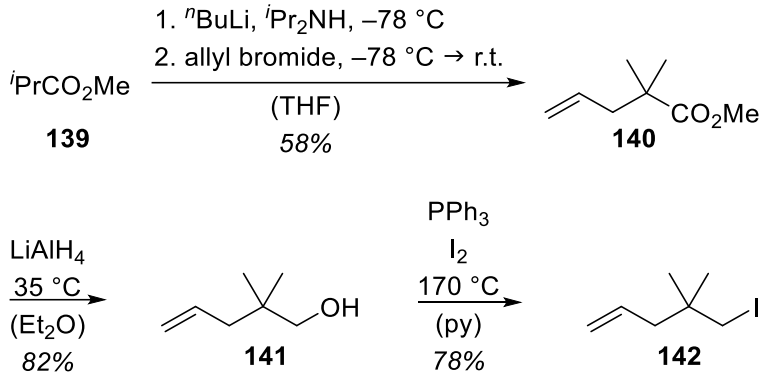
Scheme 24. Synthesis of alkenyl bromide **131** starting from ester **127**.

Alkenyl bromide **138** bearing a cyclopentene moiety was synthesized over five steps in an overall yield of 11% starting from epoxide **132** (Scheme 25). Following a literature known procedure by *Alcaraz*, trimethylsulfonium iodide was first deprotonated with butyl lithium and then the epoxide **132** was opened in a nucleophilic addition to yield allyl alcohol *rac*-**133** in 34%.[159] According to a modified protocol by *Huang*, a *Johnson-Claisen* rearrangement furnished ethyl ester **134** alongside acylated alcohol *rac*-**135**.[160] In order to enable a separation of this mixture, a reduction was carried out with lithium aluminum hydride yielding alcohols *rac*-**133** and **136** which at this stage were not yet chromatographically separable. An allylic oxidation of alcohol *rac*-**133** with manganese oxide to the corresponding ketone enabled an isolation of the desired alkenyl alcohol **136** in 38% yield over two steps. Mesylation and subsequent bromination furnished alkenyl bromide **138** in 86% yield over two steps.[157]



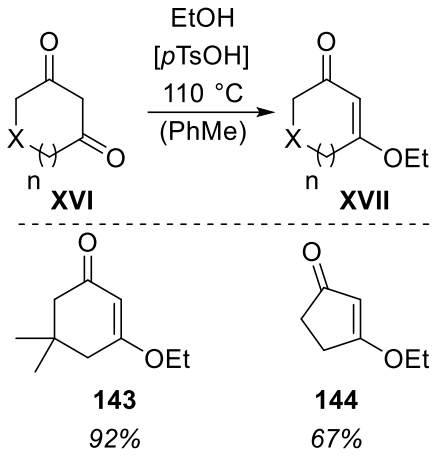
Scheme 25. Synthesis of alkenyl bromide **138** starting from epoxide **132**.

In a synthesis over three steps and an overall yield of 37%, alkenyl iodide **142** was obtained starting from ester **139** (Scheme 26). Following a modified protocol by *Wender*, ester **139** was deprotonated with lithium diisopropyl amide and the generated enolate was subsequently treated with allyl bromide yielding alkenyl ester **140** in 58%.[161] Reduction with lithium aluminum hydride furnished alcohol **141** in 82% yield.[117] After a protocol reported by our group, a *Mukaiyama* redox condensation provided alkenyl iodide **142** in 78% yield.[162]



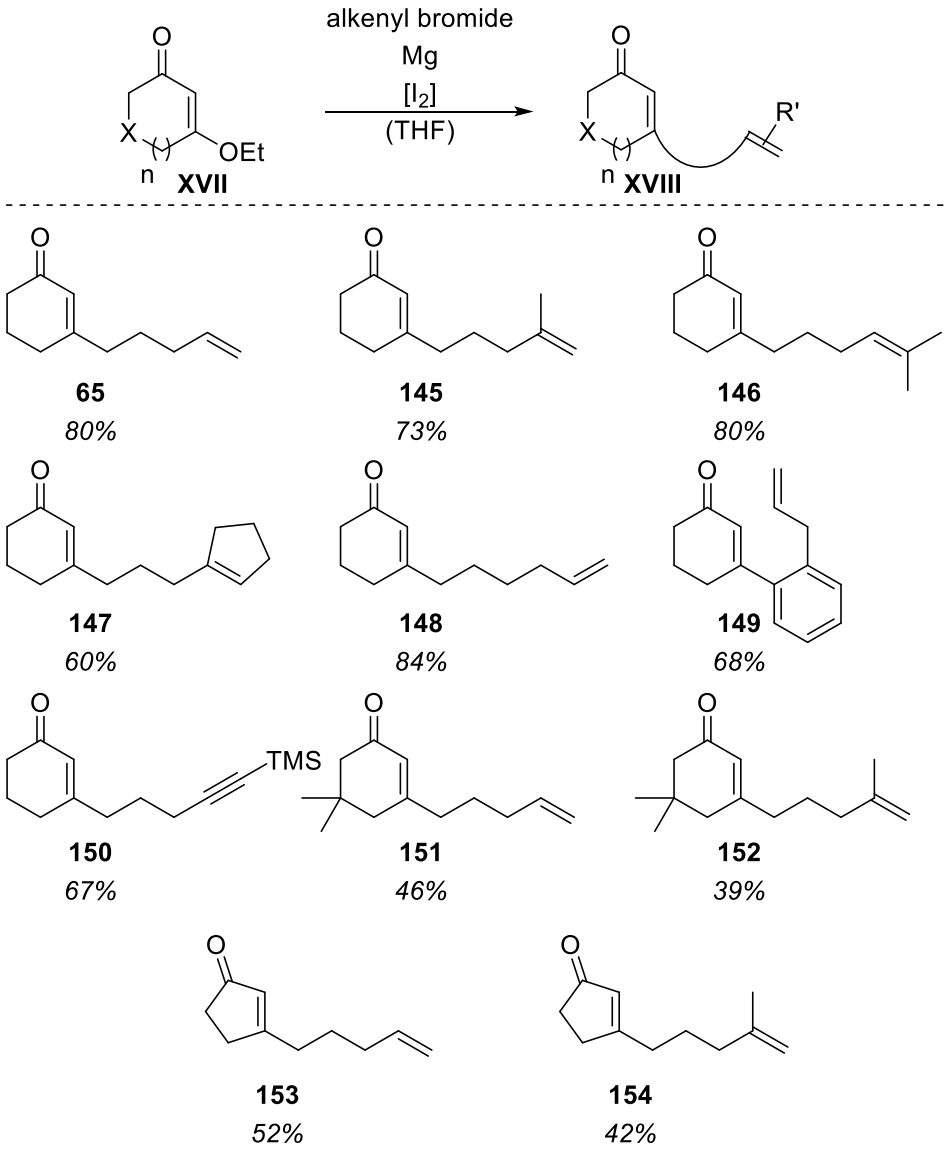
Scheme 26. Synthesis of alkenyl iodide **142** starting from ester **139**.

According to modified protocols, vinylogous esters **143** and **144** were obtained from the respective diketones **XVI** in 92% and 67% yield via an acid catalyzed condensation reaction using a *Dean-Stark* apparatus. (Scheme 27).[162,163]



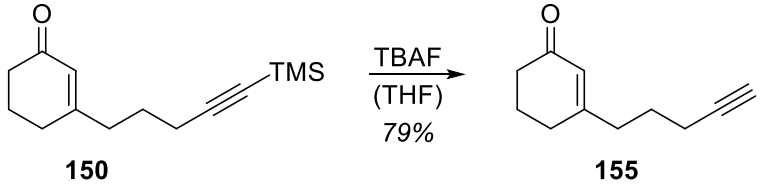
Scheme 27. Synthesis of vinylogous esters **143** and **144** starting from the respecting diketones **XVI**.

In analogy to a protocol reported by *Mattay*, irradiation precursors **XVIII** were obtained in moderate to high yields (39-84%) (Scheme 28). The reaction sequence consisted of a *Grignard* 1,2-addition of the respective alkenyl magnesium bromides on enol ethers **XVII** and an acidic work-up of the 1,2-adducts resulting in an elimination of water and ethanol furnishing enones **XVIII**. Substrates **151** and **152** were obtained in moderate yields of 46% and 39%, presumably due to the increased steric hinderance generated by the two methyl groups in **143** impeding the 1,2-addition. For cyclopentenone derived substrates **153** and **154**, the decrease in yield is caused by the formation of several by-products.



Scheme 28. Syntheses of irradiation precursors **XVIII**.

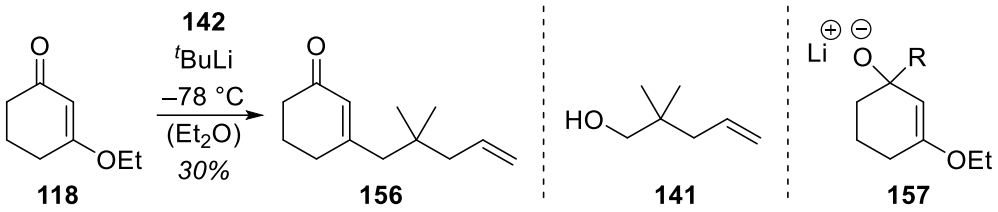
In order to obtain an irradiation precursor with an alkynyl side chain, first a TMS protected alkynyl bromide had to be employed yielding enone **150** in 67% (Scheme 28). The TMS group was removed by TBAF under mild conditions and substrate **155** was isolated in 79% yield (Scheme 29).



Scheme 29. Removal of the TMS group of **150** providing irradiation precursor **155**.

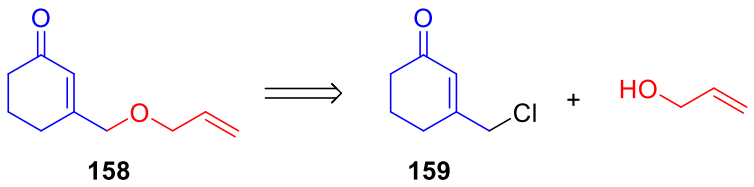
A synthesis of the irradiation precursor **156** was not possible with the standard protocol used in the previous examples. Attempts to obtain a *Grignard* reagent from alkenyl iodide **142** were

unsuccessful. Consequently, an alternative route was chosen including a halogen-lithium exchange reaction. Following a modified procedure by *Negishi*, alkenyl iodide **142** was treated with *tert*-butyl lithium generating the corresponding alkenyl lithium.[164] A 1,2-addition on enol ether **118** and subsequent acidic work-up of the adduct furnished enone **156** in 30% yield. The low observed yields are likely a result of by-product formation and/or incomplete lithium-halogen exchange. Consequently, irradiation precursor **156** was isolated alongside alcohol **141**. Presumably, the 1,2-adduct intermediate **157** was alkylated on the oxygen atom by alkenyl iodide **142** with alcohol **141** being released upon acidic work-up.



Scheme 30. Synthesis of irradiation precursor **156**.

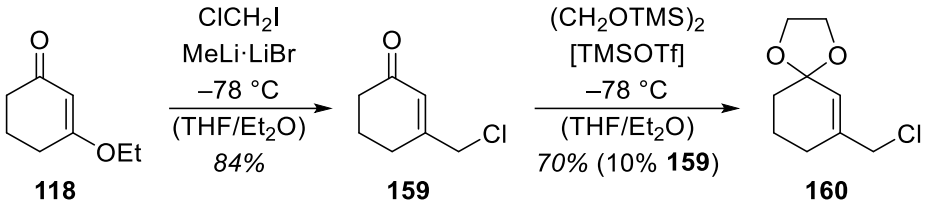
In order to synthesize irradiation precursor **158** which has an oxygen atom in the alkene side chain, a different synthetic strategy was employed (Scheme 31). The enone moiety originates from chloromethyl enone **159** (blue) and the alkene moiety from allyl alcohol (red).



Scheme 31. Retrosynthesis of the substrate **158** into its enone moiety **159** (blue) and the allyl alcohol (red).

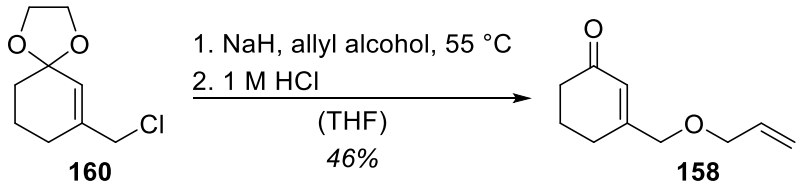
Acetal **160** was synthesized over two steps starting from enol ether **118** (Scheme 32). Following a protocol reported by *Pace*, the organometallic reagent chloromethyllithium was generated in situ by the addition of methyllithium lithium bromide complex to chloroiodomethane.[165] It was essential to carry out a slow and dropwise addition of the organolithium, to prevent the formation of side-products. Chloromethyllithium underwent a 1,2-addition into the carbonyl group of enol ether **118**. Subsequently, an acidic work-up released water and ethanol from the adduct providing enone **159** in 84% yield. Enone **159** is highly unstable. Even at a storage temperature of –20 °C (freezer) significant levels of decomposition were observed. Following a modified procedure reported by *Noyori*, an acetalization yielded allyl chloride **160** in 70% yield alongside 10% recovered enone **159**.[166,167] To ensure an efficient reaction, both reagents and solvents had to be particularly anhydrous. Traces of water can significantly inhibit the reaction course. Only freshly purchased or distilled trimethylsilyl triflate should be used. Due

to the high sensitivity towards water, the yields and conversions varied from batch to batch. Allyl chloride **160** solidified in the freezer at –20 °C and did not decompose at this temperature, however, it is not bench-stable.



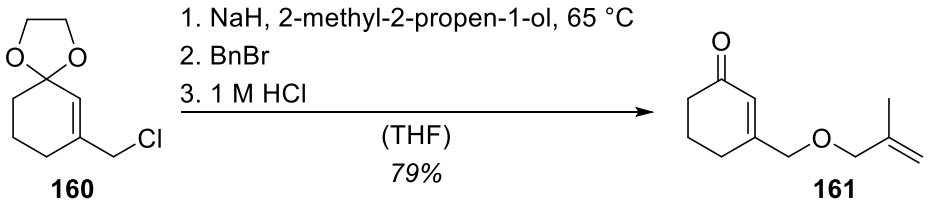
Scheme 32. Synthesis of acetal **160** starting from enol ether **118**.

In order to synthesize irradiation precursor **158**, allyl alcohol was first deprotonated with sodium hydride and subsequently treated with the electrophile **160** (Scheme 33). After the nucleophilic substitution, the acetal was hydrolyzed by aqueous hydrochloric acid providing enone **158** in 46% yield. The separation of enone **158** and the excess of allyl alcohol was not possible by column chromatography. The alcohol was extracted with water from the organic layer.



Scheme 33. Synthesis of irradiation precursor **158**.

Following a similar protocol, irradiation precursor **161** was synthesized (Scheme 34). In order to circumvent a separation issue, the excess of deprotonated 2-methyl-2-propen-1-ol was alkylated with benzyl bromide. The hydrolysis of the acetal furnished enone **161** in 79% yield.

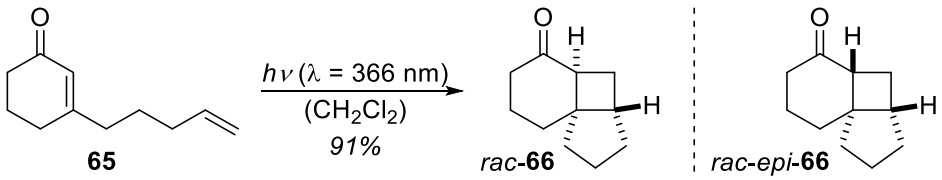


Scheme 34. Synthesis of irradiation precursor **161**.

2.5 Enantioselective Intramolecular [2+2] Photocycloadditions

2.5.1 Racemic [2+2] Photocycloaddition with the Test Substrate

The racemic intramolecular [2+2] photocycloaddition of substrate **65** proceeded well at a wavelength of $\lambda = 366$ nm in dichloromethane (c = 20 mM) yielding 91% of photoadduct *rac*-**66** (Scheme 35). No reaction was observed at a longer wavelength of $\lambda = 419$ nm. At shorter wavelengths $\lambda = 254$ nm and $\lambda = 300$ nm, the reaction was faster, albeit with increased side-product formation. The carbonyl group of photoadduct *rac*-**66** can be excited at these wavelengths and therefore cause *Norrish*-Type I and *Norrish*-Type II reactions leading to complex product mixtures and a decrease in yield of *rac*-**66**. Photoadduct *rac*-**66** is isolated alongside with its epimer *rac-epi*-**66** which was isomerized with basic alumina. Mechanistic studies by *Becker* revealed that photoreactions of enones of type **65** proceed on the triplet hypersurface with a high quantum yield of $\Phi = 0.5$.[168-170] Indeed, at $\lambda = 366$ nm the conversion of **65** is complete after four hours. Considering the weak absorption of **65** at this wavelength, the excitation of the $n\pi^*$ transition effectively provides photoadduct *rac*-**66** due to the symmetry allowed intersystem crossing of $S_1(n\pi^*)$ to $T_1(\pi\pi^*)$ according to *El-Sayed*'s rule.[171]



Scheme 35. Racemic intramolecular [2+2] photocycloaddition of substrate **65**.

With the optimal reaction conditions in hand, all irradiation precursors **XVIII** were converted with moderate to high yields up to 88%. Only photoadducts which were isolable in pure form were used in the enantioselective reactions. Some photoadducts *rac*-**162**-*rac*-**166** were not suitable for catalysis or necessitated special purification procedures (Figure 15).

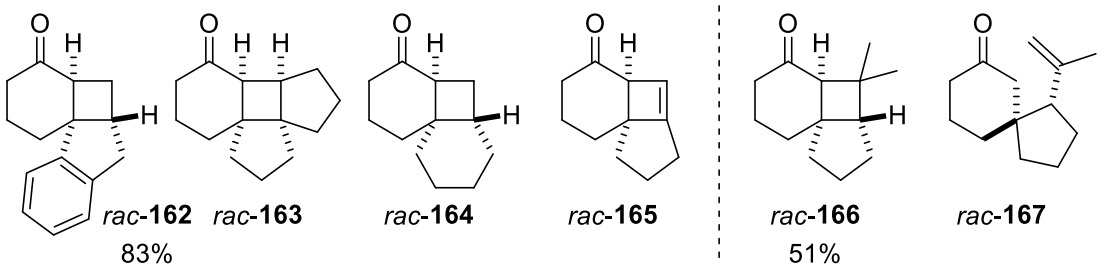


Figure 15. Photoadducts *rac*-**162**-*rac*-**166** which were not isolable or required special purification procedures.

Although *rac*-**162** could be isolated in 83% yield under the racemic conditions, an isolation under enantioselective conditions remained unsuccessful due to the formation of inseparable impurities. Photoadducts *rac*-**163**-*rac*-**165** were obtained in complex and inseparable mixtures. Terminally dimethyl-substituted enone **146** provided a mixture of adduct *rac*-**166** and spiro compound *rac*-**167**. A pure sample of *rac*-**166** was obtained after the mixture was submitted to ozonolysis. The double bond of *rac*-**167** was oxidatively cleaved providing the corresponding more polar ketone. This enabled the separation by column chromatography providing adduct *rac*-**166** in 51% yield. It is literature-known that spiro compound *rac*-**167** originates either from a 1,4-diradical or a *Norrish*-Type I or II cleavage.[172]

2.5.2 Implementation of Sensitizers

Presumably, due to a significant racemic background reaction of substrate **65**, the enantioselective [2+2] photocycloaddition yielded photoadduct **66** in an enantiomeric excess below 80% *ee*. In order to impede the background reaction, we considered the use of a photosensitizer which is excited by visible light in our catalytic conditions. At λ = 419 nm no background reaction of **65** could be observed. It was paramount that in the presence of a photosensitizer the background reaction was also negligible (Table 1). Thioxanthone provided adduct *rac*-**66** in 50% yield at room temperature. At –75 °C, however, no product formation was observed. The successful reaction in the previous case can be attributed to an endothermic triplet-triplet energy transfer from the sensitizer to substrate **65**. Using complex $[Ir(ppy)_2(dtbbpy)]PF_6$ [dtbbpy: 4,4'-di-*tert*-butyl-2,2'-bipyridine; ppy: 2-(pyridin-2-yl)phenyl] resulted in no conversion.

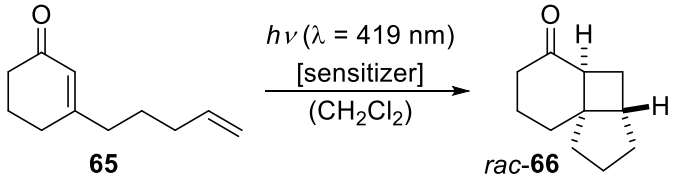


Table 1. Racemic [2+2] photocycloaddition background reaction of **65** under visible light.

Entry	Sensitizer	Loading [mol%]	Yield
1	none		0%
2	Thioxanthone	5	50% (47% **65**)
3	Thioxanthone (–75 °C)	5	0%
4	$[Ir(dtbbpy)(ppy)_2]PF_6$	5	0%

For a successful triplet-triplet energy transfer from a sensitizer to a substrate, similar triplet energies are required. The triplet energy of 3-methylcyclohexenone is reported to be E_T = 283 kJ/mol[35] which is consistent with our measurement of the triplet energy of the structurally similar substrate **65** (E_T = 290 kJ/mol). The triplet energies of thioxanthone (E_T = 265 kJ/mol)[173] and the complexes $[Ir(ppy)_2(dtbbpy)]PF_6$ (E_T = 209 kJ/mol)[174] and $[Ir((dF)(CF_3)ppy)_2(dtbbpy)]PF_6$ {(dF)(CF_3)ppy: 3,5-difluoro-2-[5-(trifluoromethyl)pyridin-2-yl]phenyl} (E_T = 249 kJ/mol)[174] are below the triplet energy of the substrate. Consequently, a lack of triplet-triplet energy transfer results in no product formation and thus no background reaction.

We hypothesized that the triplet energy of **65** is decreased upon coordination to Lewis acid **50**. The bathochromic shift observed in the UV/Vis spectra which are induced by Lewis acid coordination on substrate **65** indicate a lowering of the π* molecular orbital. If the triplet energy of the substrate-catalyst complex **65·50** was sufficiently decreased to a level that lies lower in energy than T_1 of the triplet sensitizer, then a triplet-triplet energy transfer from the sensitizer to the substrate **65** could occur.

Substrate **65** was irradiated at λ = 419 nm in the presence of catalyst **50** and various triplet sensitizers (Table 2). The reactions were carried out at –75 °C in dichloromethane (c = 20 mM) for 24 hours with a catalyst loading of 50 mol%.

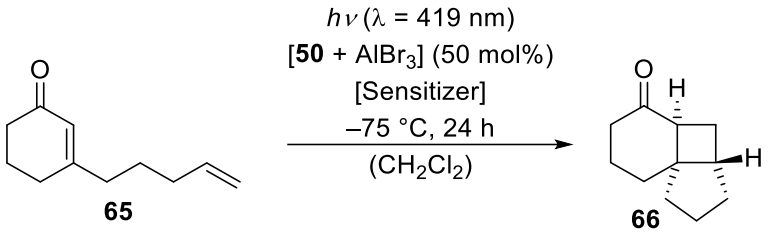


Table 2. Attempted enantioselective intramolecular [2+2] photocycloadditions employing various sensitizers with visible light.

Entry	Sensitizer	Loading [%]	Yield [%]	*ee* [%]
1	$[Ir(ppy)_2(dtbbpy)]PF_6$	5	0	0
2	$[Ir((dF)(CF_3)ppy)_2(dtbbpy)]PF_6$	5	0	0
3	Thioxanthone	5	9	21
4	Thioxanthone	25	0	0
5	Thioxanthone	50	0	0
6	2-CF_3-thioxanthone	5	0	0
7	2-Cl-thioxanthone	5	0	0

The iridium complexes (entry 1 and 2) did not lead to any product formation. Presumably, the triplet energies are too low thus preventing an energy transfer. With a loading of 5 mol%, thioxanthone provided photoadduct **66** in 9% yield with 21% *ee* (entry 3). Increasing the loading of thioxanthone up to 50 mol% (entry 4 and 5) resulted in no product formation. Derivatives of thioxanthone (entry 6 and 7) provided no photoadduct **66** either. The observation of a strong phosphorescence in the presence of thioxanthones led to the assumption that the Lewis acid **50** coordinates to the sensitizer. Consequently, the catalyst loading would be effectively decreased thus impeding the reaction. As suitable photosensitizers were not present for this reaction set up, further investigations were not pursued at this stage. The concept of employing a triplet sensitizer in this reaction might be successfully implemented via the use of a photosensitizer bearing no Lewis basic sites.[175]

2.5.3 Variation of the Activating Lewis Acid

Previous studies on oxazaborolidine catalyzed reactions employed other activating Lewis acids than aluminum bromide or Brønsted acids as activating agents.[112,113,147,148,176-180] The activation methods led to powerful catalysts which were temperature stable and moisture tolerant. Due to its high sensitivity it was decided to substitute aluminum bromide with one of the Lewis or Brønsted acids previously used in literature (Table 3).

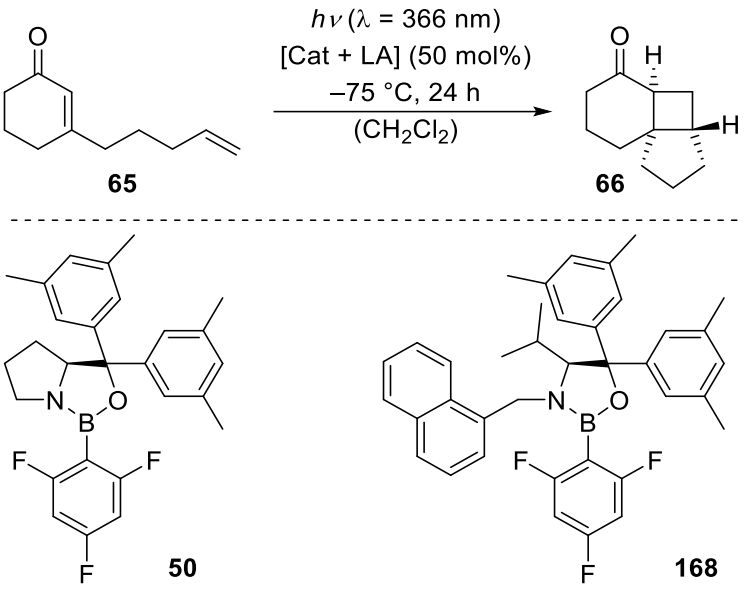


Table 3. Variation of the activating Lewis or Brønsted acid in catalysts **50** and **168**.

Entry	Lewis Acid	Catalyst	Yield [%]	*ee* [%]
1	$AlBr_3$	**50**	81	71
2	Tf_2NH	**50**	98	47
3	$(C_6F_5)Tf_2CH$	**50**	95	51
4	$SnCl_4$	**50**	96	59
5	$SiCl_4$	**50**	89	40
6	AlI_3	**50**	76	43
7	$AlBr_3$	**168**	37 (47% **65**)	19
8	$SnCl_4$	**168**	43 (42% **65**)	2
9	$(C_6F_5)Tf_2CH$	**168**	95	9

First, the influence of Lewis and Brønsted acids on catalyst **50** was investigated (entries 1-6). Aluminum bromide as an activating Lewis acid acted as the starting point of this study providing adduct **66** in 81% yield in 71% *ee* (entry 1). Brønsted acids Tf_2NH and $(C_6F_5)Tf_2CH$

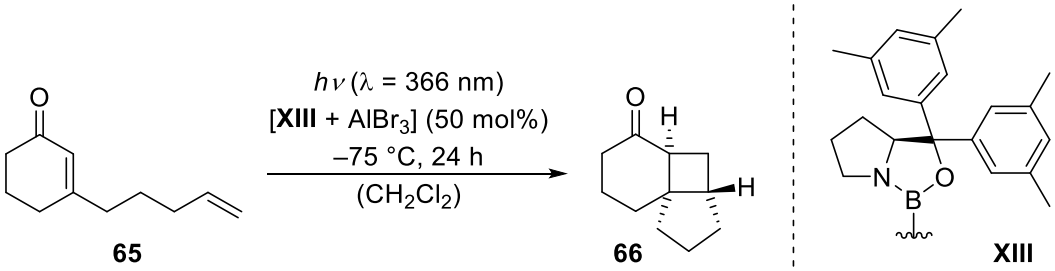
yielded 98% and 95% of adduct **66**, however, the enantiomeric excess decreased to 47% and 51% *ee* (entries 2 and 3). Additionally, tetrachloro-Lewis acids $SnCl_4$ and $SiCl_4$ provided high yields up to 96% and similarly moderate enantiomeric excesses up to 59% *ee* (entries 4 and 5). Changing to aluminum iodide resulted in a lower yield (76%) with 43% *ee* (entry 6). Since only $SnCl_4$ was commercially available as a solution, the handling of the other acids was quite time consuming and impractical. Furthermore, none of the used acids provided an enantiomeric excess higher than 71%. A theoretical study on the enantioselective intramolecular [2+2] photocycloaddition of dihydropyridones **51** reported by *Chen* and *Dolg* revealed the importance of the heavy atom effect of the bromine containing activating Lewis acid on the intersystem crossing of complexed substrates.[121] Our experimental observations therefore, are consistent with this study. A lack of intersystem crossing in substrate-Lewis acid complex **65·50** could lead to an increased background reaction and thus a decrease in enantioselectivity.

Next, the valine-based catalyst **168** was combined with a selection of acids (entries 7-9). Lewis acids aluminum bromide and $SnCl_4$ delivered adduct **66** in moderate yields (37% and 43%) alongside recovered starting material **65** with low enantiomeric excesses up to 19% *ee* (entries 7 and 8). Brønsted acid $(C_6F_5)Tf_2CH$ furnished product **66** in 95% yield with 9% *ee*. In all cases, catalyst **168** provided lower yields and enantioselectivities compared to catalyst **50**. Consequently, valine-based catalyst **168** was deemed to be unsuitable for the enantioselective intramolecular [2+2] photocycloaddition. Further optimizations were carried out with catalyst **50** activated by aluminum bromide.

2.5.4 First Variation of the Boronic Acid

In the preceding study of enantioselective intramolecular [2+2] photocycloadditions by *Brimioulle*, it was found that catalysts with fluorinated aryl groups in the boronic acid moiety are particularly powerful in the enantioselective catalysis of simple enones.[118] Bearing these results in mind, we decided to investigate the efficacy of further mono-, di-, tri-, tetra- and penta-fluorinated aryl substituted catalysts (Scheme 36). Catalysts with mono- (**169**) and difluoro aryl groups (**170**-**173**) provided photoadduct **66** in high yields up to 99%, the highest enantiomeric excess in this series was achieved by 2,3-difluoro substitution (**172**) with 73% *ee*. In total, six trifluoro-substituted boronic acids (**50**,**174**-**178**) were investigated. Yields were consistently high (81-90%) and enantiomeric excesses were above 71% *ee* with 75% *ee* (**176**) being the highest value. Tetrafluoro- and pentafluorophenyls (**179**-**182**) provided photoadduct in moderate to high yields (67-84%) with enantiomeric excesses up to 75% *ee*. Catalysts with phenyl groups bearing trifluoromethyl substituents (**183** and **184**) resulted in a decrease in both, yield (67% and 69%) and enantioselectivity (61% and 64% *ee*). Exchanging a fluorine atom in 2,6-difluorophenyl with chlorine (**185**), bromine (**186**), iodine (**187**) resulted in all cases in diminished yields (71-85%) and enantiomeric excesses (59-61%).

In conclusion, the enantiomeric excesses were highest with 2,3,4-trifluorophenyl **176** (90%, 75% *ee*) and 2,3,4,5-tetrafluorophenyl **180** (79%, 75% *ee*) boronic acids. Presumably, tri- and tetrafluoro phenyl groups appropriately increase the Lewis acidity of the boron atom resulting in a stronger bathochromic shift of the ππ* transition of the substrate **65** and leading to a more exclusive excitation of the substrate-Lewis acid complex **65**·**176'**. We deemed catalyst **176** with the 2,3,4-trifluorophenyl group to be a suitable starting point for the next stage in our optimization studies.



65 **66** **XIII**

169: *79%*, 62% *ee* **170**: *76%*, 64% *ee* **171**: *99%*, 68% *ee* **172**: *74%*, 73% *ee*

173: *66%*, 51% *ee* **174**: *88%*, 71% *ee* **175**: *84%*, 72% *ee* **50**: *81%*, 71% *ee*

176: *90%*, 75% *ee* **177**: *85%*, 71% *ee* **178**: *88%*, 69% *ee* **179**: *79%*, 68% *ee*

180: *79%*, 75% *ee* **181**: *84%*, 71% *ee* **182**: *67%*, 60% *ee* **183**: *67%*, 61% *ee*

184: *69%*, 64% *ee* **185**: *71%*, 59% *ee* **186**: *85%*, 61% *ee* **187**: *84%*, 61% *ee*

Scheme 36. Variation of the boronic acid in catalyst **XIII**.

2.5.5 Variation of the Solvent

With the new catalyst **176** in hand, we considered to investigate the solvent effect on the enantioselectivity (Table 4). Oxazaborolidine catalyst **176** does not tolerate protic, coordinating or apolar solvents. Hence, only halogenated solvents were used. As a starting point, with dichloromethane as the solvent, photoadduct **66** was obtained in 90% yield and 75% *ee* (entry 1). The use of dibromomethane required increasing the reaction temperature to –50 °C and resulted in a decrease in enantioselectivity (68% *ee*) (entry 2). The solvent mixture of 2:1 hexafluoro-*m*-xylene:trifluorotoluene was not able to dissolve activated catalyst **176'** and therefore resulted in racemic product **66** in 79% yield (entry 3). At –40 °C, both 1,2-dichloroethane and phenyl chloride provided adduct **66** in high yield (85% and 89%) and lower enantiomeric excesses (62% and 68%) (entry 4 and 5). All alternative halogenated solvents required an elevated temperature. Presumably, the enantioselectivity inducing complex **65·176'** were less stabilized due to higher temperatures and therefore decreased enantiomeric excesses were observed. The initially used solvent dichloromethane remained the solvent of choice and was employed in all further optimization experiments.

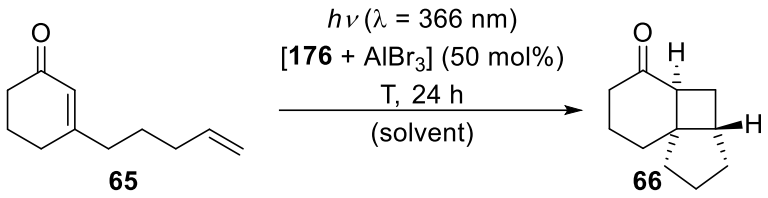


Table 4. Variation of the solvent and temperatures for the enantioselective [2+2] photocycloaddition of **65**.

Entry	Solvent	Temp [°C]	Yield [%]	*ee* [%]
1	CH_2Cl_2	–75	90	75
2	CH_2Br_2	–50	83	68
3	HFX/TFT(2/1)	–65	79	0
4	$(CH_2Cl)_2$	–40	85	62
5	PhCl	–40	89	68

2.5.6 Variation of the Photon Flux

In a previous study by our group, *Brimioulle* observed a significant correlation between the reactor power output and the enantiomeric excesses.[118,123] Hence, we decided to vary the power output in order to observe its effect on the enantioselectivity (Table 5). An incremental (32 W) decrease of the power output starting from 128 W showed no significant effect on the enantioselectivity (entries 1-3). At a power output of 32 W, adduct **66** was obtained in 37% yield alongside 60% of starting material **65** (entry 4). The enantiomeric excess decreased by 5% to 70% *ee*. The slight decrease in enantioselectivity is likely a result of incomplete conversion of substrate **65**. At higher conversions, the active catalyst loading for residual starting material is effectively increased. Consequently, the background reaction is almost entirely suppressed. A possible explanation for the different impact of the power output on our reaction could be that substrates **65** more efficiently react under catalytic conditions than alkenoxy-substituted enones **55**. Halving the power output led to doubling of the reaction time and a significant increase in enantioselectivity in the latter case.[123] Here, comparing entries 1 and 3 no such observation was made. Presumably, the quantum yield of our test reaction is higher. Consequently, a saturation of complex **65·176'** in the excited state allowing an excess of photons to carry out the background reaction can be considered to be improbable. Seemingly, the catalysis and the background reaction concurrently proceed independent from the number of photons.

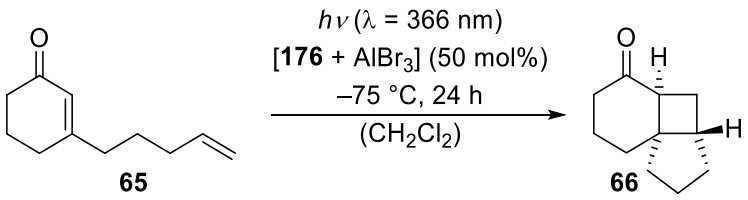


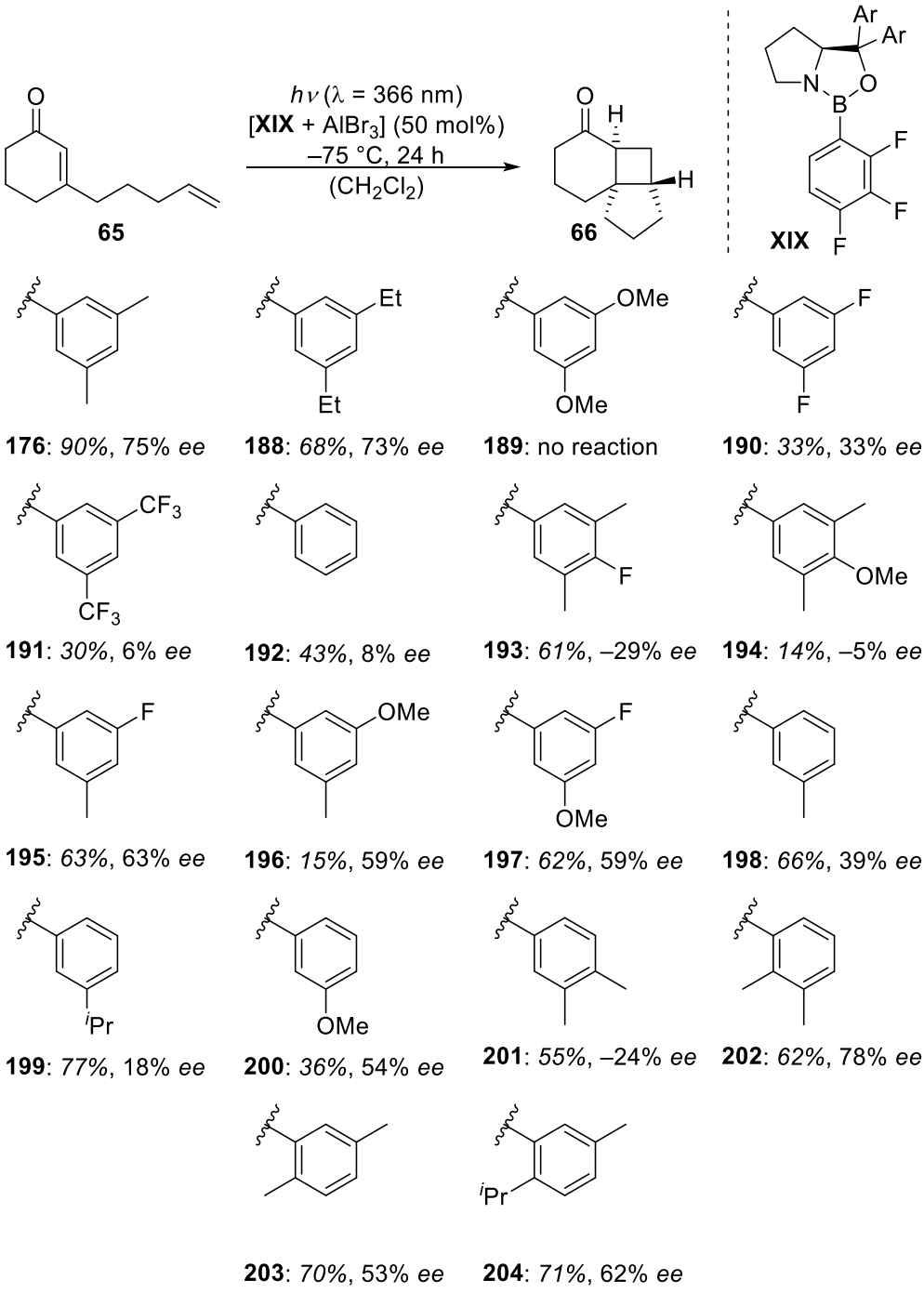
Table 5. Variation of the reactor power output.

Entry	Power [W]	Yield [%]	*ee* [%]
1	128	90	75
2	96	88	74
3	64	79 (5% **65**)	77
4	32	37 (60% **65**)	70

2.5.7 Variation of the Prolinol

The variation of the boronic acid did not result in a significant increase of enantioselectivity in the [2+2] photocycloaddition. Therefore, we decided to elucidate the impact of the prolinol-aryl moiety in catalyst **XIX** on enantioselectivity in combination with the 2,3,4-trifluorophenyl boronic acid (Scheme 37). First, a series of symmetrically 3,5-disubstituted aryl groups (**176**, **188-192**) was investigated. With decreasing electronic density at the aryl ring the enantioselectivity significantly decreased **176** (-Me, 75% *ee*)/**188** (-Et, 73% *ee*) > **190** (-F, 33% *ee*) > **191** (-CF_3, 6% *ee*). Comparing **176** (-Me, 75% *ee*) and **188** (-Et, 73% *ee*), it became evident that an increase in steric bulk is detrimental to enantioselectivity, which is consistent with previous observations when *tert*-butyl groups were employed.[118] Methoxy-substitution (**189**) resulted in a complete inhibition of the reaction. The omission of substituents at the 3- and 5-position (**192**, 8% *ee*) demonstrates the high steric influence of the aryl group on the enantioselectivity.

Varying the aryl substitution pattern from 3,5-dimethyl to *para*-fluoro (**193**, –29% ee) or *para*-methoxy (**194**, –5% *ee*) led to an inversion in enantioselectivity. This counterintuitive result was further investigated using DFT calculations, the results of which will be discussed later on this chapter. An unsymmetrical 3,5-disubstitution with methyl, fluoro and methoxy substituents (**195-197**) resulted in similar enantioselectivities (59-63% *ee*). Independent of the steric bulk of the substituents, the yields decreased across series **176** (-Me/-Me, 90%) > **195** (-Me/-F, 63%) > **197** (-F/-OMe, 62%) > **196** (-Me/-OMe, 15%). A single *meta*-substitution with methyl (**198**, 39% *ee*), isopropyl (**199**, 18% *ee*), and methoxy (**200**, 54% *ee*) substituents resulted in decreased enantioselectivity. The large isopropyl group in **199** led to severely decreased enantioselectivity (18% *ee*) in comparison to its methyl analogue **198** (39% *ee*). Dimethyl substituted catalysts furnished the desired photoproduct in high yield and enantioselectivity. Consequently, three permutations of the methyl substitution pattern were investigated. *Meta-para*-dimethyl substitution (**201**, –24% *ee*) led to an inversion of the enantioselectivity. These results are consistent with those obtained for catalysts **193** and **194**. A marginal increase in enantioselectivity was observed with a 2,3-dimethyl phenyl (**202**, 78% *ee*) substituted catalyst. Additional *ortho*-substituted aryl catalysts **203** (53% *ee*) and **204** (62% *ee*) did not lead to an increase in enantioselectivity. Consequently, catalyst **202** bearing 2,3-dimethylphenyl groups in the backbone, was deemed to be the most suitable catalyst for further optimization studies.



176: *90%*, 75% *ee*

188: *68%*, 73% *ee*

189: no reaction

190: *33%*, 33% *ee*

191: *30%*, 6% *ee*

192: *43%*, 8% *ee*

193: *61%*, –29% *ee*

194: *14%*, –5% *ee*

195: *63%*, 63% *ee*

196: *15%*, 59% *ee*

197: *62%*, 59% *ee*

198: *66%*, 39% *ee*

199: *77%*, 18% *ee*

200: *36%*, 54% *ee*

201: *55%*, –24% *ee*

202: *62%*, 78% *ee*

203: *70%*, 53% *ee*

204: *71%*, 62% *ee*

Scheme 37. Variation of the aryl substituent at the prolinol backbone of catalyst **XIX**.

The inversion in the enantioselectivity of photoadduct **66** resulting from reactions with catalysts **193**, **194** and **201** was not consistent with the proposed model for enantioface differentiation, consequently the nature of this enantioinversion was further elucidated by DFT calculations. For the enantiomer *ent*-**66** to be predominantly formed, we hypothesized two possibilities: Firstly, the irradiation precursor **65** coordinates from the *endo* face to the catalyst (*trans* to aluminum bromide). Secondly, the irradiation precursor **65** coordinates from the *exo* face to the catalyst (*cis* to aluminum bromide) but rotated by 180°.

Following classical transition state theory (TST), we first calculated the energy difference for the observed enantiodivergence $\Delta\Delta G_{RS}^{\neq}$ of the transition states leading to the (*S*) configurated product **66** and leading to the (*R*) configurated product *ent*-**66**, from the observed enantiomeric excesses. We employed equation (1) to calculate the ratio of the absolute reaction rates k_S/k_R from the enantiomeric excess. The ratio k_S/k_R was then applied to equation (2) in order to obtain the corresponding transition state energy difference $\Delta\Delta G_{RS}^{\neq}$. Detailed calculations and derivations of equations (1) and (2) are discussed in chapter 7.2.1.

$$\frac{k_S}{k_R} = -\frac{ee+1}{ee-1} \qquad (1)$$

$$\Delta\Delta G_{RS}^{\neq} = R \times T \times \ln\left(\frac{k_S}{k_R}\right) \qquad (2)$$

We sought to investigate the origin of the different reaction outcomes with catalysts **176** (75% *ee*) and **193** (–29% *ee*) due to their structural similarities and large difference in enantiomeric excess. An enantiomeric excess of 75% *ee* requires a transition state energy difference of $\Delta\Delta G_{RS}^{\neq}$ = 3.21 kJ/mol and respectively, an enantiomeric excess of the other enantiomer *ent*-**66** being –29% *ee* results in $\Delta\Delta G_{RS}^{\neq}$ = –0.98 kJ/mol. Hence, the energy difference between 75% *ee* and –29% *ee* is 4.19 kJ/mol at the reaction temperature T = 198 K.

However, for this type of photoreaction, relative population of ground state conformers ($\Delta G_{pro\text{-}R}$ and $\Delta G_{pro\text{-}S}$) which lead to photoexcited intermediates on the reaction trajectory to products of opposite absolute configuration was also considered as a plausible rationalization for the enantiodivergence. Following this approach, the product *ee* is a representation of the relative Boltzmann population of ground states (p_S and p_R) that result in the correspding (*S*)- and (*R*)-product.

$$\Delta G_{pro-R} - \Delta G_{pro-S} = R \times T \times \ln\left(\frac{p_{pro-S}}{p_{pro-R}}\right) \qquad (3)$$

This model provides the same energy difference of 4.19 kJ/mol between 75% *ee* and –29% *ee*, however, in this case as a consequence of variations in ground state energies.

Although the observed energy difference of 4 kJ/mol is only marginally above that required for reliable and accurate DFT calculations, they were carried out by *Storch*[181] in order to identify plausible explanations. Especially, in the context of substrate-bound catalyst ground states that would result in products of opposite absolute configuration after irradiation. All computations were carried out with the program *Gaussian*[182] using the B3LYP-D3BJ[183-186] functional and the cc-pVTZ[187] basis set (Figure 16). For simplicity we chose 3-methylcyclohexenone (**205**) as a model substrate and computed five possible binding modes with each activated catalyst **176'** and **193'**. As expected, the computed structures structurally differ only marginally from each other. Therefore, structures in Figure 16 are based on the catalyst **176'** and the *para*-position is marked in dark green indicating replacement with a fluoro-subsituent in **193'**. A summary of all structures for **205·193'** can be found in chapter 7.2.3. For clarity, parts of the structures are depicted as capped sticks instead of ball and stick. The nomenclature S#) indicates the binding mode leading to (*S*) configurated product **66**, conversely, R#) leads to the respective (*R*) configurated enantiomer *ent*-**66**.

Table 6. Calculated electronic energies ΔE and *Gibbs*' free energies ΔG at T = 198 K (–75 °C) for the complexes with acitvated catalysts **176'** and **193'** in different binding modes with substrate **205**.

Entry	Binding Mode	**176'** ΔE [kJ/mol]	**193'** ΔE [kJ/mol]	**176'** ΔG [kJ/mol]	**193'** ΔG [kJ/mol]
1	S1)	2.2	1.4	0.0	0.0
2	S2)	0.0	0.0	0.3	1.4
3	R1)	6.0	6.2	4.9	5.5
4	R2)	5.2	4.2	6.9	4.6
5	R3)	7.6	6.6	6.0	6.3

Our study began with the investigation of binding mode S1), which involves the proposed Lewis acid/Lewis base interaction between the oxazaborolidine boron atom and the substrate's carbonyl oxygen atom as well as a hydrogen bonding[188-190] interaction between the oxazaborolidine oxygen atom and the substrate's hydrogen atom in 2-position. Considering the close spatial proximity of one of the catalyst's aryl groups to the enone, it was apparent that π-π interactions[191] could not be excluded. Hence, an additional conformer of similar energetic profile had to be considered: This binding mode S2) consists of a Lewis acid/Lewis base

interaction [as in S1)] and a π-π interaction between the substrate and one of catalysts's aryl groups.

As expected for the (*S*)-oxazaborolidine catalysts, the 180° rotated, pro-*R*-conformers of binding mode R1) were found to be higher in energy regardless of the aryl's *para*-substituent: ΔG [kJ/mol] = 4.9 (**176'**) and 5.5 (**193'**). In contrast, when investigating binding mode R2), the *para*-fluoro-substitution seems to slightly stabilize the 180° rotated, pro-*R*-conformer (entry 4): ΔG [kJ/mol] = 6.9 (**176'**) and 4.6 (**193'**). Furthermore, the distance between the β-carbon atom of the substrate **205** and the *para*-carbon atom of the aryl group in catalysts **176'** (3.57 Å) and **193'** (3.61 Å) differs by 0.04 Å. This larger distance in **193'** could be attributed to a presumably weaker interaction due to the lower electron density of the fluoro substituted aryl group. Finally, binding mode R3) represents our initial hypothesis of substrate coordination to the *endo* face, *trans* to aluminum bromide (entry 5), but little influence of the *para*-substituent was observed.

In summary, we identified a set of conformers with π-π interactions between substrate and catalyst – binding modes S2) and R2) – in which the relative energy of a ground state conformer that leads to (*R*)-product is slightly lowered upon changing to the *para*-fluoro catalyst **193'**, most probably as a consequence of changes in π-π interaction properties. It is extremely important to stress that these calculations do not significantly substantiate any of the proposed models for catalyst-substrate interactions. Consequently, these models are still highly hypothetical. However, it can be assumed that this observation might be the reason for an inversion of the enantioselectivity in catalyst **193'**. Albeit, the computed energetic differences are minute and will, therefore, serve as a prelude to a larger DFT study involving variations in both functional and basis set.

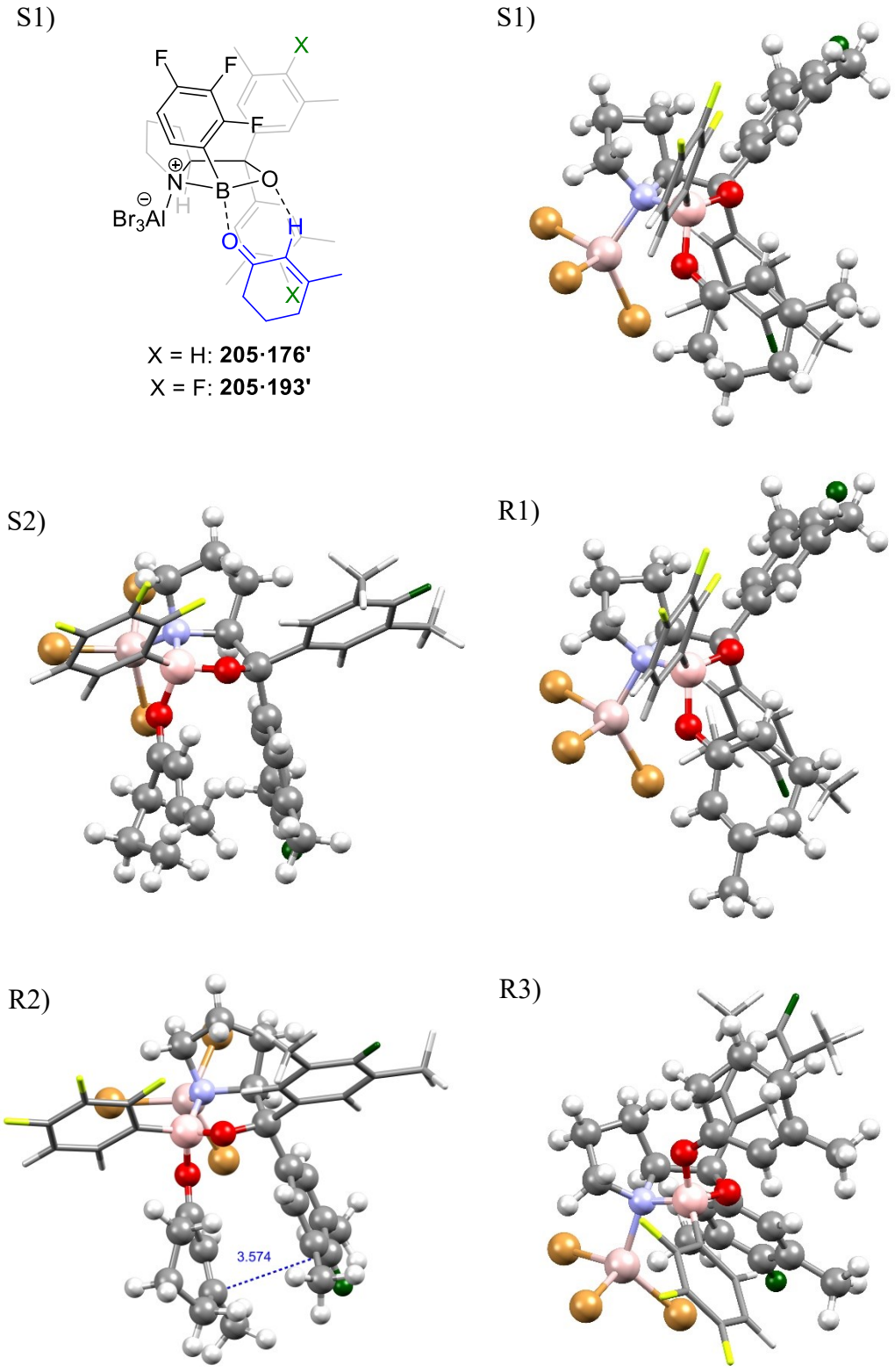


Figure 16. Putative model of the complexes **205·176'** and **205·193'**. Structures of different complexes as per DFT calculations (B3LYP-D3BJ/cc-pVTZ, PCM = CH_2Cl_2, T = 198 K). Structures S1) and S2) lead to the (*S*) configurated photoadduct and R1), R2) and R3) to the (*R*) configurated photoadduct, respectively. Atom X is indicated in dark green in the calculated structures.

2.5.8 Variation of the Photon Energy Distribution

Since the photon flux appeared to have no significant impact on the enantioselectivity, we set out to investigate the effect of UV filter solutions on yield and enantioselectivity (Figure 17). In a previous study by our group, *Tröster* had employed an iron(III) sulfate[192] UV filter solution (c = 10.5 g/L) to prevent irradiation below 400 nm when irradiating with sunlight.[89] In analogy to these results, we aimed to employ UV filter solutions to control the absolute photon energies for our experiments. Therefore, a series of iron(III) sulfate solutions with concentrations varying from 100 mg/L to 1000 mg/L in 100 mg/L increments were analyzed with respect to their transmission properties. The solutions were prepared with 10 mM aqueous hydrochloric acid in order to completely dissolve iron(III) sulfate and obtain stable solutions. The dissolution process was very slow, and solutions were therefore prepared one day prior to analysis. At concentrations below 400 mg/L, the quality of the UV filter solution significantly decreased. At concentrations above 400 mg/L, however, the shapes of the transmission spectra remained almost unchanged and are shifted towards higher wavelengths. The values for the relative emission of the 366 nm light source were multiplied with the values of the transmission spectra of UV filter solutions (400 mg/l, 600 mg/L, 800 mg/L) in order to estimate the photon energy distribution (Figure 17). The ratio of photons below and above 370 nm shifted towards longer wavelengths with increasing concentration of iron(III) sulfate. However, the photon flux simultaneously was dramatically decreased due to a lower overall transmission.

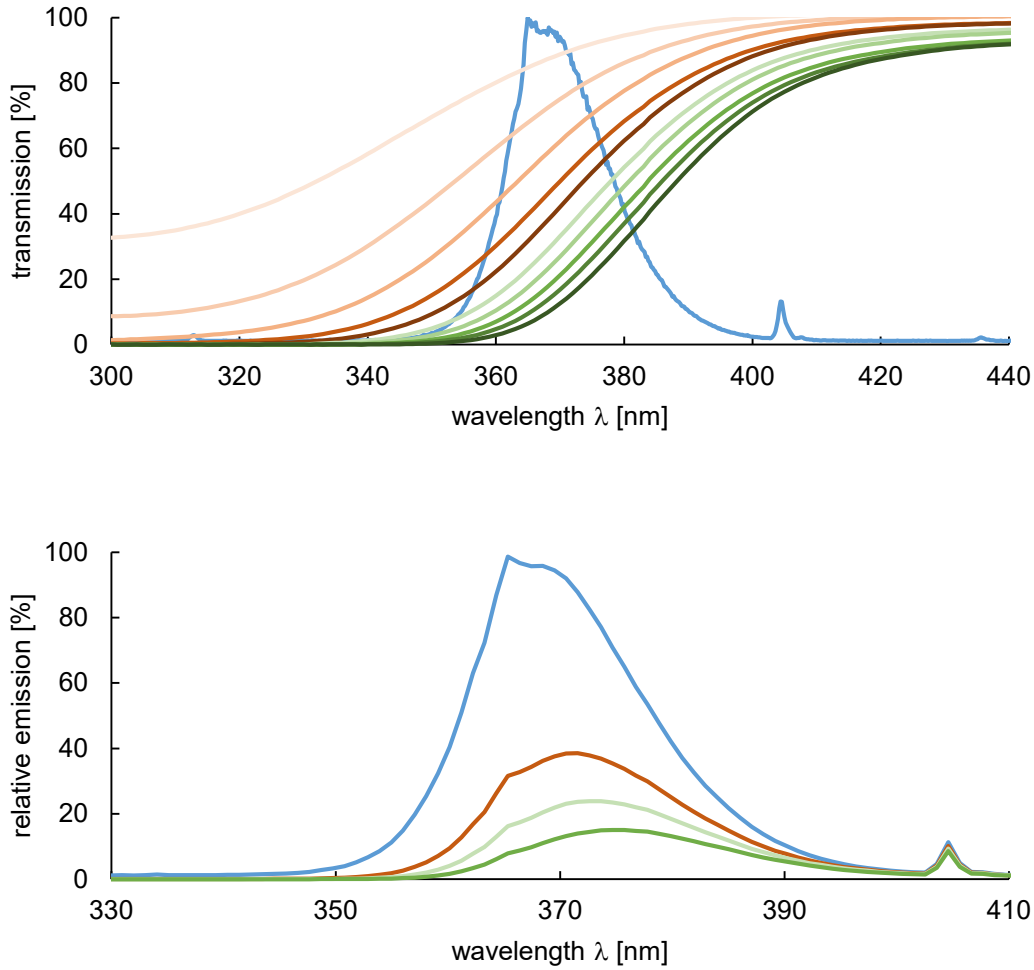


Figure 17. Transmission spectrum of iron(III) sulfate solutions in 10 mM aqueous hydrochloric acid with emission spectrum of the 366 nm light source (blue) (upper spectrum). Concentrations were increased in 100 mg/L increments from 100 mg/L (light orange) to 1000 mg/L (dark green). Calculated relative emission of the 366 nm light source without UV filter (blue), 400 mg/L (orange), 600 mg/L (light green) and 800 mg/L (green) iron(III) sulfate UV filter solutions (lower spectrum).

With these UV filter solutions in hand, we investigated the impact of the bathochromically shifted photon energy distributions on our photocatalytic reaction (Table 7). The reaction time was doubled in order to compensate for the decreased photon intensity. UV filter solutions with concentrations starting from 400 mg/L increased by 200 mg/L increments to 1000 mg/L all resulted in higher yields of the photoadduct **66**, albeit with an unchanged enantiomeric excess of 84% *ee* (entries 2-5). The variation in yield can be attributed to product loss during the isolation process.

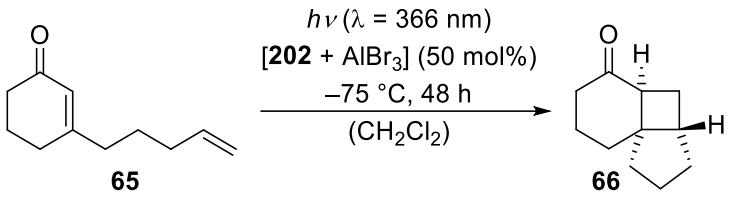


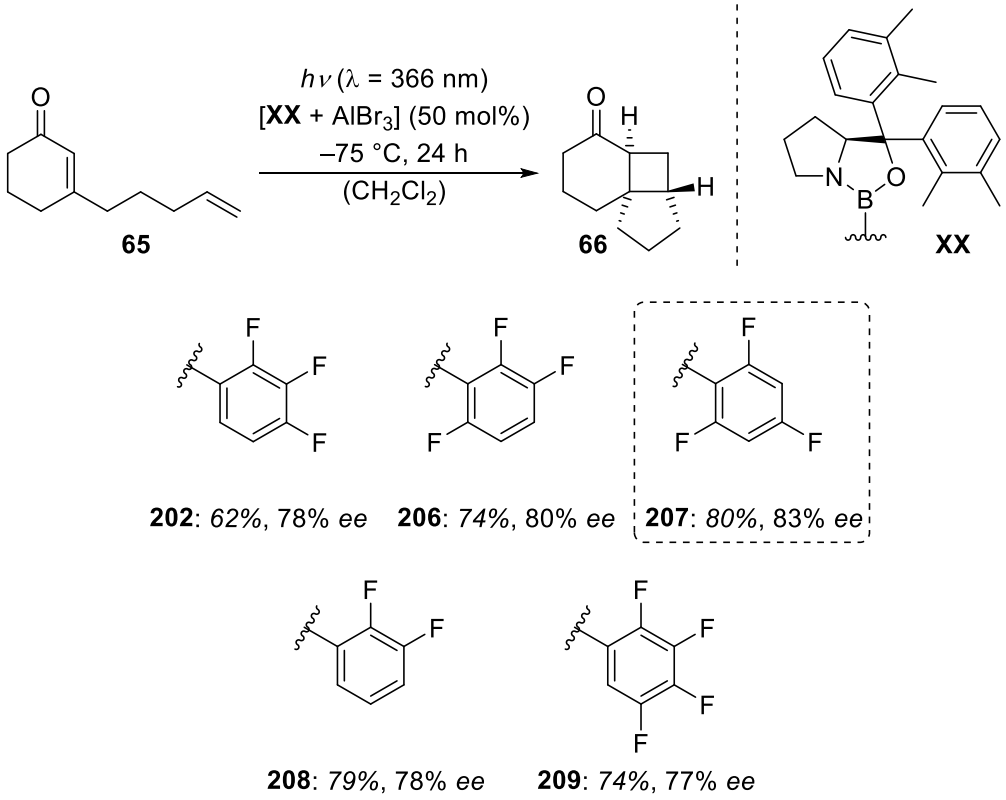
Table 7. Enantioselective intramolecular [2+2] photocycloaddition of substrate **65** with the use of iron(III) sulfate filter solutions with various concentrations.

Entry	c[$Fe_2(SO_4)_3$]	Yield [%]	*ee* [%]
1	-	62	78
2	400 mg/L	70	84
3	600 mg/L	80	84
4	800 mg/L	73	84
5	1000 mg/L	80	84

Our hypothesis that the background reaction might be responsible for a diminished enantioselectivity was thus substantiated. For the first time, photoadduct **66** could be obtained in an enantiomeric excess above 80% *ee* by employing UV filter solutions. However, this method had two major drawbacks. Firstly, the reactions were significantly prolonged and secondly, complicated and thus impractical reaction set ups were required.

2.5.9 Second Variation of the Boronic Acid

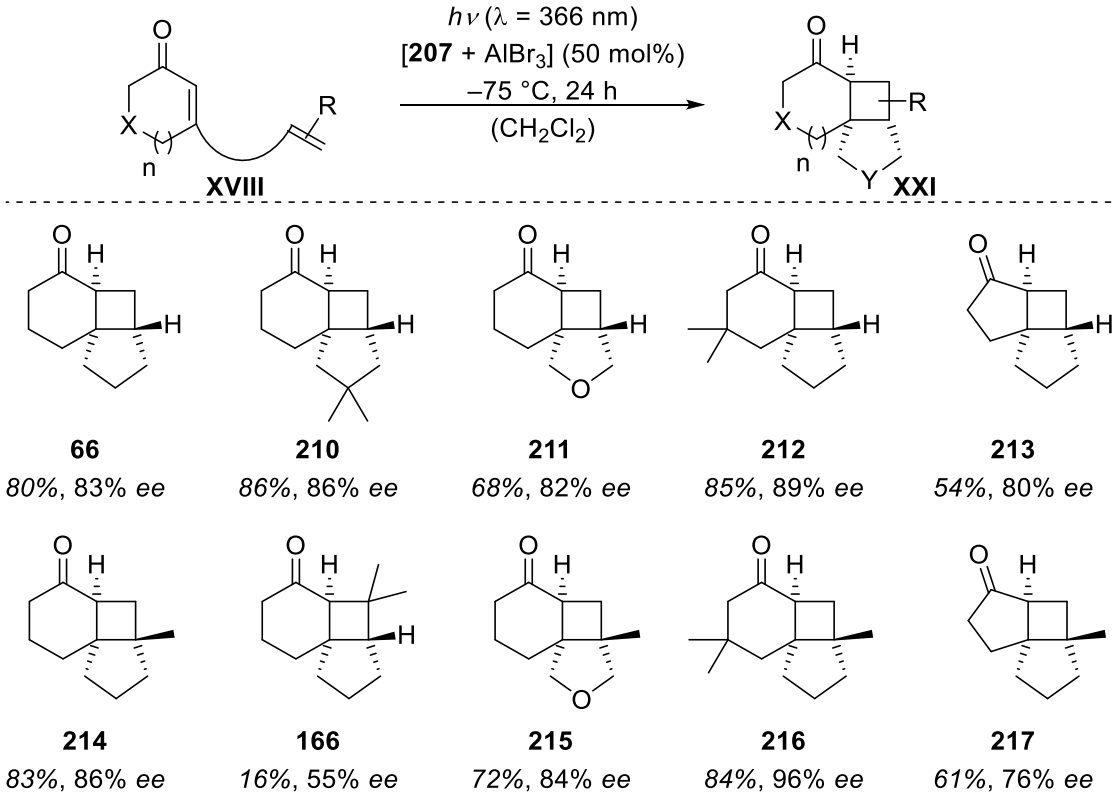
With an optimal aryl substitution pattern of the prolinol backbone identified, we moved on to the next stage of our optimization studies. We set out to investigate the effect of the aryl substitution on the boron atom of our new catalyst **XX** on yield and enantioselectivity (Scheme 38). To reduce the number of required screening experiments, only boronic acids which delivered the best results with the previous catalyst **XIII** were investigated. Di- (**208**), tri- (**202**, **206**, **207**) and tetrafluoro (**209**) substituted phenyl groups all delivered product in high yields (62-80%) and similar enantioselectivities (77-83% *ee*). The previously used 2,4,6-trifluorophenyl group in catalyst **XX** proved to be the optimal substituent which delivered photoadduct in 80% yield and 83% *ee*. From these and other studies by our group it became evident that trends with respect to yields and enantioselectivity in a series of catalysts with varied boron substitution do not necessarily translate to different prolinol backbones. Consequently, it was crucial to reinvestigate the effect of the boronic acid aryl group once the most suitable prolinol had been identified.



Scheme 38. Variation of the boronic acid in catalyst **XX**.

2.5.10 Substrate Scope

With the optimal reaction conditions and the new catalyst **207** in hand, the enantioselective intramolecular [2+2] photocycloaddition of ten irradiation precursors was carried out (Scheme 39). Cyclohexenone and cyclopentenone based irradiation precursors **XVIII** were converted to photoadducts **XXI** in high yields (68-86%) with high enantiomeric excesses (82-86%). The terminally dimethyl substituted substrate **166**, however, was obtained in significantly decreased yield of 16% and 55% *ee*. As for the racemic reaction, the isolation of **166** required an ozonolysis purification step. The 5,5-dimethyl substituted cyclohexenones **151** and **152** provided photoadducts **212** and **216** in high yields (85% and 84%) and excellent enantiomeric excesses (89% and 96%). Comparing these results to the cyclohexenone analogues (**66** and **214**) the enantiomeric excesses are 6-10% higher. Cyclopentenone derived photoadducts (**213** and **217**), however, were obtained in lower yields (54-61%) and 3-10% lower enantiomeric excesses than the corresponding cyclohexenone derivatives.



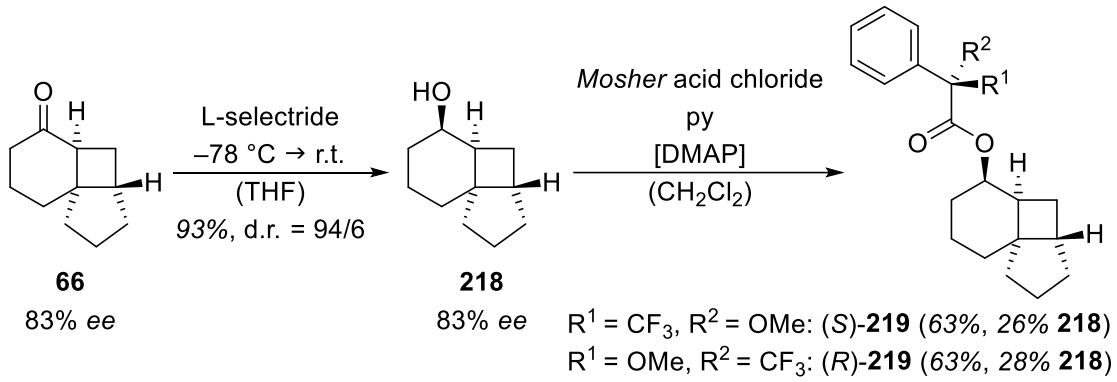
Scheme 39. Enantioselective intramolecular [2+2] photocycloaddition of substrates **XVIII**.

Substrates bearing methyl groups in their side chain (**210**, **214**, **215**, **216**) were converted with marginally increased enantioselectivity. Presumably, the increased steric bulk of the side-chain improves the enone enantioface differentiation. An apparent limitation of this method became evident for substrate **146**. Terminally substituted alkene side chains adversely affect the

enantioselectivity. We hypothesize that the catalyst methyl groups impede the sterically demanding 1,4-diradical recombination to the cyclobutane ring. This could result in possible radical side reactions being preferred. For example, a hydrogen abstraction either within the substrate or with the catalyst might occur. This could explain diminished yields and enantiomeric excesses. Cyclopentenone derived substrates **153** and **154** resulted in lower yields in comparison to their cyclohexenone analogues **65** and **145**.

2.6 Determination of the Absolute Configuration

In order to determine the absolute configuration of photoadduct **66**, we carried out a *Mosher* analysis following a protocol reported by *Hoye* (Scheme 40, Figure 18).[193,194] First, a diastereoselective reduction with L-selectride provided alcohol **218** in 93% yield with a high diastereomeric ratio of 94/6. A purification by iterative column chromatography coupled to GC analysis enabled the isolation of alcohol **218** as a single diastereomer. This was crucial in order to obtain pure NMR spectra with the corresponding *Mosher* esters (*S*)-**219** and (*R*)- **219**. Using *Mosher* acid chloride, (*R*)- for (*S*)-**219** and (*S*)- for (*R*)-**219**, in the presence of pyridine as a base and catalytic DMAP both *Mosher* esters (*S*)-**219** and (*R*)-**219** were obtained in 63% yield alongside 26% and 28% of starting material **218**.



Scheme 40. Synthesis of *Mosher* esters (*S*)-**219** and (*R*)-**219**.

After a complete assignment of all ^{1}H NMR signals, the chemical shifts δ of the two *Mosher* esters (*S*)-**219** and (*R*)-**219** were subtracted using the formula $\Delta\delta^{SR} = \delta_S - \delta_R$. The resulting differences (either positive or negative) were assigned to the corresponding hydrogen atoms (Figure 18).

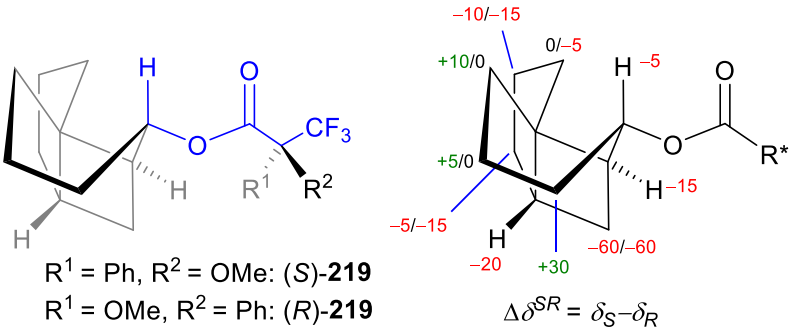


Figure 18. Analysis of the two *Mosher* esters (*S*)-**219** and (*R*)-**219**. The values of $\Delta\delta^{SR}$ [Hz] were calculated from the corresponding chemical shift differences [ppm], the ^{1}H NMR spectra were recorded at 500 MHz.

Mosher esters are known to have a preferential coplanar conformation of the blue marked atoms (Figure 18).[193] The phenyl and methoxy groups point into two different half spaces as are parts of the former alcohol **218**. The phenyl group in (*S*)-**219** and (*R*)-**219** induces an anisotropic magnetic shielding effect on the protons pointing towards its π electrons. This causes an upfield shift (lower δ value) in the NMR spectrum of all protons being in the same half space. The methoxy group only has a marginal effect on the shift of the protons. Consequently, the difference in shifts $\Delta\delta^{SR} = \delta_S - \delta_R$ of the posterior protons (marked in grey) would be negative and, conversely, positive for the anterior protons (marked in black). These results are in agreement with the expected absolute configuration of the photoadduct **66** which is consistent with previous studies.[116,119,123] The same absolute configuration was assigned for the other photoproducts **XXI**.

2.7 Diastereoselective Formal Synthesis of Italicene and Isoitalicene

Next, we set out to demonstrate the synthetic utility of our newly developed intramolecular [2+2] photocycloaddition by applying it to the total synthesis of a natural product. We identified the natural products italicene (**20**) and isoitalicene (*epi*-**20**) as suitable targets which could be accessed using our method.

A total synthesis reported by *Weyerstahl* includes an intramolecular [2+2] photocycloaddition as the key step.[135] Consequently, we set out to develop a diastereoselective variant of this route. The photochemical reaction was carried out with substrate *rac*-**220** which is comprised of a mixture of four isomers (Figure 19). We identified substrate *rac*-**221** as the most suitable irradiation precursor for our diastereoselective synthesis due to it only consisting of two enantiomers. The methyl group at the α position was then to be introduced after the [2+2] photocycloaddition.

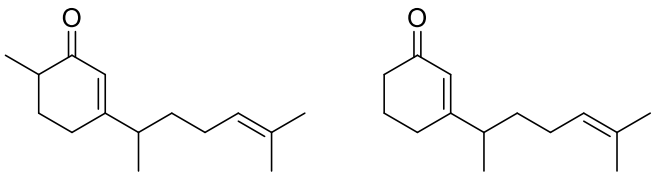
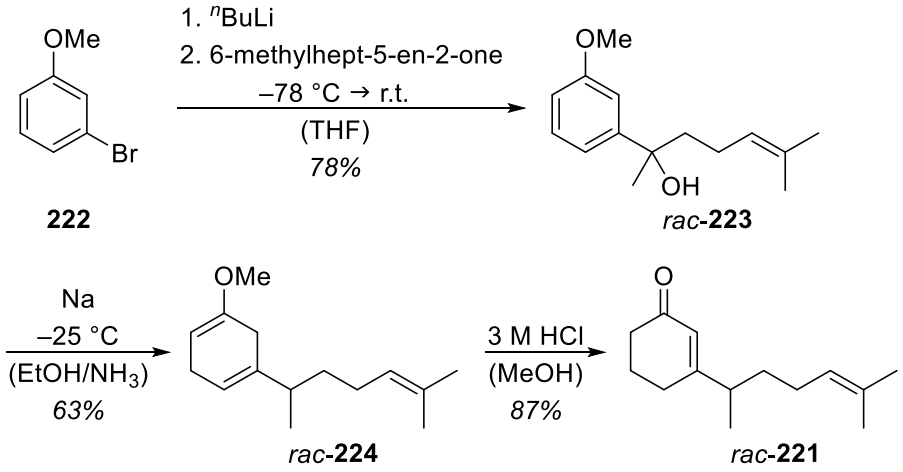


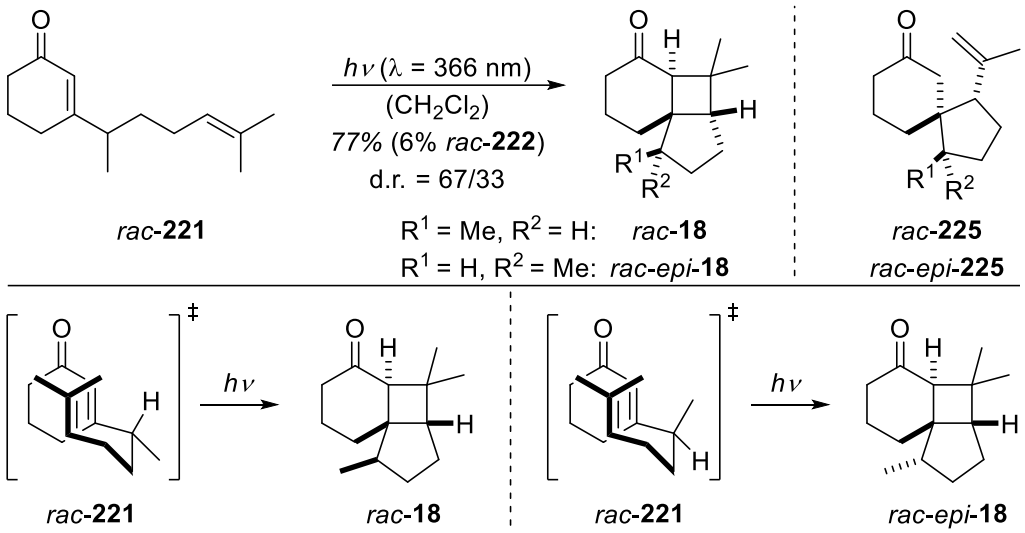
Figure 19. Irradiation precursors *rac*-**220** and *rac*-**221** which are intermediates in the total synthesis of *rac*-italicene (*rac*-**20**) and *rac*-isoitalicene (*rac-epi*-**20**).

Following a modified procedure reported by *Hoye*, irradiation precursor *rac*-**221** was synthesized over three steps in an overall yield of 43% starting from bromoanisole **222** (Scheme 41).[172] A lithium-halogen exchange generated an aryl lithium species from **222** which consecutively underwent a 1,2-addition into 6-methylhept-5-en-2-one furnishing tertiary alcohol *rac*-**223** in 78% yield. Next, a *Birch* reduction under protic conditions at reflux provided enol ether *rac*-**224** in 63% yield. Finally, hydrolysis under acidic conditions furnished the thermodynamically stable enone *rac*-**221** in 87% yield.



Scheme 41. Synthesis of irradiation precursor *rac*-**221**.

The racemic intramolecular [2+2] photocycloaddition of substrate *rac*-**221** furnished a 67/33 diastereomeric mixture of photoadducts *rac*-**18** and *rac-epi*-**18** in 77% yield alongside 6% of starting material *rac*-**221** (Scheme 42). By-products *rac*-**225** and *rac-epi*-**225** were removed by ozonolysis in order to isolate the target compounds *rac*-**18** and *rac-epi*-**18** in high purity. The diastereoselectivity likely originates from two possible transition states of *rac*-**221**. Here, the transition state with the methyl group in an equatorial position may be more favored. Thus, diastereomer *rac*-**18** is predominantly formed. However, since the steric effect of the methyl group on a 1,3-diaxial strain is relatively negligible, 33% of the other diastereomer *rac-epi*-**18** is formed.

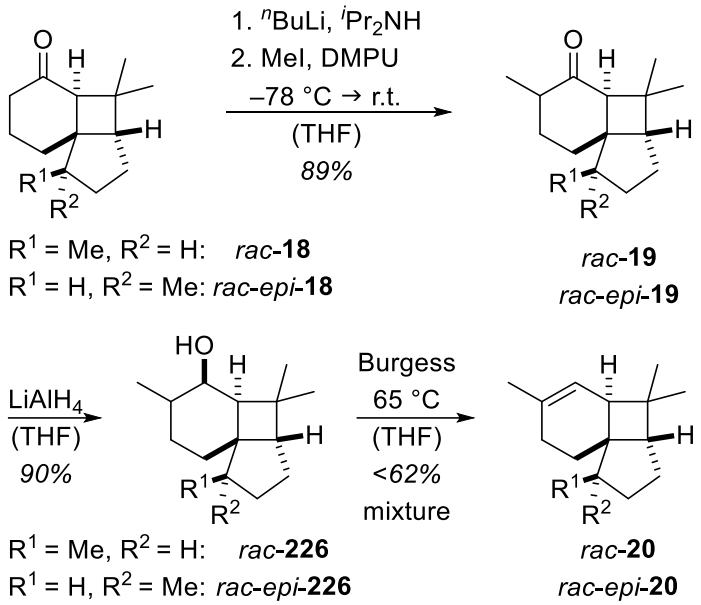


Scheme 42. Racemic intramolecular [2+2] photocycloaddition of irradiation precursor *rac*-**221** and two possible transition states of *rac*-**221** leading to the corresponding diastereomers *rac*-**18** and *rac-epi*-**18**.

Carrying out the reaction at –78 °C resulted in an increase of the diastereomeric ratio to 78/22. Furthermore, when 50 mol% aluminum bromide was employed, the diastereoselectivity was enhanced to a ratio of 82/18. Additionally, the formation of the by-products *rac*-**225** and *rac-epi*-**225** was inhibited by the Lewis acid. Presumably, the steric bulk of aluminum bromide is on the one hand responsible for increased diastereoselectivity and on the other hand impedes an intramolecular hydrogen abstraction within the 1,4-diradical intermediate. In order to obtain pure samples of the natural products *rac*-italicene (*rac*-**20**) and *rac*-isoitalicene (*rac-epi*-**20**) it was necessary to separate the diastereomers *rac*-**18** and *rac-epi*-**18**. We were unable to separate them by preparative HPLC. However, multiple purifications by column chromatography followed by GC analysis finally successfully separated the target compounds.

In order to evaluate the synthetic route by *Weyerstahl*, we started our synthesis with the diastereomeric mixture *rac*-**18** and *rac-epi*-**18** (Scheme 43). In contrast to *Weyerstahl*'s synthesis, rather than prior to the photocycloaddition, we carried out the α-methylation after the photocycloaddition. This α-methylation of photoadducts *rac*-**18** and *rac-epi*-**18**, was reported to be impossible by *Piva*.[71] However, it was possible to obtain α-methylated photoadducts *rac*-**19** and *rac-epi*-**19** in 89% yield as a complex mixture of diastereomers. Since the newly introduced stereogenic center would be removed by the introduction of a double bond, the complex mixture was used without further purification in the subsequent step. The reduction with lithium aluminum hydride proceeded diastereoselectively to alcohols *rac*-**226** and *rac-epi*-**226** in 90% yield. The last step was a dehydration by *Burgess* reagent.[137] We expected to obtain a mixture of two diastereomers *rac*-**20** and *rac-epi*-**20**. However, a complex mixture of numerous isomers with the same molecular weight (determined by GC-MS) was

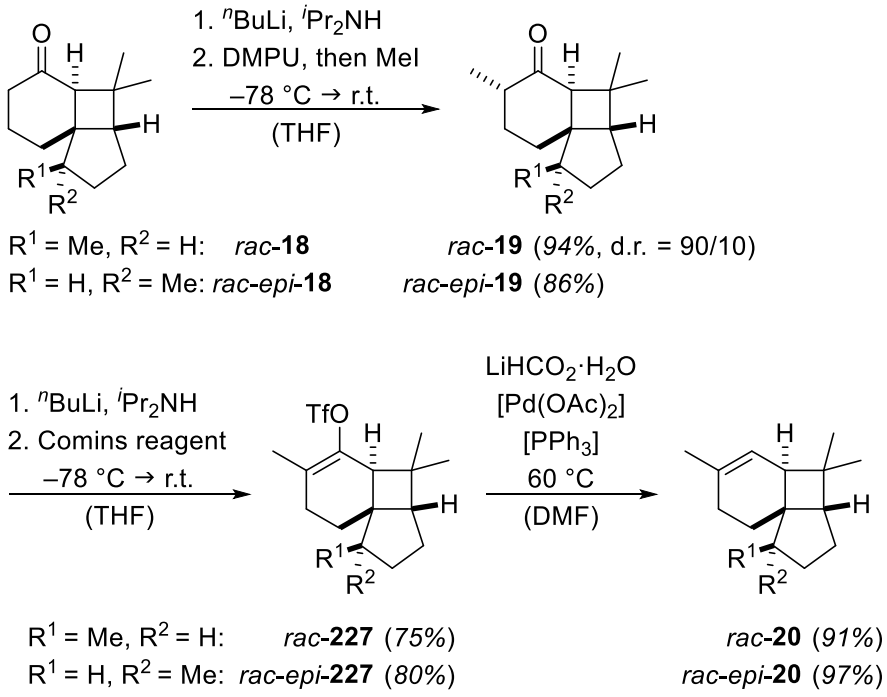
obtained in approximately 62% yield. It was mentioned in *Leimner*'s dissertation that such a complex product mixture was indeed obtained, however, a purification was possible and the title compounds *rac*-**20** and *rac-epi*-**20** were assigned.[195] The NMR analysis confirmed the formation of the target compounds *rac*-**20** and *rac-epi*-**20**, however, in our hands we were unable to reproduce their results.



Scheme 43. Attempted synthesis of natural products *rac*-italicene (*rac*-**20**) and *rac*-isoitalicene (*rac-epi*-**20**) following a procedure by *Weyerstahl*.[135]

Since we were unable to access the diastereomers in high purity, we decided to change the synthetic route towards *rac*-italicene (*rac*-**20**) and *rac*-isoitalicene (*rac-epi*-**20**) (Scheme 44). An extensive screening of reaction conditions using the diastereomeric mixture *rac*-**18** and *rac-epi*-**18** was carried out and subsequently the following synthetic route was identified: Since the diastereomeric separation of *rac*-**18** and *rac-epi*-**18** was possible, all reactions were carried out with pure samples of *rac*-**18** and *rac-epi*-**18**. An α-methylation furnished *rac*-**19** in 94% yield with a diastereomeric ratio of 90/10 and single diastereomer *rac-epi*-**19** in 86% yield. The shown relative configuration is likely a result of cyclic stereo control and was confirmed by NOE analysis. Next, enolates of *rac*-**19** and *rac-epi*-**19** generated by deprotonation with lithium diisopropyl amide were intercepted with *Comins* reagent providing triflates *rac*-**227** (75%) and *rac-epi*-**227** (80%). Chromatographic purifications involving silica stationary phases were not possible due to severe decomposition of the vinyl triflates on the stationary phases. Presumably, the acidic and active surface of silica induced the formation of vinyl cations which underwent rearrangement reactions.[196] Previous reports by *Yoon* and *Fürstner* involving vinyl triflates with similar structures did not mention any purification issues.[197,198] Changing the stationary

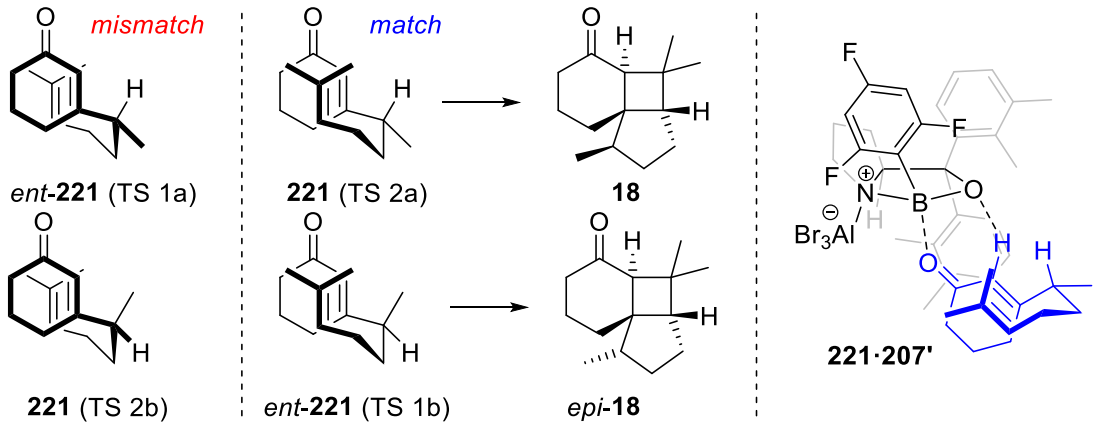
phase to deactivated neutral alumina enabled the successful chromatographic separation of all by-products yielding pure samples of the title compounds *rac*-**227** and *rac-epi*-**227**. Due to the apparent instability towards acidic conditions, triflates *rac*-**227** and *rac-epi*-**227** could not be hydrogenated under the standard conditions involving a tertiary amine and formic acid. Although attempts to carry out the reaction with triethylsilane or tributyltin hydride did provide the desired products *rac*-**20** and *rac-epi*-**20**, we were unable to separate them from the formed unpolar siloxanes and organostannanes. Next, we employed the non-acidic formic acid salt lithium formate monohydride as the hydride donor. The protodetriflation provided hydrocarbons *rac*-italicene (*rac*-**20**) in 91% yield and *rac*-isoitalicene (*rac*-**20**) in 97% yield. Both were chromatographically purified on deactivated neutral alumina, since silica led to partial isomerization. Starting from bromoanisole **222** *rac*-italicene (*rac*-**20**) was synthesized in over seven steps in an overall yield of 14% and *rac*-isoitalicene (*rac*-**20**) in an overall yield of 7%.



Scheme 44. Total synthesis of *rac*-italicene (*rac*-**20**) and *rac*-isoitalicene (*rac-epi*-**20**).

Having established a concise route to the natural products *rac*-italicene (*rac*-**20**) and *rac*-isoitalicene (*rac*-**20**), we set out to develop a diastereoselective approach. In contrast to the prochiral irradiation precursors **XVIII**, substrate *rac*-**221** consists of (*R*)-configurated **221** and (*S*)-configurated *ent*-**221**. Each enantiomer has two possible transition states (TS) for the photochemical reaction (Scheme 45). The origin of the observed stereoselectivity will be discussed by applying the previously proposed model for oxazaborolidine catalyzed

photocycloadditions to this reaction: The enantiomers *ent*-**221** and **221** result in a mismatch with the activated catalyst **207'** in TS 1a and TS 2b respectively, whereas enantiomers **221** in TS 2a and *ent*-**221** in TS 1b result in a match with catalyst **207'**. Consequently, we hypothesized TS 1b and TS 2a to be the lowest in energy resulting in the observed stereoselectivity. The mismatching species *ent*-**221** (TS 1a) leads to photoadduct *ent*-**18** and **221** (TS 2b) leads to photoadduct *ent-epi*-**18**.



Scheme 45. Transition states of irradiation precursors **221** and *ent*-**221** matching and mismatching catalyst **207'**.

Since according to our proposed model, both enantiomers of irradiation precursor *rac*-**221** could form a matched pair with catalyst **207'**, we did not anticipate high levels of enantioinduction. Preliminary results in this kinetic resolution showed that high conversion resulted in no enantiomeric excesses of **18** and *epi*-**18**. The reaction had to be terminated at low conversion in order to obtain an enantiomeric excess. We deemed a reaction time of one hour to be most suited for the study of the kinetic resolution, in which we employed the four most promising catalysts (Table 8).

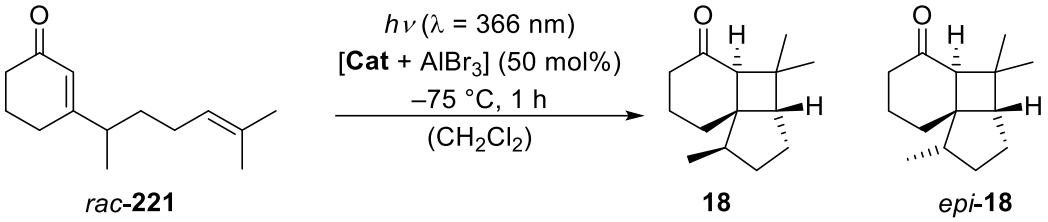


Table 8. Variation of the catalyst in the kinetic resolution of *rac*-**221**.

Entry	Catalyst	Yield	Rsm (*ent*-**221**)	d.r.
1	**50**	*13%* **18** (42% *ee*) *epi*-**18** (23% *ee*)	*71%* 10% *ee*	84/16
2	**176**	*12%* **18** (27% *ee*) *epi*-**18** (35% *ee*)	*56%* 11% *ee*	82/18
3	**207**	*<19%* **18** (37% *ee*) *epi*-**18** (n.d.)	*56%* 11% *ee*	n.d.
4	**202**	*<14%* **18** (27% *ee*) *epi*-**18** (n.d.)	*51%* 13% *ee*	n.d.

Catalysts **50** and **176** bearing the 3,5-dimethylaryl substituents at the backbone, provided products **18** and *epi*-**18** in high purity with a good mass balance. Photoadducts **18** and *epi*-**18** were obtained as diastereomeric mixtures in a ratio up to 84/16. The highest enantiomeric excess was observed with catalyst **50** (42% *ee* of *ent*-**221**). However, the yields were low (12-13%). Catalysts **207** and **202** resulted in an unclean reaction with multiple side-products. Therefore, a determination of the diastereomeric ratio and the enantiomeric excess of *epi*-**18** was not possible. Photoadduct **18** was obtained in 37% *ee* (**207**) and in 27% *ee* (**202**). In all cases, recovered starting material was obtained in 10-13% *ee*. Considering our proposed model, the predominant enantiomer is expected to be *ent*-**221**. In an ideal stereodivergent parallel kinetic resolution (PKR), both enantiomers are consumed by the catalyst each providing one diastereomer in high enantiomeric excess.[199] In order to identify the selectivity factor (s) for our catalyst with formula (6),[200] we first employed formulae (4) and (5), developed by *Kagan*

for PKRs,[201,202] to calculate the conversion of our reactions. Detailed calculations can be found in the appendix (chapter 7.3). The calculated conversions for entries 1 and 2 are 24% and 41% respectively. We were not able to calculate the conversions for entries 3 and 4, since the diastereomeric ratios and enantiomeric excesses of the minor product *epi*-**18** were not detectable. With these conversions in hand, we calculated the respective selectivity factors. For both catalysts **50** (s = 2.1) and **176** (s = 1.5) they were very low.

$$C = \frac{(1 + dr)ee_{rsm}}{dr(ee_{rsm} - ee_{minor}) + ee_{rsm} - ee_{major}} \quad (4)$$

$$dr = \frac{x_{minor}}{x_{major}} \quad (5)$$

$$s = \frac{\ln[(1 - C)(1 - ee_{rsm})]}{\ln[(1 - C)(1 + ee_{rsm})]} \quad (6)$$

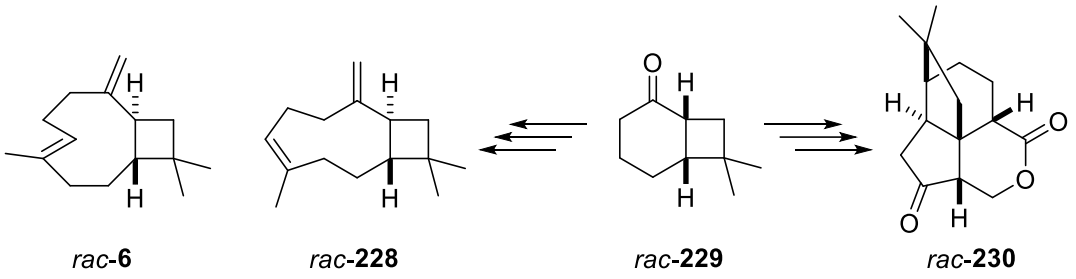
$$C = \frac{ee_{rsm}}{ee_{rsm} + ee_{product}} \quad (7)$$

In a stereodivergent PKR, a low selectivity factor does not necessarily lead to low enantiomeric excesses in the diastereomeric products if the d.r. is close to 50/50. In such a case, one enantiomer of the starting material affords ds_1 and the other enantiomer of the starting material affords ds_2. In our case, however, the reaction is intrinsically highly diastereoselective, leading to low enantioselectivities for each diastereomer. If one approximates this reaction to be a simple kinetic resolution where only a single product is afforded (in this case the major diastereomer **18**), then equations (6) and (7) can be applied.[200] To achieve a product *ee* of 90% in a simple kinetic resolution, at 24% and 41% conversion the s-factors would have to be 25 and 36 respectively. Consequently, this method does not meet the requirements for a high yielding and selective kinetic resolution of *rac*-**221**. Nevertheless, we have developed a new formal diastereoselective synthesis of italicene (**20**) and isoitalicene (*epi*-**20**).

3. Intermolecular [2+2] Photocycloadditions of Cyclic Enones

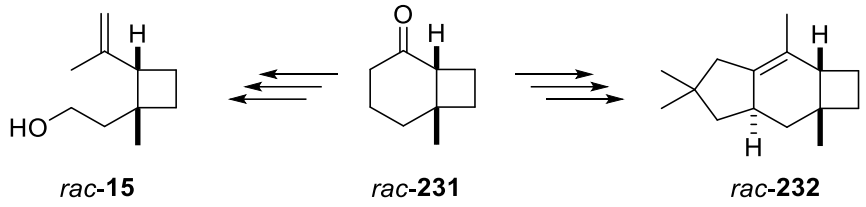
3.1 Literature Background and Project Aims

The intermolecular [2+2] photocycloaddition is a powerful synthetic tool for the synthesis of numerous natural products.[17-20,34] Especially, cyclohexenone (**235**), cyclopentenone (**238**) and their derivatives, are most commonly employed as starting materials. In 1963, *Corey* reported his landmark synthesis of *rac*-caryophyllene (*rac*-**6**) and *rac*-isocaryophyllene (*rac*-**228**) (Scheme 46).[15,16] This was the first time an intermolecular [2+2] photocycloaddition reaction was implemented as the key step for a natural product synthesis. A formal stereoselective synthesis of caryophyllene (**6**) was later achieved by an enantioselective *Michael* addition or an auxiliary-based diastereoselective [2+2] photocycloaddition.[203,204] In both cases, a multistep sequence was necessary to obtain enantioenriched photoadduct *ent*-**229**. Starting from the same photoadduct *rac*-**229**, the group of *Yoshii* synthesized *rac*-quadrone (*rac*-**230**) which is a fungal metabolite from *Aspergillus terreus* (Scheme 46).[205]



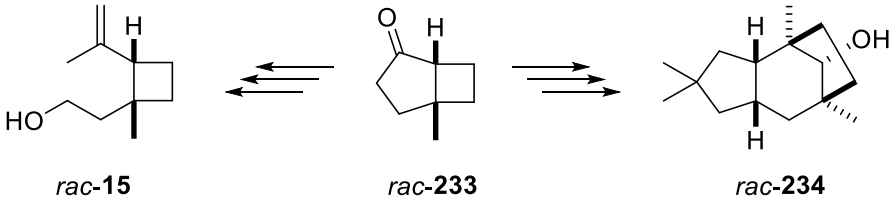
Scheme 46. Synthesis of *rac*-caryophyllene (*rac*-**6**), *rac*-isocaryophyllene (*rac*-**228**) and *rac*-quadrone (*rac*-**230**) starting from photoadduct *rac*-**229**.[15,16,205]

Vast synthetic efforts have been invested in the syntheses of the cyclobutane natural product *rac*-grandisol (*rac*-**15**) (Scheme 47 and Scheme 48).[18] The aggregation pheromone of the cotton boll weevil *Anthonomus grandis* is mainly comprised of this natural product. Several syntheses provided enantiomerically enriched product, yet, none of these employed an enantioselective [2+2] photocycloaddition reaction as the key step.[65,66,206-222] The photoadduct *rac*-**231** was also converted to *rac*-sterpurene (*rac*-**232**), a fungal metabolite of *Stereum purpureum*, by the group of *Helquist*.[223]



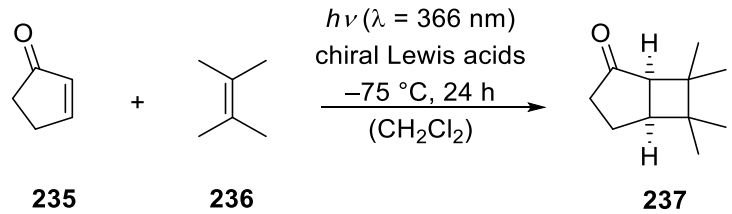
Scheme 47. Synthesis of *rac*-grandisol (*rac*-**15**) and *rac*-sterpurene (*rac*-**232**) starting from photoadduct *rac*-**231**.[209,223]

The group of *Fitjer* transformed photoadduct *rac*-**233** into the sesquiterpene *rac*-cerapicol (*rac*-**234**) (Scheme 48).[224] It is a metabolite of the fungus *Ceratocystis picea*.



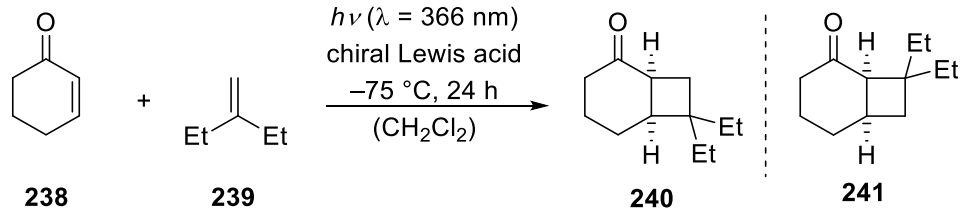
Scheme 48. Synthesis of *rac*-grandisol (*rac*-**15**) and *rac*-cerapicol (*rac*-**234**) starting from photoadduct *rac*-**233**.[207,224]

Prior to our work, no synthetic method had been reported which enables a catalytic enantioselective version of an intermolecular [2+2] photocycloaddition reaction between a simple cyclic enone and an alkene. Taking into account the synthetic relevance of this reaction, it was considered to reinvestigate this project. *Mayr* from our research group previously attempted to develop an enantioselective intermolecular [2+2] photocycloaddition reaction.[225] For his study he used cyclopentenone (**235**) as a test substrate and 2,3-dimethylbutene (**236**) as an alkene. The reason for this choice was the selective formation of a single product without any side-products which would complicate the analysis and separation of the title compound **237**. Various chiral Lewis acids were employed, among them oxazaborolidine **50**. In all cases, no significant enantiomeric excess of photoadduct **237** was detected. The yields were moderate (46-56%) and the highest observed *ee* was 2%. In contrast to the intramolecular [2+2] photocycloaddition, the intermolecular [2+2] photocycloaddition presented a major challenge for the development of an enantioselective version.



Scheme 49. Cyclopentenone (**235**) and alkene **236** in an attempted enantioselective [2+2] photocycloaddition reaction to adduct **237**.[225]

In the previous chapter (2.5) an extensive screening of the oxazaborolidine catalyst is described for the intramolecular [2+2] photocycloaddition of the test substrate **65**. With the new catalyst **207** in hand, which performed best for the substrate class of simple cyclic enones, it was considered to change the strategy for the intermolecular [2+2] photocycloaddition. In contrast to *Mayr*'s work, the test substrate was cyclohexenone (**238**). In contrast to its smaller homologue **235**, generally cleaner photochemical reactions with higher yields are observed. The previous chapter on the enantioselective intramolecular [2+2] photocycloaddition demonstrated that cyclopentenone derived substrates result in lower yields and enantiomeric excesses than cyclohexenone derived substrates. Furthermore, the reactions were unclean for substrates with alkene side-chains carrying a terminal methyl substituent. Consequently, it was crucial to employ a 1,1-disubstituted alkene in the optimization of the intermolecular [2+2] photocycloaddition. In order to minimize the number of diastereomers, only alkenes with a symmetrical 1,1-disubstitution were employed. Hence, 2-ethylbutene (**239**) was deemed to be a suitable alkene for the optimization studies (Scheme 50). Still, it should be noted that we anticipated regioselectivity issues with respect to the formation of head-to-head (**241**) and head-to-tail (**240**) products. It has been shown for similar alkenes that the formation of head-to-tail products is preferred.[43]



Scheme 50. New test substrate **238** and alkene **239** for an enantioselective [2+2] photocycloaddition reaction to adduct **240**.

Another important reason for the choice of alkene **239** was its similarity to isobutene which was used in the natural product syntheses of *rac*-caryophyllene (*rac*-**6**), *rac*-isocaryophyllene (*rac*-**228**) and *rac*-quadrone (*rac*-**230**) (Scheme 46). An enantioselective variant of the reaction in Scheme 50 was therefore of great synthetic interest.

3.2 UV/Vis Measurements

The UV/Vis properties of cyclohexenone (**238**) were investigated to determine the appropriate excitation wavelength for a photochemical reaction. As the solvent, dichloromethane was chosen as it is commonly used in chiral oxazaborolidine catalyzed enantioselective photochemical reactions. Cyclohexenone (**238**) shows two absorption bands with only one

being visible in a more concentrated sample. The strong absorption band at λ_{max} = 224 nm (ε = 13402 $M^{-1}cm^{-1}$) represents the allowed $\pi\pi^*$ transition (Figure 20). The forbidden $n\pi^*$ transition of **238** is responsible for the weak absorption band at λ_{max} = 330 nm (ε = 33 $M^{-1}cm^{-1}$) (Figure 20).

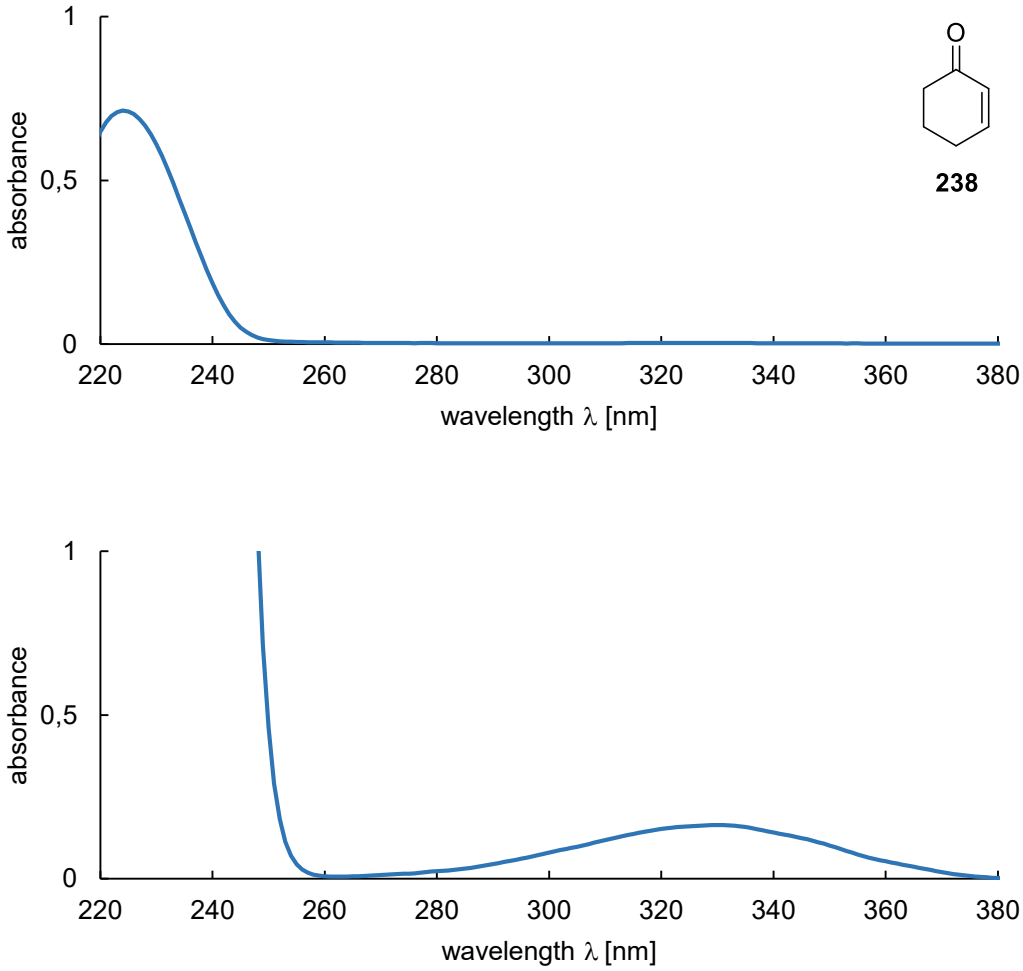


Figure 20. UV/Vis-spectra of cyclohexenone (**238**) in dichloromethane depicting the $\pi\pi^*$ transition (c = 500 µM, upper spectrum) and the $n\pi^*$ transition (c = 50 mM, lower spectrum).

Substrate **238**, used in the intermolecular [2+2] photocycloaddition, and enone **65**, show similarities in the UV/Vis spectra. This is due to the chromophores being nearly identical in both **238** and **65**. Consequently, an enantioselective variant of the [2+2] photocycloaddition with enone **238** using the previously established optimal conditions seemed plausible.

To solidify this hypothesis, enone **238** was treated with 20 equivalents of two strong Lewis acids to ensure complete complexation of **238**. The spectra were measured with the same concentration (500 µM) in dichloromethane. The complex **238**·$EtAlCl_2$ absorbs at λ_{max} = 260 nm (ε = 9670 $M^{-1}cm^{-1}$) which means the bathochromic shift of the $\pi\pi^*$ transition is

approximately $\Delta\lambda_{max} = 36$ nm (Figure 21). The absorption band is lower in the absorbance but is wider and tails to $\lambda = 350$ nm. A stronger bathochromic shift of the $\pi\pi^*$ transition of $\Delta\lambda_{max} = 42$ nm was observed with complex **238**·BCl_3. The absorption band is present at $\lambda_{max} = 266$ nm ($\varepsilon = 13080\ M^{-1}cm^{-1}$) and tails to $\lambda = 330$ nm (Figure 21). Both complexes **238**·$EtAlCl_2$ and **238**·BCl_3 show a higher absorbance at $\lambda = 330$ nm than the uncomplexed enone **238** (Figure 21). An $n\pi^*$ transition band was not observed in either of the complexes.

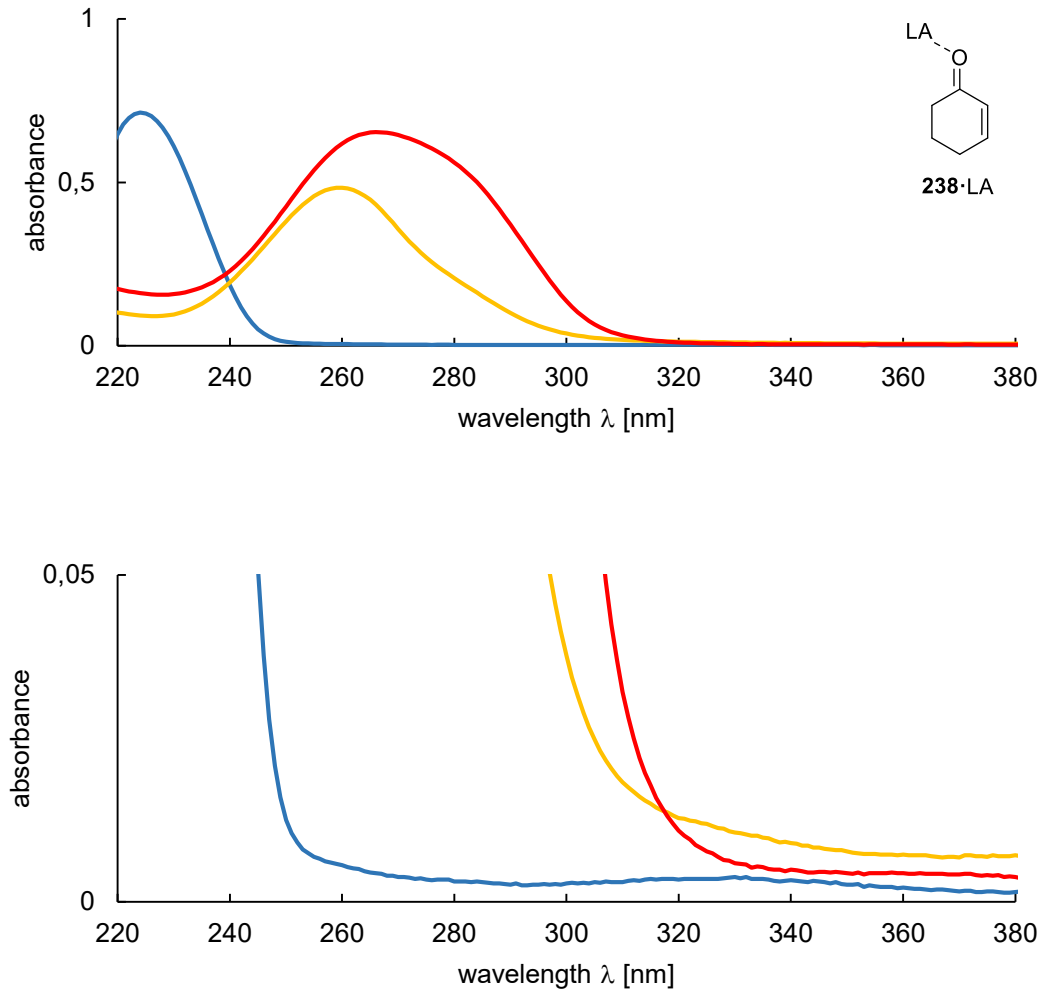
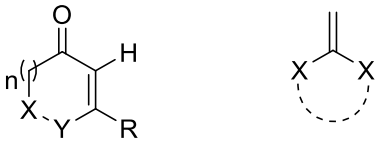


Figure 21. UV/Vis-spectra of cyclohexenone (**238**) in the absence of a Lewis acid (blue) and in the presence of 20 equiv EtAlCl2 (orange) and and 20 equiv BCl3 (red). The lower figure shows a magnification of the upper spectrum. The measurements were carried out in dichloromethane (c = 500 µM).

We concluded that selective excitation of a complex **238**·LA could be possible with light sources emitting a wavelength of $\lambda > 300$ nm. The absorbance of a complex **238**·LA is higher in the region of $\lambda > 300$ nm than of uncomplexed **238**, thus a favored excitation of a Lewis acid complex **238**·LA appeared to be feasible.

3.3 Synthesis of Irradiation Precursors and Alkenes

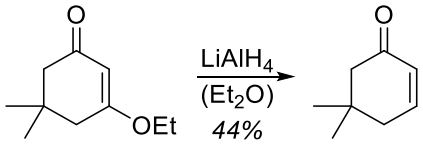
The scope with respect to the irradiation precursors **XXII** had two limitations which had to be considered. First, the α-proton had to be present in order to provide the binding motif for the oxazaborolidine catalyst. Second, no heteroatoms with direct connection to the β-carbon of **XXII** were possible, since this would dramatically change the properties of the chromophore (Figure 22). Although many alkenes are commercially available, only a limited number are symmetrically 1,1-disubstituted. In order to be able to access a broader substrate scope, terminal and symmetrical alkenes **XXIII** were synthesized (Figure 22).



XXII **XXIII**

Figure 22. General structure of irradiation precursors **XXII** and alkenes **XXIII**.

5,5-Dimethyl substituted enone **242** was synthesized according to a protocol by *Wawrzeńczyk* starting from enol ether **143** (Scheme 51).[163] The carbonyl group of **143** was reduced by lithium aluminum hydride. After an acidic work-up, resulting in the elimination of water, enone **242** was isolated in 44% yield. The isolated yields of **242** varied from batch to batch due to its volatility.

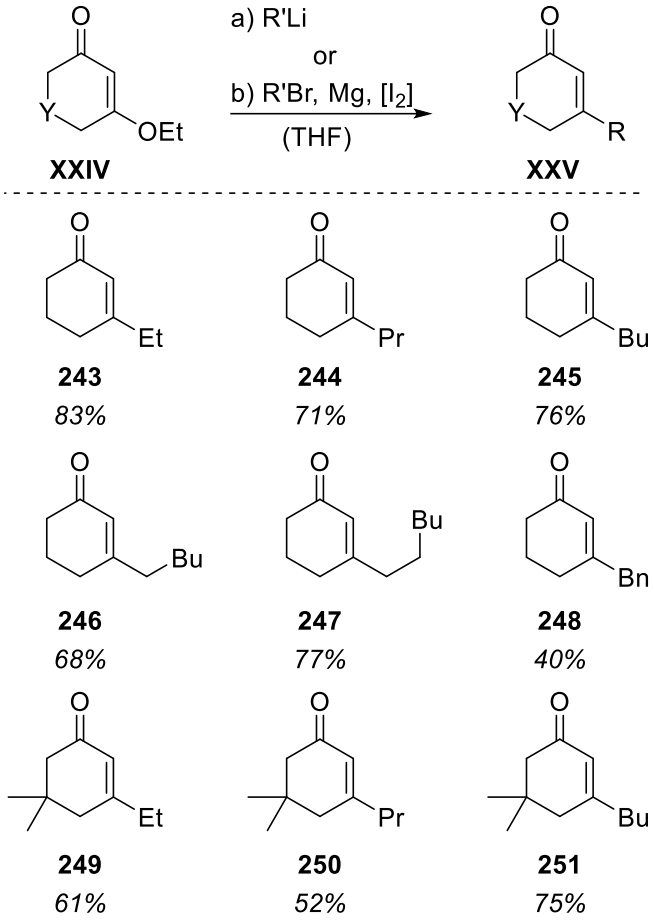


143 **242**

Scheme 51. Synthesis of irradiation precursor **242**.[163]

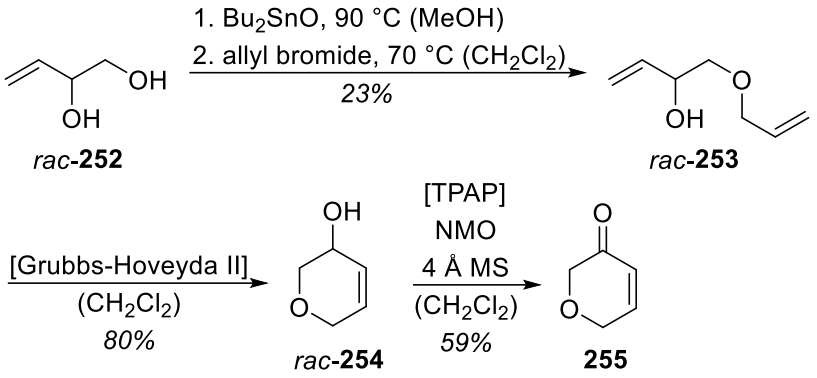
Six cyclic enones (**243**-**248**) and three 5,5-dimethyl substituted cyclic enones (**249**-**251**) with a substitution at the β-position were synthesized starting from the corresponding enol ethers **XXIV** according to a modified protocol by *Mattay* (Scheme 52). [133] Either a commercially available lithium reagent [condition a)] or a *Grignard* reagent, formed with the appropriate alkyl bromide, [condition b)] were employed as nucleophiles. After a 1,2-addition of the organometallic reagent to the ester and subsequent elimination of water and ethanol via an acidic work-up, the photoprecursors **XXV** were obtained in moderate to high yields (40-83%). It is noteworthy that unsubstituted enol ether **118** was converted in high yields with a particularly short reaction time. An exception was enone **248** (Y = CH_2) with a benzyl group.

Presumably, the 1,2-addition was impeded due to an increased steric bulk. Similar steric influence was observed in case of the 5,5-dimethyl substituted enol ether **143** (Y = CMe_2). Here, a prolongation of the reaction time was necessary to achieve full conversion.



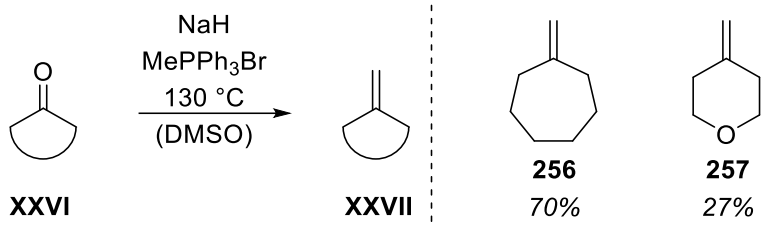
Scheme 52. Synthesis of irradiation precursors **XXV**.[133]

Pyranone **255** was synthesized, following a protocol by *Hoveyda*, starting from diol *rac*-**252** (Scheme 53).[226] Diol *rac*-**252** was converted with dibutyltin oxide to a tin orthoester, which enabled a selective alkylation of the primary alcohol with allyl bromide.[227] The diene *rac*-**253** was obtained in 23% yield. In this case, the low yield is attributed to a highly unselective reaction course resulting in the formation of many side products. Using the transition metal carbene complex *Grubbs-Hoveyda* II, the linear diene *rac*-**253** was converted via an olefin metathesis furnishing cyclic alcohol *rac*-**254** in 80% yield. Finally, an oxidation of alcohol *rac*-**254** was carried out with catalytic amounts of TPAP and stochiometric oxidant NMO in the presence of molecular sieves with pyranone **255** being isolated in 59% yield. This irradiation precursor was stored in the freezer (–20 °C) as significant decomposition was observed at ambient temperature.



Scheme 53. Synthesis of irradiation precursor **255**.[226]

Following a procedure by *Xu* and *Li*, cyclic ketones **XXVI** were converted to the symmetrical alkenes **XXVII** (Scheme 54).[228] Dimethyl sulfoxide was deprotonated by sodium hydride to generate sodium methylsulfinylmethylide as a strong base which in turn deprotonated methyltriphenylphosphonium bromide. The ketones **XXVI** underwent a *Wittig* reaction with the phosphonium ylide providing alkenes **XXVII** in low and good yields (27% and 70%). The alkene **257** containing an ether bridge was obtained in particularly low yield. The major issue was the isolation from the dimethyl sulfoxide slurry. In contrast to the aliphatic alkene **256**, the cyclic ether **257** is polar and thus more difficult to separate from the polar solvent containing reaction mixture via distillation. An aqueous work-up failed, due to the high water solubility of **257**.

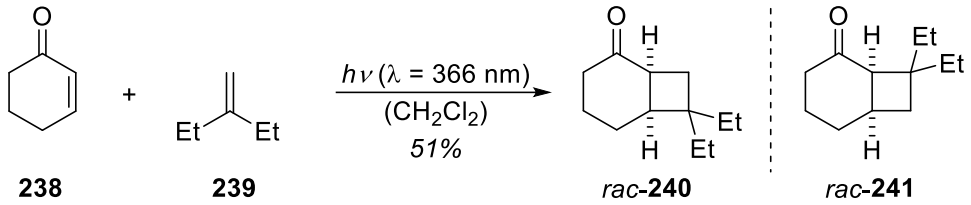


Scheme 54. Synthesis of symmetric alkenes **XXVII**.[228]

3.4 Enantioselective Intermolecular [2+2] Photocycloaddition

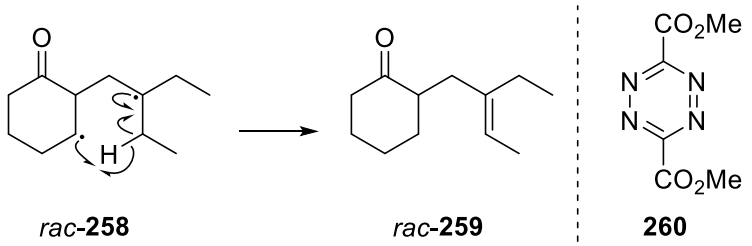
3.4.1 Racemic [2+2] Photocycloaddition with the Test Substrate

As a starting point, the established test reaction between cyclohexenone (**238**) and symmetric alkene **239** was further investigated (Scheme 55). It was found that at a wavelength of λ = 366 nm the reaction proceeded with the highest yield of 51% for the HT product (*rac*-**240**). Irradiation with light sources of shorter wavelengths, such as 300 nm and 350 nm, resulted in more complex product mixtures.



Scheme 55. Racemic [2+2] photocycloaddition of enone **238** with alkene **239**.

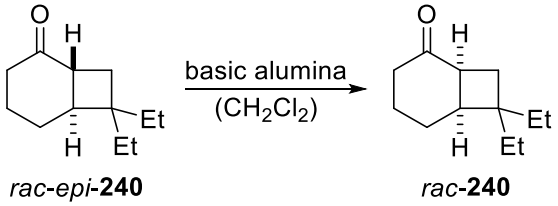
In order to isolate *rac*-**240**, a considerably more complex work-up procedure was unavoidable. The crude product mixture consisted of side-products with olefinic functional groups and the HH product (*rac*-**241**). Due to impurities, it was not possible to quantify the yield of *rac*-**241**. As it was the undesired product, further attempts of its isolation were deemed to be unnecessary. The olefinic side products, however, contaminated the HT product *rac*-**240** even after purification by column chromatography. Due to the complex nature of the mixtures, a precise quantification or structure elucidation of the olefinic products was not possible. However, an NMR analysis showed signals indicative of olefinic protons and carbons. These side products likely stem from the 1,4-diradical *rac*-**258** forming *rac*-**259** by an intramolecular hydrogen abstraction (Scheme 56). It should be noted that additional reaction pathways forming olefinic side products are likely.



Scheme 56. Intramolecular hydrogen abstraction in *rac*-**258** leading to *rac*-**259**. Structure of 3,6-bis(methoxy-carbonyl)-1,2,4,5-tetrazine (**260**).

We developed two methods to remove the olefinic side products, such as *rac*-**259**. First, the product mixture was treated with ozone in dichloromethane. The ozonolysis entirely removed

all olefinic by-products. After reductive quenching with dimethyl sulfide, the by-products were converted to polar ketones or aldehydes. A further purification by column chromatography then provided photoadduct *rac*-**240** in high purity. As this method is rather time consuming, we decided to employ a different purification procedure. The removal of unwanted olefinic side products using tetrazine **260** is not only faster, it is also a practically simpler procedure (Scheme 56). Tetrazine **260** is comprised of an electron-deficient diene which particularly reacts with electron rich alkenes in a *Diels-Alder* reaction. A spatula tip of tetrazine **260** was added to a solution of the product mixture in dichloromethane. Upon addition, the dissolution of tetrazine **260** caused the reaction solution to turn light purple. In case this color faded, a further portion of tetrazine **260** was added. We deemed this method to be the most efficient and consequently, it was used throughout the study when necessary.



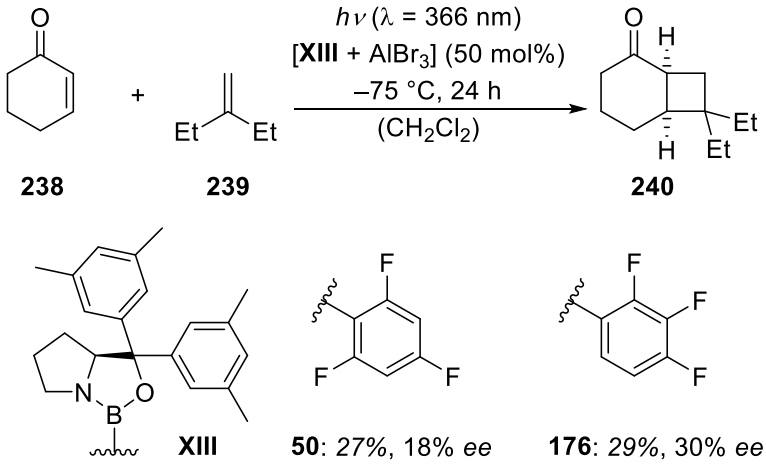
rac-epi-**240** *rac*-**240**

Scheme 57. Isomerization of *rac-epi*-**240** using basic alumina.

Photoadduct *rac*-**240** was isolated alongside its epimer *rac-epi*-**240**. An isomerization to the thermodynamically more stable *rac*-**240** was carried out with basic alumina (Scheme 57). In summary, the work-up procedure involved a purification by column chromatography, removal of residual olefinic by-products and the isomerization with basic alumina.

3.4.2 Optimization of the Enantioselective [2+2] Photocycloaddition Conditions

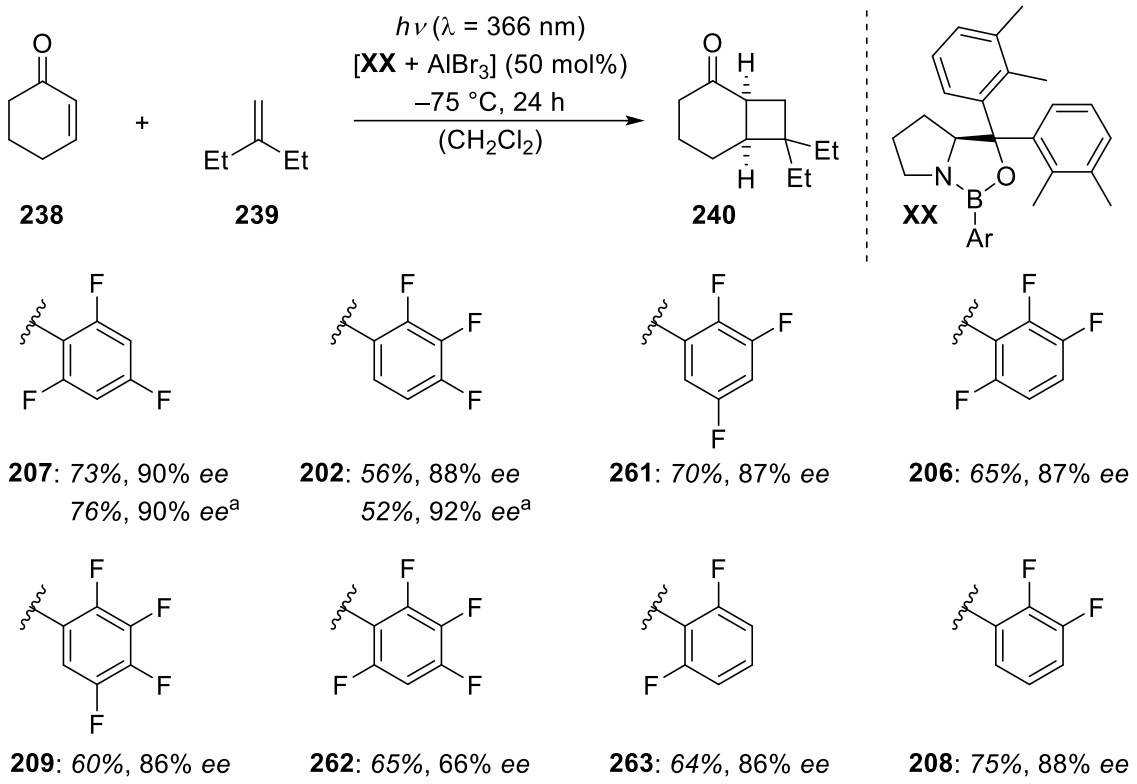
As a starting point for our investigations, we chose the conditions of *Mayr* using oxazaborolidine **50** (Scheme 58). Photoadduct **240** was obtained in a low yield of 27% and a low enantiomeric excess of 18%. In contrast to *Mayr*'s test reaction with cyclopentenone (**235**) as the irradiation precursor, the use of cyclohexenone (**238**) was promising with respect to obtaining enantiomerically enriched product. Employing oxazaborolidine **176** led to a slight increase in yield to 29% and the enantiomeric excess to 30% *ee*. At this stage however, these results did not yet meet the requirements of a synthetically relevant method.



Scheme 58. Variation of the boronic acid in oxazaborolidine **XIII**.

With promising initial results at hand, it was considered to use the oxazaborolidine **207** which proved to be the most proficient catalyst in the intramolecular [2+2] photocycloaddition (Scheme 59). Using catalyst **207**, photoadduct **240** was furnished in a good yield of 73% and high enantiomeric excess of 90% *ee*. It is noteworthy that the yield is higher than in the racemic reaction. Additionally, a cleaner reaction course was observed. Olefinic side products were indeed found in traces, however these could easily be removed with tetrazine **260**. An isomerization with basic alumina, however, was still necessary. Next, we investigated the effect of the nature of the fluorine substitution pattern of the boronic acid in oxazaborolidines **XX** on the photocycloaddition. Catalysts bearing trifluorinated (**202**, **206**, **261**), tetrafluorinated (**209**, **262**) and difluorinated (**208**, **263**) boronic acids all performed worse than the initially used catalyst **207**. The yields were moderate to good (56-75%) and the enantiomeric excess (66-88% *ee*) remained below 90% *ee* (Scheme 59). The application of an iron(III) sulfate UV-filter solution improved the enantiomeric excess to 92% *ee* when catalyst **202** was used. There was no improvement of the enantiomeric excess when using catalyst **207**. Since the reaction time

doubles to 48 hours when using a UV-filter solution and the improvement is only marginal, our following experiments were not carried out with a filter solution. We concluded that the optimal catalyst for the enantioselective intermolecular [2+2] photocycloaddition reaction was oxazaborolidine **207**.



Scheme 59. Variation of the boronic acid in oxazaborolidine **XX**. [a]Reaction was carried out for 48 hours using an iron(III) sulfate UV-filter solution (c = 600 mg/L in 10 mM aqueous hydrochloric acid solution).

Comparing the structures of catalyst **50** and **207**, it is apparent that the only difference is the substitution pattern on the prolinol backbone. By changing the position of the methyl group from the 5-position (**50**) to the 2-position (**207**), a major enhancement of both yield and enantioselectivity was observed. Such a remarkable difference in catalyst performance of **50** and **207** was not observed in the intramolecular [2+2] photocycloaddition, although the substrate classes are structurally similar. A model from previous mechanistic studies for the intramolecular [2+2] photocycloaddition reaction with oxazaborolidines does not explain the effect of the methyl substitution pattern on the intermolecular [2+2] photocycloaddition reaction.[119,120]

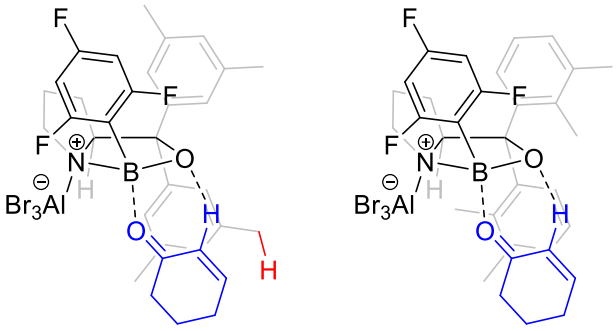


Figure 23. Hypothetical structures of the catalyst-substrate complexes **238·50'** and **238·207'**.

In contrast to the intramolecular [2+2] photocycloaddition, the irradiation precursor of the intermolecular reaction is not in close proximity to its alkene reaction partner. The rate of reaction strongly depends on the concentration of the alkene. Consequently, a longer half-life of the unreacted excited triplet species of **238** can be assumed. The excited substrate **238** in the Lewis acid-substrate complex **238·50'** could abstract a hydrogen atom (marked in red) intramolecularly (Figure 23).[229,230] This would lead both to a lower yield of photoadduct **240** and a decomposition of the catalyst **50'**. Consequently, a lower enantioselectivity would be expected due to a decrease in catalyst loading. Because of the different arrangement of the methyl groups in complex **238·207'**, however, such a hydrogen abstraction might not be possible resulting in a better yield and no decomposition of catalyst **207'**. It is important to note however, that this model is mere speculation and would require further experimental and theoretical mechanistic studies to solidify our understanding of the photocycloaddition.

3.4.3 Product Scope

During our studies concerning the racemic photocycloaddition, numerous combinations of irradiation precursors with alkenes and alkynes were investigated. Only reaction partners which furnished isolable photoadducts in high purity, were used for the enantioselective reactions. The yields of the racemic reactions were generally lower, due to decreased selectivity between HH and HT products and the formation of olefinic by-products. Photoreactions with ethylene and 1,1-dichloroethylene did not result in the formation of such side products.

In order to illustrate the limits of the intermolecular [2+2] photocycloaddition, examples of unsuccessful attempts to obtain photoadducts are discussed below (Figure 24). All reactions were carried out at a wavelength of $\lambda = 366$ nm in dichloromethane. Alkenes or alkynes were used in 50-fold excess.

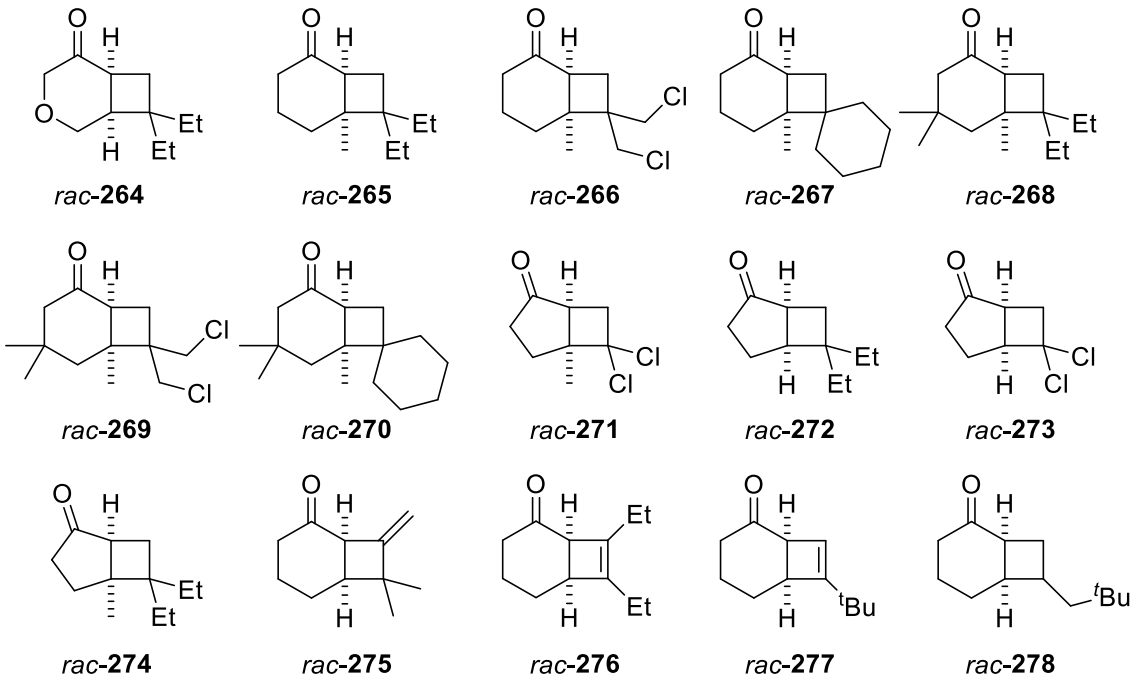


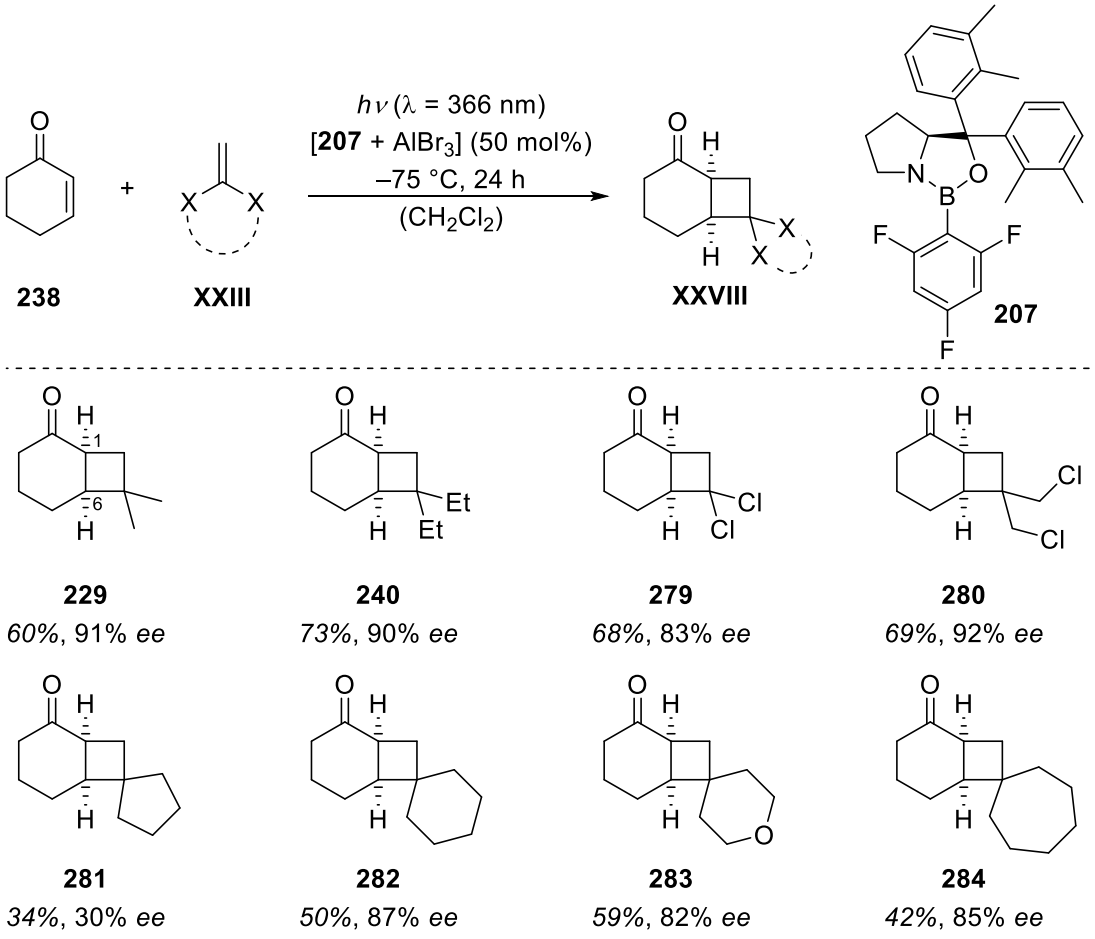
Figure 24. Photoadducts *rac*-**264**-*rac*-**278** which were not isolable due to inseparable impurities, instability of the products or lack of conversion.

Attempts towards obtaining photoadduct *rac*-**264** from pyranone **255** led to unpurifiable product mixtures. Employing stochiometric amounts of $EtAlCl_2$ did improve the selectivity towards a major product. However, too many impurities were still present, thus preventing a correct assignment of the desired product. These results are consistent with observations made by *Margaretha*. [231,232] Examples *rac*-**265**-*rac*-**267** and *rac*-**269**-*rac*-**270** were not isolable due to a lack of chemoselectivity. While the same alkenes reacted well with cyclohexenones **238** and **242**, this was not the case with β-alkyl-substituted cyclohexenones. No conversion was observed for *rac*-**268** (trimethylenone). Presumably, this is due to excessive steric hinderance impeding the recombination of the 1,4-diradical resulting in numerous radical side-reactions or a dissociation of the reaction partners. There is a plethora of studies on intermolecular [2+2] photocycloaddition reactions using cyclopentenone (**235**).[47,233-241] However, under the optimized conditions it was not possible to obtain the photoadducts *rac*-**271**-*rac*-**274**. Product formation was indeed observed, albeit the yields were too low. Additionally, in our hands the purification of *rac*-**271**-*rac*-**274** was not possible. The use of allenes and alkynes resulted in either unpurifiable mixtures (*rac*-**275** and *rac*-**276**) or no significant conversion (*rac*-**277**). A monosubstituted alkene provided adduct *rac*-**278** as a mixture of four isomers which we were unable to separate by column chromatography.

Using the optimized reaction conditions for the enantioselective [2+2] photocycloaddition it was possible to obtain 32 examples with low to excellent yields (12-93%) and low to excellent

enantiomeric excesses (30-96%). The product scope has been divided into five categories to allow for a clear and comprehensive discussion.

It is crucial to note that reactions involving gaseous alkenes such as isobutene or ethylene necessitated special procedures. First, a balloon was filled with the appropriate alkene. Next, an evacuated phototube was placed under an atmosphere of the appropriate alkene using a balloon. Following this, the gaseous alkene was condensed directly into the phototube (at –75 °C for isobutene and –195 °C for ethylene), after which the reaction mixture was added. Isobutene has a high solubility in dichloromethane and does not significantly evaporate from the solution at room temperature. Ethylene, however, has a lower solubility in dichloromethane and still evaporates from the solution at –40 °C or –75 °C. Consequently, reactions with ethylene solutions were warmed gradually from –195 °C to –75 °C prior to irradiation. This allowed the excess of ethylene to be captured in the argon balloon without the solution vigorously effervescing.

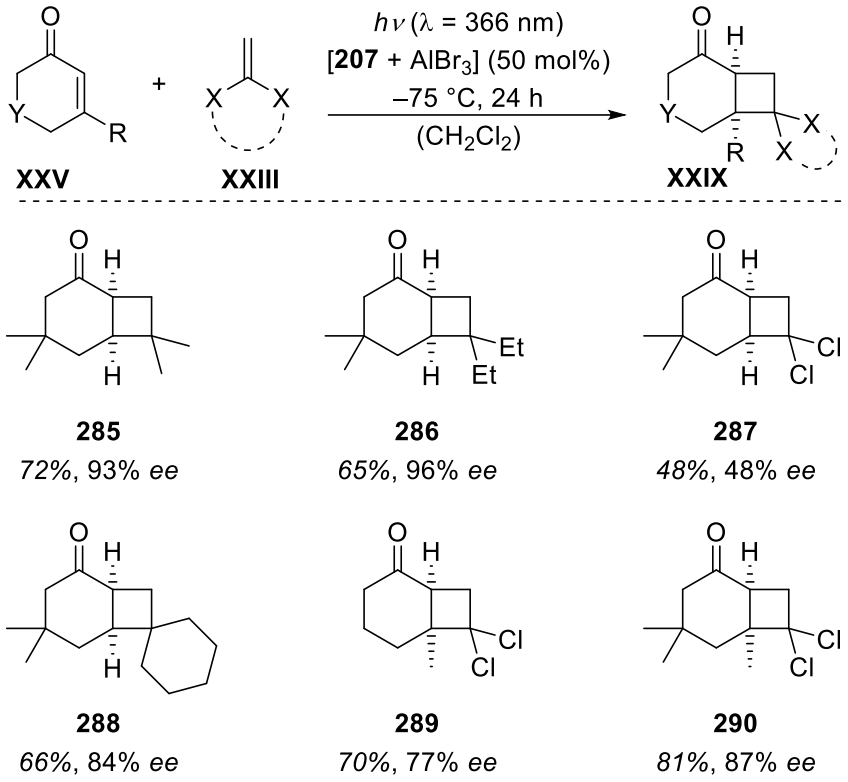


Scheme 60. Product scope **XXVIII** of the enantioselective reaction of cyclohexenone (**238**) and 1,1-disubstituted alkenes **XXIII**.

Under the enantioselective reaction conditions, it was possible to convert cyclohexenone (**238**) with six different 1,1-disubstituted alkenes **XXIII** (Scheme 60). Olefins, chloro- and oxygen- substituted alkenes were well tolerated and provided moderate to good yields (42-73%) with high enantiomeric excesses (82-92%). Methylenecyclopentane, however, provided the adduct **281** in only 34% yield and 30% *ee*. Careful drying and degassing of the alkene increased neither yield nor enantioselectivity. Enantioenriched photoadduct **229** represents the starting material for the syntheses of caryophyllene (**6**), isocaryophyllene (**228**) and quadrone (**230**).[15,16,205]

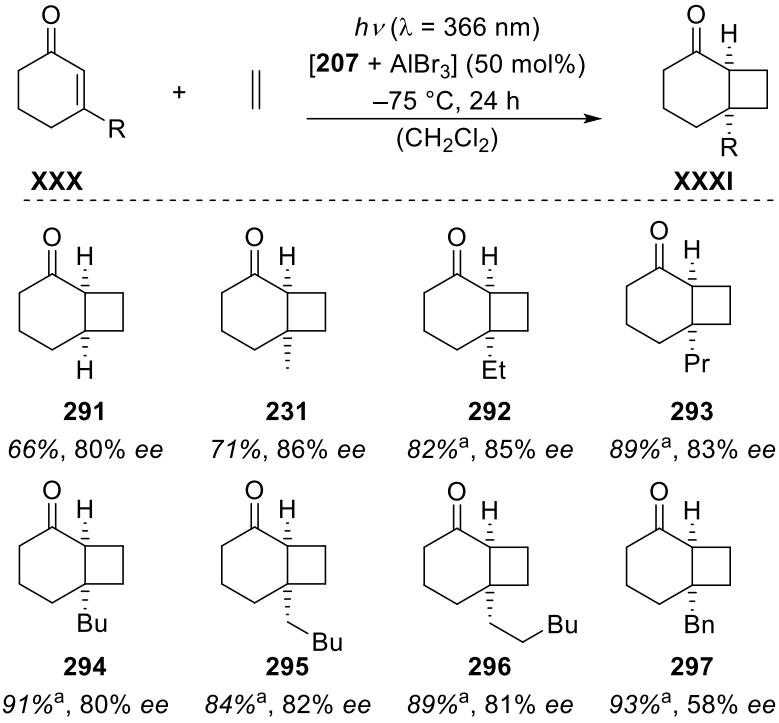
In a previous report by *Corey*, the adduct *ent*-**229** was synthesized. The absolute configuration of the two stereogenic centers of the bicyclo[4.2.0]octane skeleton of the levorotatory enantiomer *ent*-**229** ($[\alpha]_D^{23} = -153$, c = 1.4 in chloroform) was confirmed to be (1*R*,6*R*).[203,204] The dextrorotatory ($[\alpha]_D^{25} = +163$, c = 1.4 in dichloromethane) photoadduct **229** therefore has the opposite absolute configuration (1*S*,6*S*). The observed absolute configuration is consistent with the proposed model of Lewis acid-substrate complex **238·207'** (Figure 23). Consequently, we assumed the remaining photoproducts to be of the same absolute configuration.

Our initial observations (with a few exceptions) had shown that the yields were higher in the enantioselective reaction than in the racemic version. As an example, photoadduct *rac*-**240** was isolated in 51% yield, whereas the enantioenriched product **240** was obtained in 73% yield. We hypothesized that the nature of the Lewis acid could be responsible for the difference in yield. Consequently, test reactions with various Lewis acids and temperatures were carried out. Aluminum bromide inhibits the formation of olefinic side products both at room temperature and low temperatures (–75 °C), and at the same time enhances the selectivity towards the HT product. A possible explanation for this could be an increased polarization of the enone α- and β-carbon atoms resulting in improved regioselectivity.



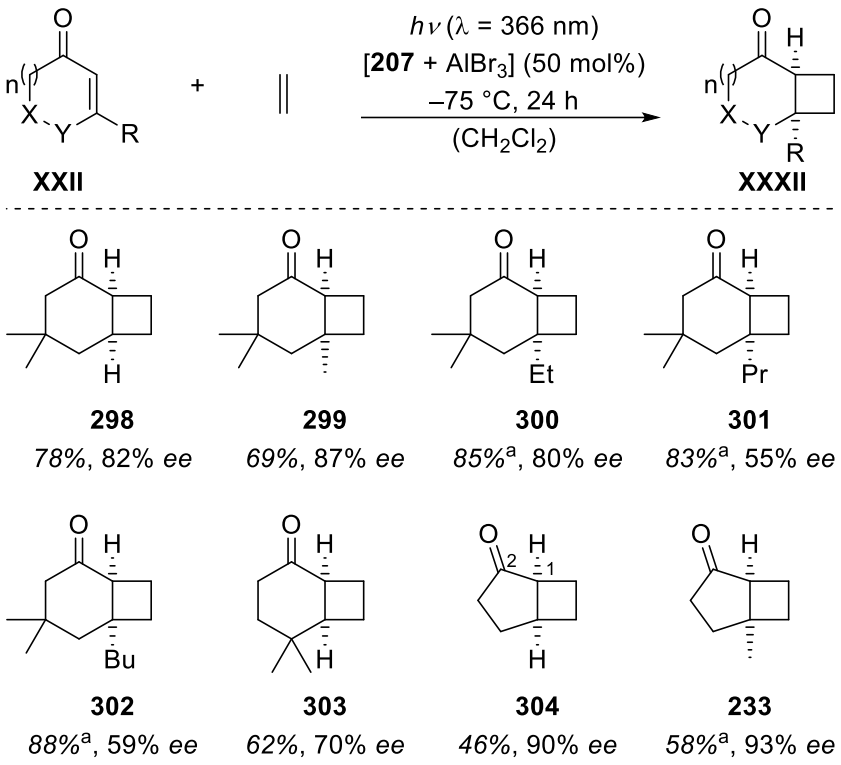
Scheme 61. Product scope **XXIX** of the enantioselective reaction of enones **XXV** and 1,1-disubstituted alkenes **XXIII**.

Further enantioselective reactions with 1,1-disubstituted alkenes were carried out with 5,5-dimethylcyclohexenone (**242**), 3-methylcyclohexenone **205** and isophorone (Scheme 61). Aliphatic alkenes in combination with dimethyl substituted enone **242** provided adducts **285**, **286** and **288** in good yields (65-72%) and high to excellent enantiomeric excesses (84-96%). 1,1-Dichloroethylene furnished adducts **287**, **289** and **290** in moderate to good yields (48-81%) and moderate to high enantiomeric excesses (48-87%). Photoadduct **287** was obtained in a moderate yield of 48% with 48% *ee*. Careful drying and degassing of the alkene failed to increase yield or enantioselectivity.



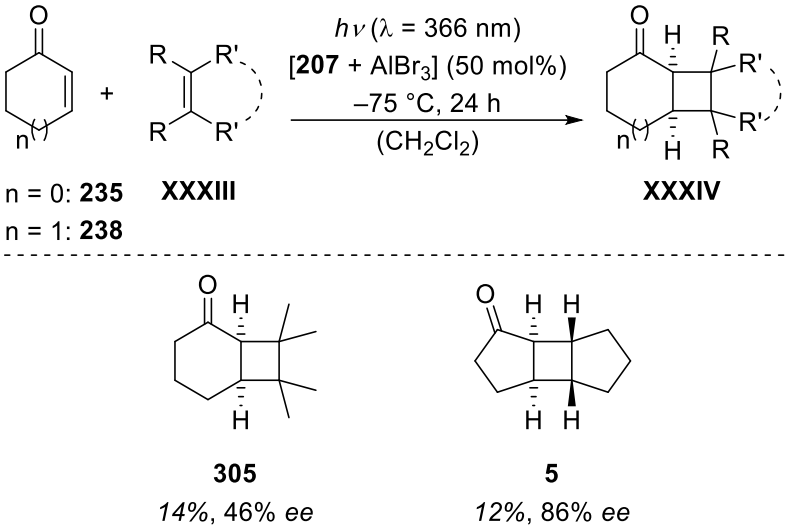
Scheme 62. Product scope **XXXI** of the enantioselective reaction of enones **XXX** and ethylene. [a]Yields are based on recovered starting material.

Both, cyclohexenones without (**238**) and with alkyl substitution at the β-position (**205**, **243**-**247**) were enantioselectively converted with ethylene (Scheme 62). The adducts were isolated in good to excellent yield (66-93%) and the enantiomeric excesses were moderate to high (58-86%). Photoadducts **231**, **292**-**296** represent a series in which the alkyl chain substitution in β-position is incrementally elongated by one methylene group from methyl (**231**) to hexyl (**296**). The enantiomeric excess drops gradually from methyl (**231**, 86% *ee*) to butyl (**294**, 80% *ee*) and then remains at circa 80% *ee*. With longer chain lengths, the yields are higher which we attribute to a decreased product volatility. Benzyl substituted enone **248** provided photoadduct **297** in 58% *ee*. The benzyl group is sterically more demanding than the linear alkyl chains. This may result in poor catalyst coordination, therefore potentially favoring the background reaction of the uncomplexed enone **248**. The natural products (–)-grandisol (**15**) and sterpurene (**232**) can be accessed from enantioenriched adduct **231**.[18,223]



Scheme 63. Product scope **XXXII** of the enantioselective reaction of enones **XXII** and ethylene. [a]Yields are based on recovered starting material.

Various cyclic enones **XXII** enantioselectively furnished photoadducts **XXXII** with ethylene (Scheme 63). The photoadducts **XXXII** were isolated in 46-88% yield and 55-93% *ee*. A further series of incremental alkyl chain elongation from methyl to butyl in photoadducts **299**-**302** was investigated. In contrast to our previous observations of adducts **231**, **292**-**296**, here, there is a significant decrease in enantioselectivity from ethyl (**300**, 80% *ee*) to propyl (**301**, 55% *ee*). Product **302** bearing a butyl side chain shows a slightly higher enantiomeric excess of 59%. Comparing the photoadducts with 4,4-dimethyl (**298**) and 5,5-dimethyl (**303**) substitution, the latter shows a lower enantiomeric excess (70% *ee*). Photoadducts **304** and **233** originating from cyclopentenones were obtained with excellent enantiomeric excess (90% and 93%). The low isolated yields are attributed to an observed increased product volatility. Photoadduct **233** can be converted to (–)-grandisol (**15**) and cerapicol (**234**).[207,224] It is noteworthy that the yield of photoadduct **304** (46%) was higher when using catalyst **207**, in contrast to the racemic reaction yielding photoadduct *rac*-**304** in 14%. In accordance with previous reports, upon irradiation, photoadduct *rac*-**304** undergoes a *Norrish*-Type I cleavage between carbon atom 1 and 2 followed by a γ hydrogen abstraction providing cyclobutenylpropanal.[236,242-245] The formation of this side product is inhibited by the catalyst **207** and therefore a higher yield was obtained.

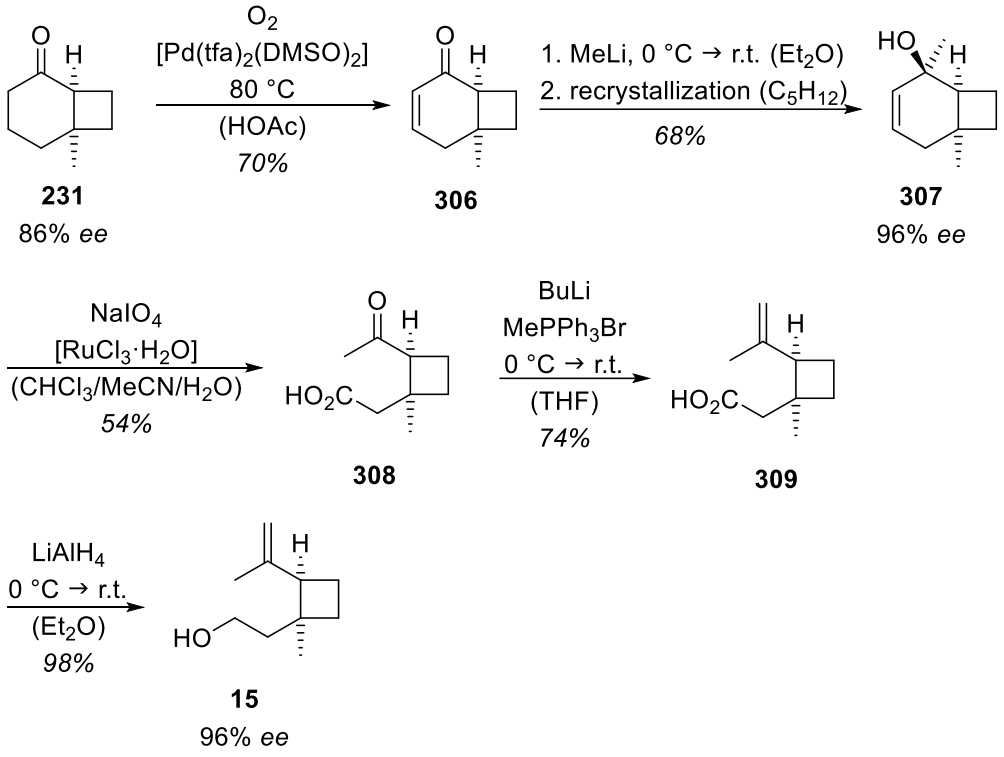


Scheme 64. Product scope **XXXIV** of the enantioselective reactions of enones **235** and **238** and various alkenes **XXXIII**.

The limits of this method became evident when 2,3-dimethylbutene (**236**) and cyclopentene were employed (Scheme 64). Photoadduct **305** was obtained in a low yield of 14% with 46% *ee*. The combination of cyclopentenone and cyclopentene provided photoadduct **5** with high enantiomeric excess (86%) but in low yield of 12%. Consequently, alkenes with terminal substitution and cyclic alkenes were not well tolerated.

3.5 Enantioselective Total Synthesis of (–)-Grandisol

In order to showcase the applicability of this method, (–)-grandisol (**15**) was chosen as a target compound. Starting from photoadduct **231**, a modified version of the synthetic route first reported by *Silverstein* was followed (Scheme 65).[209]



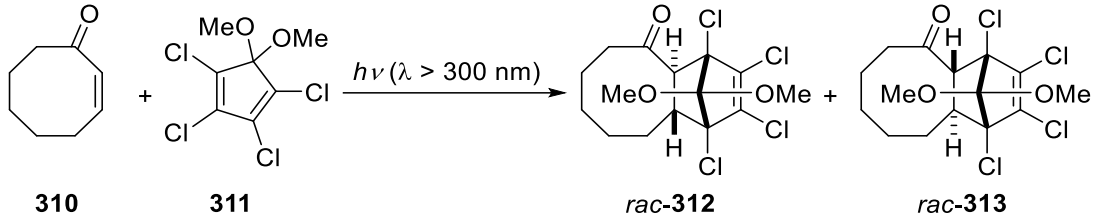
Scheme 65. Total synthesis of enantioenriched (–)-grandisol (**15**).

A catalytic *Saegusa* oxidation of photoadduct **231** provided α,β-unsaturated ketone **306** in 70% yield. The reaction was carried out following a protocol reported by the group of *Stahl*.[246,247] Methyllithium was added to the carbonyl group yielding allyl alcohol **307**. A recrystallization from pentane at –20 °C resulted in an increased enantiomeric excess from 86% to 96% and 68% isolated yield. The double bond of **307** was oxidatively cleaved with sodium periodate and catalytic ruthenium(III) chloride. Keto acid **308** was isolated in 54% yield. Due to the formation of side products, the isolated yield was moderate. A methylenation of **308** was achieved by a *Wittig* reaction generating acid **309** in 74% yield. Finally, a reduction of acid **309** with lithium aluminum hydride furnished the target compound (–)-grandisol (**15**) in excellent yield (98%) and 96% *ee*. Consequently, we have developed a concise route to (–)-grandisol (**15**) within six steps and an overall yield of 13% starting from 3-methylcyclohexenone (**205**).

4. *Cis-Trans* Isomerizations of Cyclic Enones

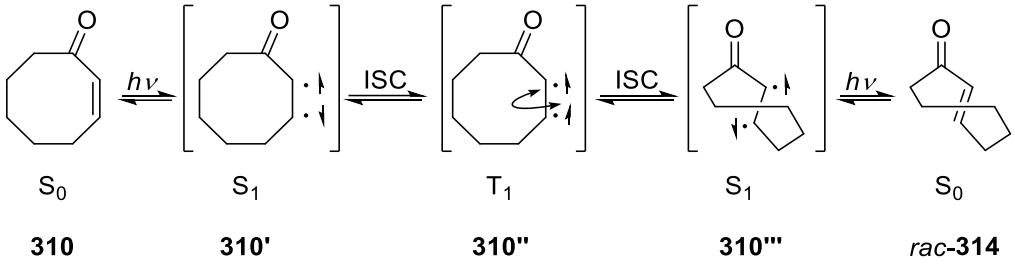
4.1 Literature Background and Project Aims

The isomerization of *cis*-cyclooctenone (**310**) to its *trans* isomer *rac*-**314** upon irradiation with UV light was first described by *Eaton* in 1964. It was shown that the reactivity of *cis*-enone **310** towards 1,3-diene **311** was dramatically increased under UV light irradiation (Scheme 66). The relative stereochemistry of the former ethylenic protons in the products *rac*-**312** and *rac*-**313** was observed to be *trans*. This indicates that the thermal *Diels-Alder* reaction proceeds only via the energetically higher *trans*-species *rac*-**314**.[248]



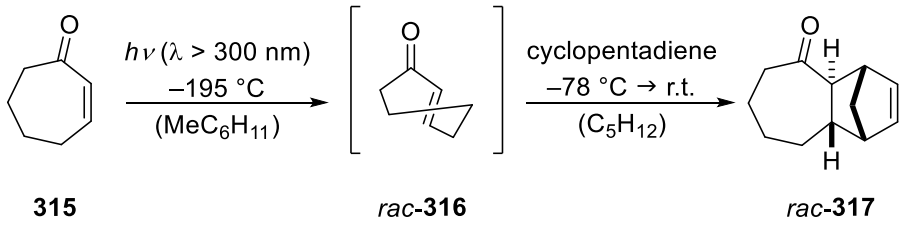
Scheme 66. *Diels-Alder* reaction of enone **310** with 1,3-diene **311** in the presence of UV light at room temperature.[248]

The eight-membered cyclic enone **310**, analogously to its smaller homologues, can be excited by UV light ($\lambda > 280$ nm) to the singlet state S_1 (**310'**). Here, the double-bond character is lost due to diradical formation (Scheme 67). Typically, enones rapidly undergo ISC to the triplet state T_1 (**310''**). The triplet state **310''** can then either be trapped in a subsequent excited state reaction or it can undergo radiative or nonradiative decay back to the singlet state S_0 via rotation about the α,β-bond (via S_1). This provides either the original conformation *cis* of enone **310** or the planar chiral *trans* isomer *rac*-**314**. As there are two possible ways for the rotation about α,β-bond to occur, the *trans* isomer *rac*-**314** is yielded as a racemate. Both isomers **310** and *rac*-**314** are in a photoequilibrium. Due to an internal ring strain-induced twist of the molecule, the π-orbitals in the *trans* isomer *rac*-**314** of the ethylenic carbons and the carbonyl group are not coplanar. This deconjugation leads to a loss of the ππ* transition, but as the nπ* transition tails into the region of 300 nm *rac*-**314** can still be photoexcited. Under the given conditions, the equilibrium of **310**: *rac*-**314** is 20:80.[248] The choice of a lightsource with a longer wavelength, e. g. $\lambda = 350$ nm, can shift the equilibrium in favor of *trans* isomer *rac*-**314**.



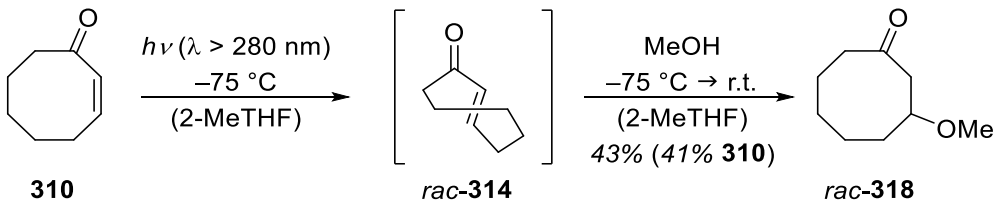
Scheme 67. Mechanistic pathway of a photo-induced isomerization of cyclooctenone (**310**).

In 1965, *Corey* and *Eaton* published back-to-back studies on the characterization and chemical properties of *trans*-cycloheptenone (*rac*-**316**). Due to its smaller ring size, the internal ring-strain of *trans*-cycloheptenone (*rac*-**316**) generated by photo-isomeriation is much higher. The highly reactive *trans* isomer *rac*-**316** was frozen in a low-temperature matrix. Upon treatment with cyclopentadiene as reaction partner in the absence of light, a *Diels-Alder* reaction led to the crossed adduct *rac*-**317** (Scheme 68).[249,250]



Scheme 68. *Diels-Alder* reaction of enone **315** with cyclopentadiene with UV light at low temperatures.[249]

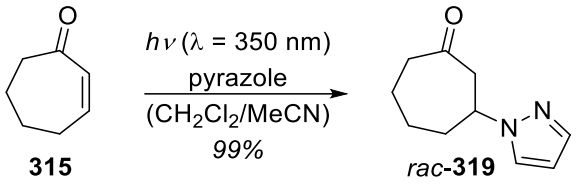
The group of *Noyori* investigated the reactivity of strained cyclic enones **310** and **315** towards protic solvents. The reactions proceeded with moderate yields. As was observed for the *Diels-Alder* reactions (see above), it was possible to conduct a *Michael* addition with a trapping experiment forming the alcohol adduct *rac*-**318** (Scheme 69). A trapping of *trans*-cycloheptenone (*rac*-**316**) with methanol, however, proved not to be possible.[251,252] The reactive *trans* isomer *rac*-**316** reacted with itself forming 1:1 adducts. This indicates a decreased reactivity towards *Michael* additions.



Scheme 69. Trapping of the instable *trans* isomer *rac*-**314** with methanol.[252]

A study by *Beauchemin* from 2007 reinvestigated the *Michael* addition reaction with *trans* configurated cyclic enones using nitrogen containing heterocycles as nucleophiles. High yields

as well as a broad product scope were obtained. Cycloheptenone (**315**) was converted with pyrazole in the presence of UV light with an excellent yield of adduct *rac*-**319** (Scheme 70).[253]



Scheme 70. *Michael* addition of pyrazole onto cycloheptenone **315** in the presence of UV light.

The photochemical *cis-trans* isomerization of cyclic enones with a ring size larger than six enables a simple access to highly energetic *trans* intermediates. Consequently, a method which achieves an enantioselective variant of the *cis-trans* photo-isomerization is of synthetic interest. To this date, the generation of enantiomerically pure *trans* isomers of cyclic enones has not been reported. Chiral oxazaborolidines proved to be suitable catalysts for cyclic enones in enantioselective [2+2] photocyclization addition reactions.[119,123] Having the same binding motif, enones **310** and **315** could bind analogously to the oxazaborolidines as cyclohexenone **238**. Here, the α,β-bond of complex **310·50'** could preferantially rotate clockwise away from the steric bulk of the aryl group of the catalyst **50'** (Figure 25).

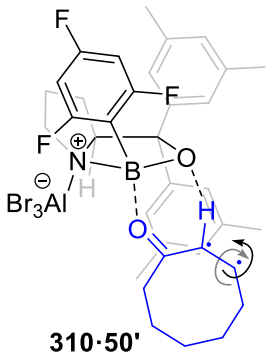
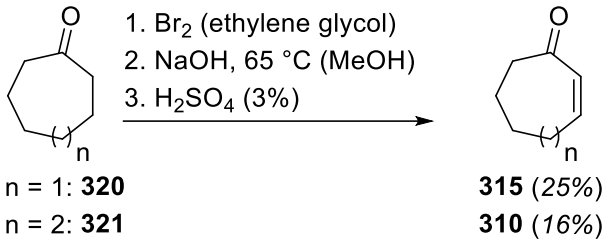


Figure 25. Putative model of the excited state complex **310·50'** with a favored (black arrow) and disfavored (grey arrow) rotation.

In order to establish an enantioselective *cis-trans* isomerization and a trapping of the enantiopure *trans* isomer, the following experimental procedure was considered: First, the substrates **310** or **315** should be irradiated in the presence of the oxazaborolidine catalyst **50** at –75 °C. After stopping the irradiation after an appropriate time, the formed *trans* conformer should be treated with a solution of pyrazole in dichloromethane. Finally, the resulting mixture should slowly warm to room temperature enabling the trapping of the *trans* isomer yielding an enantiopure adduct.

4.2 Synthesis of Irradiation Precursors and Isomerization Reactions

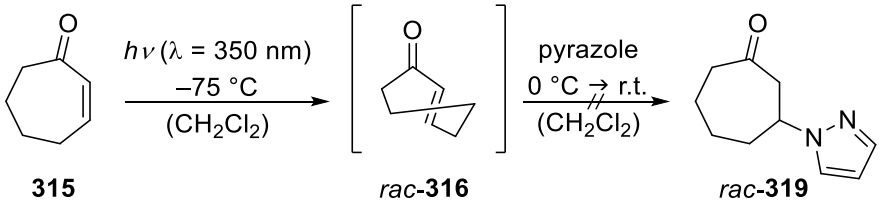
The synthesis of both cycloheptenone (**315**) and cyclooctenone (**310**) starting from the corresponding cyclic ketones **320** and **321** was conducted following a literature-known procedure by *Hanack* (Scheme 71).[254]



Scheme 71. Oxidation of ketones **321** and **322** to the corresponding enones **315** and **310** via elimination of hydrogen bromide.[254]

The commercially available ketones **320** and **321** were α-brominated in ethylene glycol. Concurrently, an acetalization was auto-catalyzed by the released hydrogen bromide. In the following step, hydrogen bromide is eliminated in an E1cB mechanism under basic conditions. The acetal is hydrolyzed with sulfuric acid providing the α,β-unsaturated ketones **315** and **310**. The observed low yields are presumably a result of the harsh reaction conditions and complex purification steps due to the unselective reaction course.

Similar to the protocol by *Beauchemin*, cycloheptenone (**315**) was irradiated in the presence of pyrazole in dichloromethane yielding 88% of the adduct *rac*-**319** (analogously to Scheme 70). Although, acetonitrile was omitted as the solvent, the yield remained high. The reaction still proceeded using dichloromethane as a single solvent thus demonstrating compatibility with the previously optimized conditions for enantioselective photoreactions with oxazaborolidines. The trapping experiment of *trans*-cycloheptenone (*rac*-**316**) with pyrazole proved to be unsuccessful (Scheme 72).

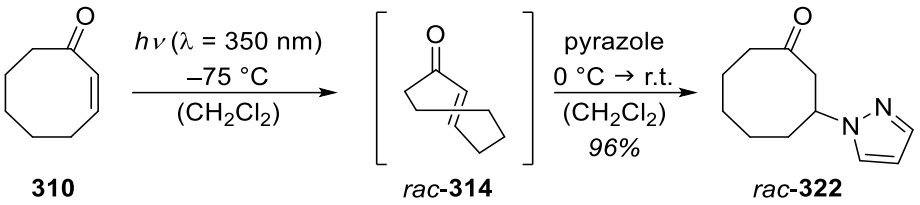


Scheme 72. Unsuccessful trapping of *trans*-cycloheptenone (*rac*-**319**) with pyrazole.

After a photochemical *cis-trans* isomerization of enone **315** to *trans*-enone *rac*-**316** at –75 °C, it was attempted to convert the highly reactive *trans* isomer *rac*-**316** with pyrazole in the absence of light. No product formation was observed, yet, there was nearly full conversion of

the starting material. A GC analysis revealed that the complex product mixture mainly consisted of 1:1 adducts of the starting material **315**. The *trans*-isomer **316** reacted with itself or the enone **315** even at 0 °C, before it could react in a *Michael* addition with pyrazole.

The trapping experiment was repeated with cyclooctenone (**310**) which proved to be suitable for such reaction conditions. Using the same reaction procedure, the trapping of the reactive *trans*-intermediate *rac*-**314** with pyrazole provided adduct *rac*-**322** in 96% yield (Scheme 73).

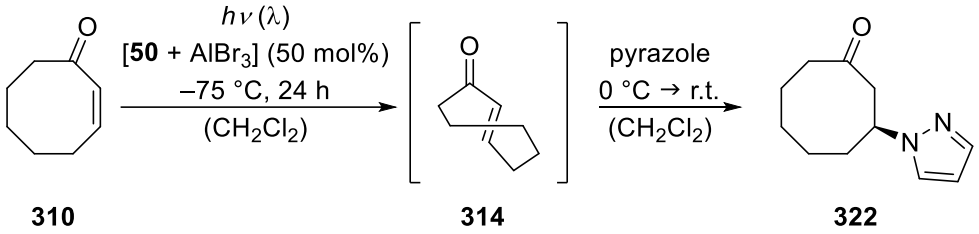


Scheme 73. Successful trapping of *trans*-cyclooctenone (*rac*-**314**) with pyrazole.

The occurence of a thermal background reaction between enone **310** and pyrazole had to be ruled out. Therefore, a solution of both **310** and pyrazole in dichloromethane was stirred at room temperature in the absence of light for 24 hours. No product formation was observed. In the presence of UV light ($\lambda = 350$ nm), the ketone *rac*-**322** was isolated in 97% yield (analogously to Scheme 70). Consequently, cyclooctenone (**310**) and pyrazole were chosen as appropriate reactants for the enantioselective version of the trapping experiment.

4.3 Attempted Enantioselective Isomerization Reactions

Analogously to the established racemic trapping reaction conditions, it was attempted to carry out the isomerization enantioselectively. The catalyst **50** was chosen as it had been proven to be highly effective in catalyzing enantioselective [2+2] photocycloaddition reaction of cyclic enones.[123] The catalyst loading was set at 50 mol%, since this proved to be the optimal catalyst loading for enantioselective [2+2] photocycloaddition reactions involving oxazaborolidines.[116,117,119,123]



310 **314** **322**

Table 9. Variation of the wavelength of the light source in the attempted enantioselective isomerization of **310**.

Entry	λ [nm]	Yield [%]	*ee* [%]
1	300	40	0
2	350	76	0
3	366	56	0
4[a]	350	92	0

[a]The irradiation took place over four hours and the nucleophile was added at –75 °C followed by warming to room temperature.

The irradiation of cyclooctenone (**310**) in the presence of catalyst **50** was carried out with light sources of different wavelengths λ (Table 9). The wavelength was increased stepwise: 300 nm, 350 nm and 366 nm (entry 1-3). The yields were moderate (40-76%) and no enantiomerically enriched product **322** was observed. Since the reaction provided the highest yield at a wavelength of λ = 350 nm, it was attempted to establish enantioselectivity by adding the nucleophile at –75 °C (entry 4). The yield was increased to 92%. An enantiomeric excess remained undetectable.

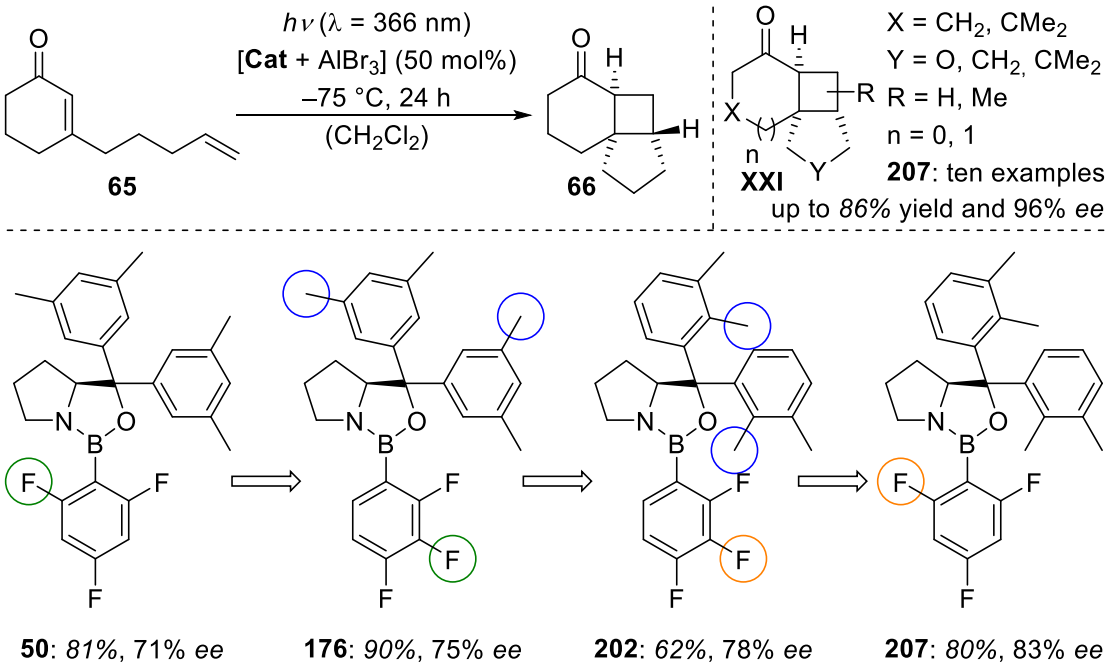
It was observed by *Eaton* that traces of mineral acid can trigger an isomerization of the *trans* isomer back to the *cis* isomer.[248] Aluminum bromide activated oxazaborolidines are sensitive towards traces of water and, thus upon hydrolysis can easily release traces of hydrogen bromide. This acid could be responsible for the relaxation of the *trans* isomer **314**. Comparing reaction conditions from entry 2 and 4, it is apparent that a lower temperature leads to higher yields. It

is possible that *trans*-enone **314** could be stable at –75 °C towards acid catalyzed isomerization. Nevertheless, an absence of enantiomeric access is not explained by the instability of the *trans* isomer **314**. The lack of enantioinduction is like due to catalyst **50** not being able to provide the required steric hinderance for an enantioselective reaction pathway.

In conclusion, the combination of *cis*-cyclooctenone (**310**) with catalyst **50** did not lead to the respective enantioenriched *trans*-cyclooctenone (**314**). A possible solution to the lack of enantioinduction in such a reaction could be a new choice of substrates which have a different binding motif. These could coordinate to more appropriate catalysts which have a more suitable steric environment for efficient enantiodifferentiation.

5. Conclusion And Future Work

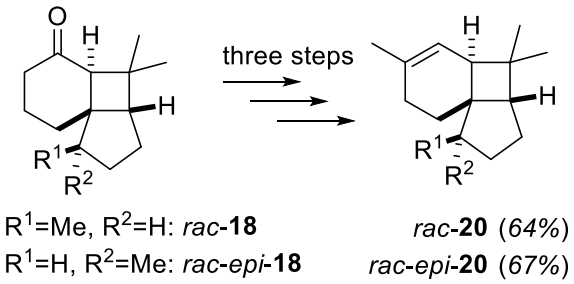
Following up on previous studies,[118] the aim of the first project was to identify the optimal reaction conditions and the optimal catalyst for the enantioselective intramolecular [2+2] photocycloaddition of irradiation precursor **65**. A library of catalyst precursors was synthesized and first results showed that prolinol derivatives were more proficient than their valine-derived analogues. We identified catalyst **207** as the optimal catalyst for the enantioselective transformation of substrate **65** (Scheme 74). The optimization involved screenings of the boronic acid (**50** to **176**) and the prolinol backbone (**176** to **202**) and a final variation of the boronic acid (**202** to **207**). The activating Lewis acids were varied and aluminum bromide proved to be the most powerful with respect to yield and enantioselectivity. Having established the optimal reaction parameters, ten substrates were subjected to the enantioselective catalytic reaction conditions furnishing photoadducts **XXI** in yields up to 86% and enantiomeric excesses up to 96% *ee*. Terminally substituted alkenes were not well tolerated by catalyst **207**. Finally, the absolute configuration of the product was identified by a *Mosher* ester analysis.



Scheme 74. Summary of the enantioselective intramolecular [2+2] photocycloadditions.

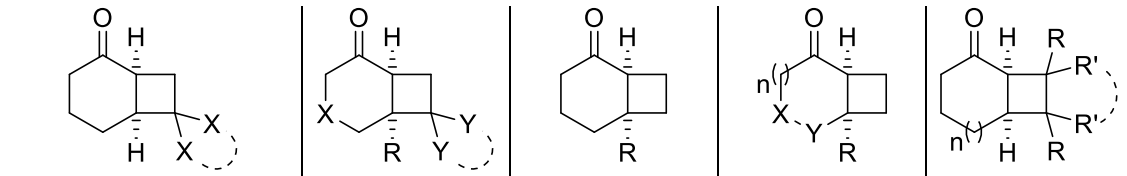
Following this, we established a concise synthetic route to *rac*-italicene (*rac*-**20**) and *rac*-isoitalicene (*rac-epi*-**20**) starting from previously separated diastereomeric photoadducts *rac*-**18** and *rac-epi*-**18** respectively (Scheme 75). The reaction sequence involved an α-methylation, enolate triflation and protodetriflation furnishing *rac*-**20** and *rac-epi*-**20** in overall yields of 64% and 67% respectively. In an attempt to diastereoselectively synthesize the

natural products, a stereodivergent parallel kinetic resolution was carried out in order to obtain enantiomerically enriched photoadducts **18** and *epi*-**18**. The selectivity factors, however, of catalysts **50** (2.1) and **176** (1.5) were low. Due to low yields and moderate enantioselectivities of the photoadducts **18** and *epi*-**18**, the method proved to be impractical for the stereoselective total synthesis of italicene (**20**) and isoitalicene (*epi*-**20**).



Scheme 75. New synthetic route to *rac*-italicene (*rac*-**20**) and *rac*-isoitalicene (*rac*-*epi*-**20**).

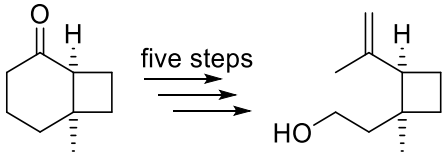
The intermolecular [2+2] photocycloaddition of simple enones with ethylene and isobutene represents a powerful synthetic tool for the synthesis of numerous natural products.[19] In this context we set out to employ the optimal catalyst for the enantioselective intramolecular [2+2] photocycloaddition in the intermolecular variant with structurally similar cyclohexenone and cyclopentenone derivatives as irradiation precursors. Catalyst **207** tolerated symmetrically 1,1-disubstituted alkenes which were simple hydrocarbons bearing chloro-substituents, ether groups or no functionalizations. Four categories of irradiation precursor and alkene combinations were well tolerated by the catalyst. The product scope of these categories consists of 30 combinations of cyclopentenone and cyclohexenone derivatives with ethylene and 1,1-disubstituted alkenes with yields up to 93% and enantiomeric excesses up to 96%. The fifth category involves combinations with miscellaneous alkenes such as 2,3-dimethylbut-2-ene and cyclopentene, which were not tolerated by the catalyst. Several photoadducts represent starting materials for enantioselective formal syntheses of the natural compounds caryophyllene (**6**), isocaryophyllene (**228**)[15,16], quadrone (**230**)[205], sterpurene (**232**)[223], (–)-grandisol (**15**)[207] and cerapicol (**234**)[224]. This showcases the potential synthetic utility of our method.



XXVIII	XXIX	XXXI	XXXII	XXXIV
X: Me, Et, Cl, CH_2Cl **X--X:** $-(CH_2)_n-$ n = 4–6 $-(CH_2)_2O(CH_2)_2-$	**X:** CH_2, CMe_2 **Y:** Me, Et, Cl **Y--Y:** $-(CH_2)_5-$ **R:** H, Me	**R:** H, Me, Et, Pr, Bu, Pent, Hex, Bn	**n** = 0, 1 **X:** CH_2, CMe_2 **Y:** CH_2, CMe_2 **R:** H, Me, Et, Pr, Bu	**R,R':** Me **R'--R':** $-(CH_2)_3-$
eight examples up to 73% yield and 92% *ee*	six examples up to 81% yield and 96% *ee*	eight examples up to 93% yield and 86% *ee*	eight examples up to 88% yield and 93% *ee*	two examples up to 14% yield and 86% *ee*

Figure 26. Photoproducts of the enantioselective intermolecular [2+2] photocycloaddition divided in five categories. Conditions: $h\nu$ (λ = 366 nm), [**207**+$AlBr_3$] (50 mol%), –75 °C, 24 h in dichloromethane.

Following a modified literature-known synthetic route,[209] we applied our method to the first enantioselective total synthesis of (–)-grandisol (**15**). Starting from photoadduct **231** (86% *ee*), the target compound **15** was obtained in an overall yield of 19% over five steps. Purification by recrystallization increased the enantiomeric excess to 96%.



231 86% *ee* — **15** *19%*, 96% *ee*

Scheme 76. Enantioselective total synthesis of (–)-grandisol (**15**) starting from photoadduct **231**.

Our studies on oxazaborolidine catalyzed enantioselective intra- and intermolecular [2+2] photocycloadditions showed that it is possible to expand the scope of irradiation precursors as long as the chromophore is not substantially influenced by substituents. Furthermore, it was possible to carry out enantioselective intermolecular [2+2] photocycloadditions which were considered to be impossible taking into account the previous results obtained in our group.[225] We hypothesize, that it is possible to individually find a suitable oxazaborolidine catalyst for each chromophore, by employing the following optimization procedure: 1st variation of the boronic acid, variation of the prolinol backbone, 2nd variation of the boronic acid. In recent years, visible light has played a major role in photochemistry.[87] Consequently, it should be considered to employ chromophores that potentially can absorb light at higher wavelengths. Derivatives of chromone[255] **323**, thiochromone[256] **324**, 4-oxoquinolone[257] **325**, naphtoquinone[258] **326**, benzoquinone[259] **327**, methyl cinnamate[260] **328**, benzalacetone[261]

329, and chalcone[262] **330** could be potential irradiation precursors that can be directly excited with visible light upon coordination to our catalysts (Figure 27). Furthermore, it is likely that the triplet energy of these substrates could be lowered, hence, enabling the sensitization with an iridium- or ruthenium-based photocatalysts. In this case, the activating Lewis acid aluminum bromide, which is crucial in the direct excitation variant,[121] could be substituted with a Brønsted acid in order to establish a more moisture tolerant and temperature stable catalyst.

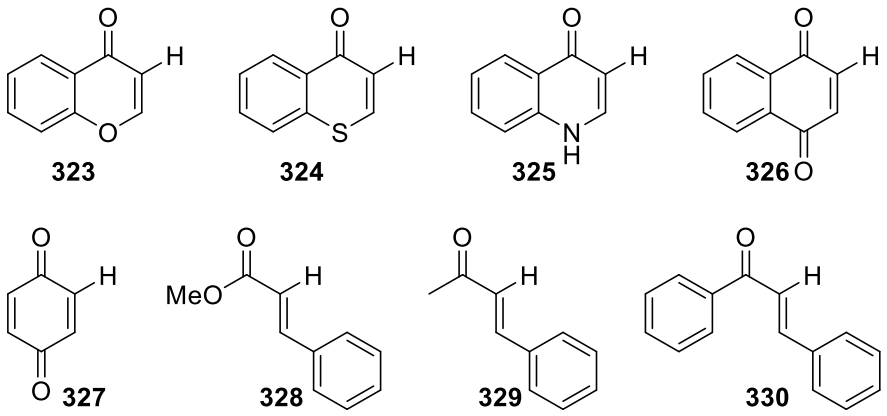
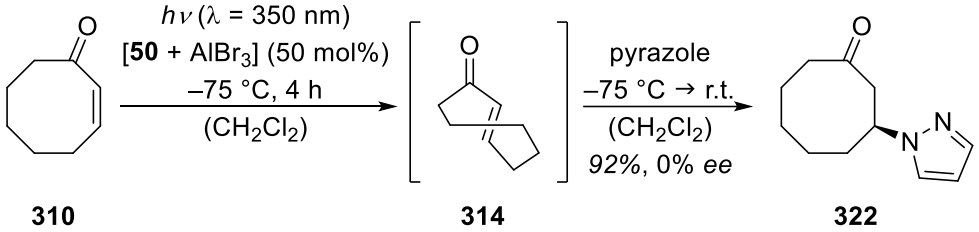


Figure 27. Potential irradiation precursors for enantioselective intermolecular [2+2] photocycloadditions.

Since oxazaborolidines proved to be powerful catalysts for the enantioselective [2+2] photocycloaddition, we considered the application of this catalyst class in further photochemical reactions. It is known that seven- and eight-membered cyclic enones can be photochemically isomerized to the respective *trans* isomers.[248-250] These highly energetic intermediates caught our attention because of their potential synthetic utility. Consequently, we attempted to enantioselectively *cis-trans* isomerize *cis*-cyclooctenone (**310**) by employing catalyst **50** (Scheme 77). However, no enantioselectivity was detected in our trapping reactions with pyrazole. We assume that a modified substrate class with further functionalities might be necessary in order to establish different binding motifs for appropriate catalysts.



Scheme 77. Attempted enantioselective *cis-trans* isomerization of cyclooctenone (**310**).

In a recent study of our group it was demonstrated that oxazaborolidine catalysts can be employed in enantioselective intermolecular *ortho*-photocycloadditions of phenanthrene-9-carboxaldehydes with various olefins.[263] Consequently, it is highly probable

that oxazaborolidines could be employed as catalysts in enantioselective variants of further photochemical reactions, e. g. *meta*-photocycloaddition[264] and oxa-di-π-rearrangement[265], which would lead to new enantiomerically enriched complex structures.

6. Experimental

6.1 General Information

6.1.1 Reaction Conditions

All air and moisture sensitive reactions were carried out in heat gun-dried glassware under an argon atmosphere using standard *Schlenk* techniques. Room temperature refers to 22-26 °C. Temperatures of 0 °C were obtained using an ice/water bath. Temperatures of –78 °C were obtained using a dry ice/*iso*-propanol bath. Temperatures of –116 °C were obtained using a liquid nitrogen/ethanol bath.

6.1.2 Solvents

For moisture sensitive reactions, tetrahydrofuran (THF), diethyl ether (Et_2O) and dichloromethane (CH_2Cl_2) were dried using a MBSPS 800 *MBraun* solvent purification system. The following columns were used: Tetrahydrofuran: 2 × MB-KOL-M type 2 (3 Å molecular sieve); Diethyl ether: 1 × MB-KOL-A type 2 (aluminum oxide), 1 × MB-KOL-M type 2 (3 Å molecular sieve); Dichloromethane: 2 × MB-KOL-A type 2 (aluminum oxide). The following dry solvents are commercially available and were used without further purification: Toluene: *Acros Organics*, 99.8% extra dry, over molecular sieves. For photochemical reactions, dry dichloromethane was degassed by three freeze-pump-thaw cycles and stored over 4 Å molecular sieves. Technical solvents [pentane (P), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), methanol (MeOH), *n*-hexane (nHex), ethyl acetate (EtOAc), cyclohexane (cHex)] were distilled prior to column chromatography.

6.1.3 Reagents

Commercially available chemicals were purchased from the suppliers *ABCR*, *Acros*, *Alfa-Aesar*, *Sigma-Aldrich* (now *Merck* KGaA), and *TCI*, and were used without further purification. For isomerizations of the photoproducts, basic alumina (*Merck*, aluminum oxide 90 active basic, 0.063-0.200 mm) was used.

6.2 Analytical Methods and Equipment

6.2.1 Irradiation Equipment

Photochemical experiments were carried out in heat gun-dried *Duran* tubes in a positive geometry setup (cylindrical array of 16 fluorescent tubes, 8 W nominal power) with the sample placed in the center of the illumination chamber. Fluorescent tubes of the type *Rayonet* RPR-3000 Å (λ_{max} = 300 nm), *Hitachi* UV-A (BI-B) (λ_{max} = 350 nm), *Philips* Blue Light (λ_{max} = 366 nm) and *Rayonet* RPR-4190 Å (λ_{max} = 419 nm) were employed. Enantioselective reactions were carried out at –75 °C using a *Duran* cooling finger which was attached to a high-performance cryostat (*Huber* CC80).

6.2.2 Ozonolysis Equipment

Ozone was generated by a *FisherTechnology* ozone-generator Type 502.

6.2.3 Chromatography

Flash column chromatography was performed with silica 60 (*Merck*, 230-400 mesh) as the stationary phase with the indicated eluent mixtures. Deactivation of neutral alumina (*Merck*, aluminum oxide 90 active neutral, 70-230 mesh) was carried out by the addition of 36 wt% water in small portions. Subsequently, the powder was spreaded in a petri dish and was allowed to dry on air for at least two days. Thin Layer Chromatography (TLC) was performed on silica coated glass plates (*Merck*, silica 60 F254) with detection by UV-light (λ = 254 nm) and/or by staining with a potassium permanganate solution [$KMnO_4$] or with a cerium ammonium molybdate solution [CAM] followed by heat treatment: $KMnO_4$-staining solution: potassium permanganate (3.00 g), potassium carbonate (20.0 g) and aqueous sodium hydroxide solution (5 wt%, 5.00 mL) in water (300 mL). CAM-staining solution: cerium sulfate tetrahydrate (1.00 g), ammonium molybdate (25.0 g) and concentrated sulfuric acid (25.0 mL) in water (250 mL).

6.2.4 Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR-spectra were recorded at room temperature either on a *Bruker* AVHD-300, AVHD-400, AVHD-500 or an AV-500 cryo. ^{1}H NMR spectra were referenced to the residual proton signal of chloroform-d_1 (δ = 7.26 ppm), methanol-d_4 (δ = 3.31 ppm), benzene-d_6 (δ = 7.16 ppm) or deuterium oxide (δ = 4.79 ppm). ^{13}C NMR spectra were referenced to the ^{13}C-D triplet of $CDCl_3$ (δ = 77.16 ppm), to the ^{13}C-D septet of CD_3OD (δ = 49.00 ppm) or to the ^{13}C-D triplet

of C_6D_6 (δ = 128.06 ppm). ^{19}F NMR spectra were referenced to the ^{19}F signal of CCl_3F (δ = 0 ppm). Apparent multiplets which occur as a result of coupling constant equality between magnetically non-equivalent protons are marked as virtual (*virt*.). The following abbreviations for single multiplicities were used: *br*-broad, s-singlet, d-doublet, t-triplet, q-quartet, quint-quintet, sext-sextet, sept-septet. Assignment and multiplicity of the ^{13}C NMR signals were determined by two-dimensional NMR experiments (COSY, HSQC, HMBC). Protons oriented above the molecular plane are labeled as α and those oriented below as β.

6.2.5 Infrared (IR) Spectroscopy

Infrared spectra were recorded on a *Perkin Elmer* Frontier IR-FTR spectrometer by ATR technique. The signal intensity is assigned using the following abbreviations: br (broad), vs (very strong), s (strong), m (medium), w (weak).

6.2.6 Mass Spectrometry (MS/HRMS)

Low resolution and high resolution mass spectra were recorded on a *Thermo Scientific* LTQ-FT Ultra (ESI) or a *Thermo Scientific* DFS-HRMS spectrometer (EI).

6.2.7 Melting Points (Mp)

All melting points were determined using a *Büchi* M-565 melting point apparatus, with a range quoted to the nearest integer.

6.2.8 UV/Vis Spectroscopy

UV/Vis spectra were measured on a *Perkin Elmer* Lambda 35 UV/Vis spectrometer. Spectra were recorded using a *Hellma* precision cell made of quartz SUPRASIL® with a pathway of 1 mm or 1 cm. Solvents and concentrations are given for each spectrum.

6.2.9 Chiral Gas Chromatography (GC)

Chiral GC analysis was performed on an *Agilent* 7890 B gas chromatograph using an *Agilent* Cyclosil-B column (30 m × 0.25 mm × 0.25 µm, SN: USF620714H) or a *Macherey-Nagel* Lipodex E column (25 m × 0.25 mm, SN: 23393-92) with a flame ionization detector. The temperature method is given for the corresponding compounds.

6.2.10 High-Performance Liquid Chromatography (HPLC)

Chiral HPLC was performed on a *Thermo-Fisher* HPLC system comprising a SR3000 solvent rack, a LPG3400 SD pump, a WPS-3000 SL autosampler, a TCC-3000 SD column compartment and a DAD-3000 UV/Vis detector fitted with the appropriate *Daicel* column as chiral stationary phase (flow rate: 1.0 mL/min, *Daicel* column, time and eluent are given for the corresponding compounds).

6.2.11 Polarimetry

Optical rotations were recorded on a Bellingham+Stanley ADP440+ polarimeter using a cuvette with a path length of 0.05 dm. All measurements were performed using the sodium D line ($\lambda = 589$ nm) at room temperature. The specific rotation is reported as follows: $[\alpha]_D^T = 100\times\alpha/(l\times c)$ [10^{-1} grad cm^2 g^{-1}] (α: optical rotation [deg], l: path length [dm], c: concentration of sample [g/100 cm^3]).

6.3 Synthetic Procedures and Analytical Data

6.3.1 General Procedures

General Procedure 1: *Grignard* Addition to Benzylprolinesters

In analogy to a modified literature procedure:[152]

Grignard Reagent: Iodine (1.00 mol%) and *the respective aryl bromide* (5.00 mol%) were added in sequence to a suspension of activated magnesium turnings (2.50 equiv) in tetrahydrofuran (2.50 M) at room temperature. The reaction mixture was heated to 50 °C and as soon as the color changed from purple to brown to pale yellow, *the respective aryl bromide* (2.50 equiv) was added dropwise by a syringe pump (0.1 mL/min). The reaction mixture was stirred for one hour at 65 °C and subsequently cooled to 0 °C. In case the reaction mixture solidified, upon cooling, tetrahydrofuran was added until desolidification was observed.

Addition of Ester: A solution of proline methyl ester **77** (1.00 equiv) in tetrahydrofuran (2.50 M) was added dropwise by a syringe pump (0.1 mL/min) to *the respective arylmagnesium bromide* suspension. The reaction mixture was stirred at room temperature for *the respective amount of time*. After cooling to 0 °C, saturated aqueous ammonium chloride solution was added in order to quench the excess *Grignard* reagent. The layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried with brine and over sodium sulfate. After filtration, the solution was concentrated in vacuo. The residue was purified by column chromatography.

General Procedure 2: Hydrogenolysis of the Benzyl-Group

In analogy to a modified literature procedure:[152] Palladium on carbon (10 wt%) was added to a solution of *the respective benzyl-protected prolinol* **XIV** in methanol (125 mM) and acetic acid (6 vol%). [*Caution*: Prior to the addition of palladium on carbon, the reaction vessel should be flushed with inert gas since spontaneous combustion may occur.] The reaction vessel was first evacuated and purged with inert gas and subsequently evacuated and purged with hydrogen gas to ensure a complete hydrogen atmosphere. After stirring for *the respective amount of time* at room temperature, the reaction mixture was filtered through a pad of Celite and washed with small portions of methanol. The solvent was removed in vacuo and the residue was dissolved in a 1:1 mixture of ethyl acetate and aqueous sodium hydroxide solution (1.00 M). The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried with brine and over sodium sulfate. After filtration, the solution was concentrated in vacuo. The

residue was purified by column chromatography. Residual methanol was removed by azeotropic distillation (dichloromethane) and the product was dried for at least 24 hours in vacuo.

General Procedure 3: Synthesis of the Oxazaborolidine-Catalyst

In analogy to a modified literature procedure:[123] In a *Schlenk* round-bottom flask equipped with a toluene-filled *Dean-Stark* apparatus, a solution of *the respective prolinol* **XV** (1.00 equiv) and *the respective boronic acid* (1.00 equiv) in toluene (concentrations may vary) was heated at reflux. After three hours, the collected toluene was removed. Subsequently, half of the volume of toluene in the reaction vessel was distilled into the *Dean-Stark* trap and removed. The removed volume of toluene was replaced with anhydrous toluene and this procedure was repeated a second time. After stirring for 16 hours, toluene was slowly distilled under an argon flow. [*N.b.*: The level of the oil bath ought to remain below the level of solvent in the reaction vessel to avoid thermal decomposition of the catalyst.] Any remaining toluene was removed in vacuo over night. The oxazaborolidine should be freshly prepared for every enantioselective reaction to ensure reproducibility of the results.

General Procedure 4: Activation of the Oxazaborolidine-Catalyst

In analogy to a modified literature procedure:[123] A solution of aluminum bromide (1.00 M in dibromomethane, 1.00 equiv) was added to a solution of *the respective oxazaborolidine* (1.00 equiv) in dichloromethane (1.00 mL) at room temperature. The pale yellow solution turned, depending on the oxazaborolidine, to a color between brown and purple and was immediately transferred to the phototube, which was pre-filled with *the respective photoprecursor*, and the reaction vessel was subsequently washed with dichloromethane (2 × 1 mL).

General Procedure 5: *Grignard* Addition to Vinylogous Esters

In analogy to a modified literature procedure:[133]

Grignard Reagent: Iodine (1.00 mol%) and *the respective alkenyl bromide* (5.00 mol%) were added in sequence to a suspension of activated magnesium turnings (1.30 equiv) in tetrahydrofuran (2.50 M) at room temperature. The reaction mixture was warmed to 50 °C and after the color changed from purple to brown to pale yellow, *the respective alkenyl bromide* (1.30 equiv) was added dropwise by a syringe pump (0.1 mL/min). The reaction mixture was stirred for one hour at 65 °C and subsequently cooled to 0 °C. In case the reaction mixture solidified, upon cooling, tetrahydrofuran was added until desolidification was observed.

Addition of the Vinylogous Ester: A solution of *the respective vinylogous ester* (1.00 equiv) in tetrahydrofuran (2.50 M) was added dropwise by a syringe pump (0.1 mL/min) to the alkenylmagnesium bromide suspension. The reaction mixture was stirred at room temperature for *the respective amount of time*. After cooling to 0 °C, aqueous hydrochloric acid solution (1.00 M) was added and the resulting mixture was stirred for 15 minutes. The layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried with brine and over sodium sulfate. After filtration, the solution was concentrated in vacuo. The residue was purified by column chromatography.

General Procedure 6: Racemic Intramolecular [2+2] Photocycloaddition

A solution of *the respective irradiation precursor* (1.00 equiv) in dichloromethane (1-3 mL) was transferred to a Duran phototube. Dichloromethane was added until a concentration of 20 mM was reached. The solution was irradiated at λ = 366 nm for *the respective amount of time*. After complete conversion, the solvent was removed in vacuo. The residue was purified by column chromatography with the given eluent mixture. The obtained *cis*/*trans*-mixture was equilibrated over basic alumina in a small amount of dichloromethane over night. The suspension was filtered, washed with small portions of diethyl ether, and the filtrate was concentrated.

General Procedure 7: Enantioselective Intramolecular [2+2] Photocycloaddition

A solution of *the respective irradiation precursor* (1.00 equiv) in dichloromethane (1-3 mL) was transferred to a heat-gun dried Duran phototube and the vessel was washed twice with small portions of dichloromethane. Then, a solution of *the respective activated oxazaborolidine catalyst* (50.0 mol%) in dichloromethane (1-3 mL) was transferred to the reaction mixture and the vessel was washed with small portions of dichloromethane. Dichloromethane was added until a concentration of 20 mM was reached. The solution was cooled to –75 °C within 30 minutes and was subsequently irradiated at λ = 366 nm for 24 hours. The reaction mixture was poured into suspended silica in dichloromethane and the solvent was removed in vacuo. The dry-loaded product was purified by column chromatography with a given eluent mixture. The obtained *cis*/*trans*-mixture was equilibrated over basic alumina in a small amount of dichloromethane over night. The suspension was filtered, washed with small portions of diethyl ether, and the filtrate was concentrated.

General Procedure 8: *Grignard* Addition to Vinylogous Esters

In analogy to a modified literature procedure:[133]

Grignard Reagent: Iodine (1.00 mol%) and *the respective alkyl bromide* (5.00 mol%) were added in sequence to a suspension of activated magnesium turnings (1.30 equiv) in tetrahydrofuran (2.50 M) at room temperature. The reaction mixture was warmed to 50 °C and after the color changed from purple to brown to pale yellow, *the respective alkyl bromide* (1.30 equiv) was added dropwise by a syringe pump (0.1 mL/min). The reaction mixture was stirred for one hour at 65 °C and subsequently cooled to 0 °C. In case the reaction mixture solidified, upon cooling, tetrahydrofuran was added until desolidification was observed.

Addition of the Vinylogous Ester: A solution of *the respective vinylogous ester* (1.00 equiv) in tetrahydrofuran (2.50 M) was added dropwise by a syringe pump (0.1 mL/min) to the alkenylmagnesium bromide suspension. The reaction mixture was stirred at room temperature for *the respective amount of time*. After the cooling to 0 °C, aqueous hydrochloric acid solution (1.00 M) was added and the resulting mixture was stirred for 15 minutes. The layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried with brine and over sodium sulfate. After filtration, the solution was concentrated in vacuo. The residue was purified by column chromatography.

General Procedure 9: *Wittig*-Reaction of Ketones

In analogy to a modified literature procedure:[228] In a 250 mL three-necked round-bottom flask, sodium hydride (1.00 equiv) was washed with pentane (4 × 20 mL) under an argon atmosphere. Residual pentane was removed in vacuo. Dimethylsulfoxide (2.00 M) was added and the suspension was heated to 70 °C. After ten minutes, hydrogen gas evolved from the reaction mixture. The suspension was stirred with a balloon as a pressure equalizer for one hour until no gas evolution was observed. A solution of methyltriphenylphosphonium bromide (1.00 equiv) in dimethylsulfoxide (1.00 M) warmed at 60 °C was added continuously to the sodium methylsulfinylmethylide suspension which was cooled at 0 °C. The resulting yellow ylide solution was allowed to warm to room temperature and was stirred for 30 minutes. After cooling to 0 °C, *the respective ketone* (1.10 equiv) was added in one portion. The resulting mixture was allowed to warm to room temperature and was stirred for 15 minutes. Then, the reaction mixture was heated to 130 °C and the product was distilled in vacuo using a condensation bridge. The collected product was filtered through a short pad of silica in order to remove residual dimethylsulfoxide. A fractioned distillation was performed to remove the byproduct benzene.

Condensation Procedure for Gaseous Alkenes

The respective gaseous alkene was collected in a balloon and condensed into a phototube using liquid nitrogen and subsequently used at either –116 °C (for ethylene) or –78 °C (for isobutene). [*N.b.*: Condensation of the alkene was achieved by evacuating a Duran tube and refilling the vessel with *the respective gaseous alkene*. Subsequently, the vessel was cooled with liquid nitrogen (–196 °C) after which, condensation of *the respective gaseous alkene* was observed. Finally, the vessel was placed under an argon atmosphere (balloon).]

General Procedure 10: Racemic Intermolecular [2+2] Photocycloaddition

A solution of *the respective irradiation precursor* (1.00 equiv) in dichloromethane (1-3 mL) was added to a Duran phototube containing *the respective alkene* (50.0 equiv). Dichloromethane was added until a concentration of 20 mM was reached. The solution was irradiated at λ = 366 nm for *the respective amount of time* and after complete conversion, the solvent was removed in vacuo. The residue was subjected to a work-up procedure (see WP1 or WP2).

When gaseous alkenes were used, see Condensation Procedure for Gaseous Alkenes. Approximately 1 mL of gaseous alkene was condensed into the phototube. Using ethylene, reactions were performed at –75 °C or –40 °C since ethylene has a low solubility in dichloromethane. Reactions with isobutene were performed at room temperature.

General Procedure 11: Enantioselective Intermolecular [2+2] Photocycloaddition

A solution of *the respective irradiation precursor* (1.00 equiv) in dichloromethane (1-3 mL) was added to a heat-gun dried Duran phototube containing *the respective alkene* (50.0 equiv) and the vessel was washed twice with small portions of dichloromethane. Then, a solution of *the respective activated oxazaborolidine catalyst* (50.0 mol%) in dichloromethane (1-3 mL) was transferred to the reaction mixture and the vessel was washed with small portions of dichloromethane. The phototube was filled with dichloromethane until a concentration of 20 mM was reached. The solution was cooled to –75 °C within 30 minutes and was subsequently irradiated at λ = 366 nm for 24 hours. The reaction mixture was poured into suspended silica in dichloromethane and the solvent was removed in vacuo. The dry-loaded product was then subjected to a work-up procedure (see WP1 or WP2).

When gaseous alkenes were used, see Condensation Procedure for Gaseous Alkenes. Approximately 1 mL of *the respective gaseous alkene* was condensed into the phototube.

Work-up Procedure 1:

The crude product was first subjected to a short column with a given eluent mixture. The obtained *cis*/*trans*-mixture was equilibrated over basic alumina in a small amount of dichloromethane over night. The suspension was filtered, washed with small portions of diethyl ether, and the filtrate was concentrated. The residue was dissolved with a small amount of dichloromethane and a catalytic amount of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**260**) was added. After three hours the solvent was removed in vacuo and the product mixture was purified by column chromatography with a given eluent mixture.

Work-up Procedure 2:

The crude product was subjected to column chromatography with a given eluent mixture. The obtained *cis*/*trans*-mixture was equilibrated over basic alumina in a small amount of dichloromethane over night. The suspension was filtered, washed with small portions of diethyl ether, and the filtrate was concentrated.

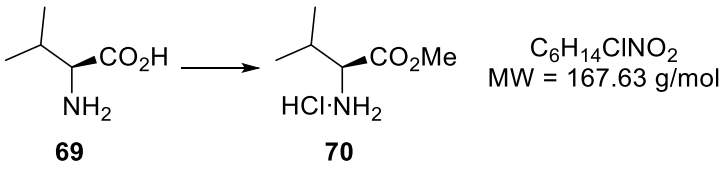
General Procedure 12: Oxidation of Ketones to Enones

In analogy to a modified literature procedure:[254] Bromine (1.00 equiv) was added dropwise to a solution of *the respective ketone* (1.00 equiv) in ethylene glycol (1.00 M) at 0 °C and the resulting brown solution was stirred for ten minutes. The reaction mixture was warmed to room temperature. After stirring for ten minutes, the mixture was poured into a stirring suspension of sodium carbonate (224 mg/mmol) in pentane (1.12 mL/mmol). Subsequently, water (1.12 mL/mmol) was added which turned the reaction mixture into an orange emulsion. The layers were separated and the aqueous layer was extracted with pentane three times. The organic layers were combined, dried over sodium sulfate and filtered. After removal of the solvent in vacuo, the residue was dissolved in methanol (2.23 M). Sodium hydroxide (112 mg/mmol) was added and the resulting solution was heated at reflux for three days. After cooling to room temperature, brine (1.12 mL/mmol) was added to the brown suspension and the layers were separated. The aqueous layer was extracted with pentane four times. The combined organic layers were washed with semi saturated aqueous sodium hydrogen carbonate solution, dried over sodium sulfate and filtered. After removal of the solvent in vacuo, the residue was partitioned between a 1:1 mixture of sulfuric acid (3 wt%) and diethyl ether (20 mL). The resulting emulsion was shaken for five minutes. The layers were separated and the aqueous layer was extracted with diethyl ether three times. The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate and dried over sodium sulfate. After

filtration, the solution was concentrated in vacuo. The residue was purified by column chromatography (silica, P/Et_2O = 9/1). [*N.b.*: This substrate is not bench-stable and should be stored under argon at –20 °C.]

6.3.2 Synthesis of Catalyst Precursors

Methyl L-valinate hydrochloride (70)



69 **70**

According to a literature procedure:[149] Thionyl chloride (30.5 g, 18.6 mL, 256 mmol, 3.00 equiv) was added dropwise to a suspension of amino acid **69** (10.0 g, 85.4 mmol, 1.00 equiv) in dry methanol (854 mM, 100 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was subsequently stirred for 29 hours. The solvent and the excess of thionyl chloride were removed in vacuo at 55 °C. After washing the residue with diethyl ether (5 × 50 mL) and drying in vacuo, ester **70** (13.3 g, 79.3 mmol, 93%) was obtained as a colorless solid.

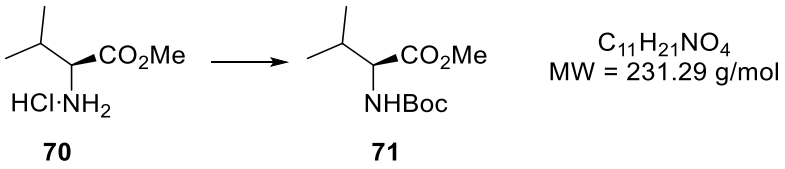
Mp: 170 °C.

^{1}H NMR (400 MHz, D_2O, 298 K): δ [ppm] = 1.04 (d, ^3J = 5.7 Hz, 3 H, CH*Me*Me), 1.06 (d, ^3J = 5.7 Hz, 3 H, CHMe*Me*), 2.37 (*virt.* septd, $^3J_1 \approx {}^3J_2$ = 7.0 Hz, $^3J_3$ = 4.7 Hz, 1 H, C*H*Me_2), 3.87 (s, 3 H, CO_2*Me*), 4.05 (d, ^3J = 4.7 Hz, 1 H, C*H*NH_3Cl).

^{13}C NMR (101 MHz, D_2O, 300 K): δ [ppm] = 17.0 (q, CH*Me*Me), 17.3 (q, CHMe*Me*), 29.3 (d, *C*HMe_2), 53.4 (q, CO_2*Me*), 58.4 (d, $CHNH_3Cl$), 170.4 (s, *C*O_2Me).

The analytical data obtained matched those reported in the literature.[149]

Methyl (*tert*-butoxycarbonyl)-L-valinate (71)



70 **71**

According to a literature procedure:[150] Sodium hydrogen carbonate (7.52 g, 89.5 mmol, 3.00 equiv) and di-*tert*-butyl dicarbonate (9.76 g, 44.7 mmol, 1.50 equiv) were added in sequence to a solution of ester **70** (5.00 g, 29.8 mmol, 1.00 equiv) in a 4:1 mixture of tetrahydrofuran and methanol (80 mL, 373 mM) at 0 °C. The resulting reaction mixture was allowed to warm to room temperature and was stirred for three days. Water (55 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 160 mL).

The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate solution (2 × 55 mL), dried with brine (2 × 55 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. After purification by column chromatography (silica, P/EtOAc = 30/1 → 4/1), ester **71** (6.77 g, 29.3 mmol, 98%) was obtained as a colorless oil.

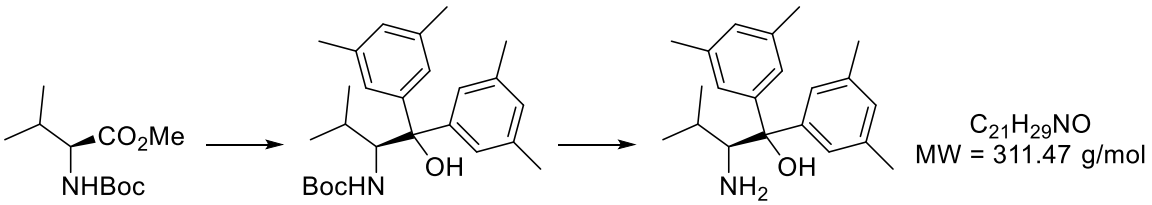
TLC: R_f = 0.28 (P/EtOAc = 6/1) [$KMnO_4$].

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.88 (d, ^3J = 6.9 Hz, 3 H, CH*Me*Me), 0.95 (d, ^3J = 6.9 Hz, 3 H, CHMe*Me*), 1.44 (s, 9 H, CO_2CMe_3), 2.01-2.18 (m, 1 H, C*H*Me$_2$), 3.73 (s, 3 H, CO_2Me), 4.22 (dd, $^3J_1$ = 9.4 Hz, $^3J_2$ = 3.0 Hz, 1 H, C*H*NHBoc), 5.01 (d, ^3J = 9.4 Hz, 1 H, CHN*H*Boc).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 17.8 (q, CH*Me*Me), 19.1 (q, CHMe*Me*), 28.5 (q, 3 C, CO_2CMe_3), 31.5 (d, *C*HMe$_2$), 52.2 (q, CO_2Me), 58.7 (d, *C*HNHBoc), 79.9 (s, CO_2CMe_3), 155.8 (s, *C*O_2CMe$_3$), 173.1 (s, *C*O_2Me).

The analytical data obtained matched those reported in the literature.[150]

(*S*)-2-Amino-1,1-bis(3,5-dimethylphenyl)-3-methylbutan-1-ol (73)



According to a literature procedure:[151]

Grignard Reagent: Iodine (11.0 mg, 43.2 μmol, 1.00 mol%) and 1-bromo-3,5-dimethyl-benzene (5.00 mol%) were added in sequence to a suspension of activated magnesium turnings (525 mg, 21.6 mmol, 5.00 eq) in tetrahydrofuran (21.6 mL, 1.00 M). The resulting mixture was heated at 55 °C until the color changed from purple to pale yellow. 1-Bromo-3,5-dimethylbenzene (2.94 mL, 4.00 g, 21.6 mmol, 5.00 equiv) was added dropwise by a syringe pump (0.1 mL/min) to the slightly boiling reaction mixture. The reaction mixture was heated at reflux at 66 °C and was subsequently stirred for one hour and subsequently cooled to 0 °C.

Addition of Ester: A solution of ester **71** (1.00 g, 4.32 mmol, 1.00 equiv) in tetrahydrofuran (1.73 mL, 2.50 M) was added dropwise by a syringe pump (0.1 mL/min) to the freshly prepared arylmagnesium bromide suspension. After stirring for one hour at 0 °C, the mixture was poured into ice-cooled saturated aqueous ammonium chloride solution (50 mL) in order to quench the

excess *Grignard* reagent. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 75 mL). The combined organic layers were dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. The crude product **72** was used without further purification in the next step.

Removal of the Boc-Group: Acetyl chloride (924 µL, 1.02 g, 13.0 mmol, 3.00 equiv) was added dropwise to dry methanol (11 mL) at 0 °C which resulted in a methanolic hydrochloric acid solution (1.25 M). The crude alcohol **72** was added dropwise to the acidic solution at room temperature. The reaction mixture was then heated at reflux at 90 °C for five hours. Sodium hydrogen carbonate was added until no gas evolution was observed in order to neutralize the excess of hydrochloric acid. The solvent was removed in vacuo and the residue was partitioned between a 1:1 mixture of aqueous sodium hydroxide solution (1.00 M) and ethyl acetate (150 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. Purification of the residue by column chromatography (silica, CH_2Cl_2/MeOH/NH_4OH(25%) = 100/1/0.5) afforded valinol **73** (824 mg, 2.65 mmol, 61% over two steps) as a yellow solid.

Mp: 153 °C.

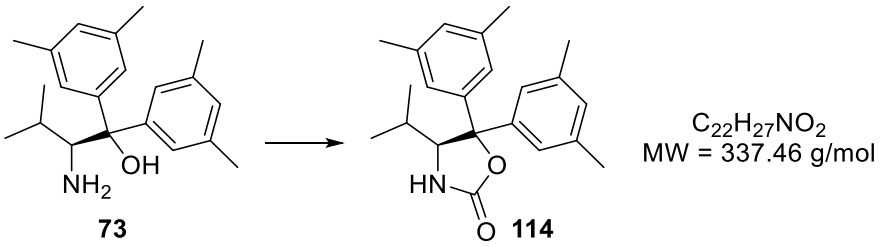
TLC: R_f = 0.49 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.89 (d, ^3J = 6.9 Hz, 3 H, CH*Me*Me), 0.94 (d, ^3J = 6.9 Hz, 3 H, CHMe*Me*), 1.73-1.82 (m, 1 H, C*H*Me$_2$), 2.28 (s, 6 H, 2 × C*H*$_3$-*m*-Ar), 2.30 (s, 6 H, 2 × C*H*$_3$-*m*-Ar), 3.79 (d, ^3J = 2.1 Hz, 1 H, C*H*NH$_2$), 6.80 (s, 1 H, H-*p*-Ar), 6.81 (s, 1 H, H-*p*-Ar), 7.09 (s, 2 H, 2 × H-*o*-Ar), 7.20 (s, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 16.4 (q, CH*Me*Me), 21.7 (q, 2 C, 2 × *C*H$_3$-*m*-Ar), 21.8 (q, 2 C, 2 × *C*H$_3$-*m*-Ar), 23.2 (q, CHMe*Me*), 27.8 (d, *C*HMe$_2$), 60.5 (d, CHNH$_2$), 79.8 (s, COH), 123.3 (d, 2 C, 2 × C-*o*-Ar), 123.7 (d, 2 C, 2 × C-*o*-Ar), 128.1 (d, C-*p*-Ar), 128.5 (d, C-*p*-Ar), 137.5 (s, 2 C, 2 × C-*m*-Ar), 137.9 (s, 2 C, 2 × C-*m*-Ar), 144.9 (s, C-*i*-Ar), 147.8 (s, C-*i*-Ar).

The analytical data obtained matched those reported in the literature.[151]

(*S*)-5,5-Bis(3,5-dimethylphenyl)-4-isopropyloxazolidin-2-one (114)



According to a modified literature procedure:[153] A solution of triphosgene (28.6 mg, 96.3 µmol, 1.00 equiv) in dichloromethane (1.5 mL, 64.2 mM) was added to a solution of valinol **73** (30.0 mg, 96.3 µmol, 1.00 equiv) and pyridine (15.5 µL, 15.2 mg, 2.00 equiv) in dichloromethane (1.5 mL, 64.2 mM) at 0 °C. The reaction mixture was allowed to warm to room temperature and was subsequently stirred for 16 hours. The excess triphosgene was quenched with brine (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. After purification by column chromatography (silica, cHex/EtOAc = 4/1), oxazolidinone **114** (31.5 mg, 93.3 µmol, 97%, 99% *ee*) was obtained as a colorless solid.

Mp: decomp. >270 °C.

TLC: R_f = 0.60 (P/EtOAc = 3/2) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3415 (m, NH), 2964 (m, sp^3-CH), 2923 (w, sp^3-CH), 2873 (w, sp^3-CH), 1757 (vs, C=O), 1235 (s).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.68 (d, ^3J = 6.5 Hz, 3 H, CH*Me*Me), 0.92 (d, ^3J = 7.0 Hz, 3 H, CHMe*Me*), 1.83-1.92 (m, 1 H, C*H*Me$_2$), 2.27 (s, 6 H, 2 × C*H*$_3$-*m*-Ar), 2.29 (s, 6 H, 2 × C*H*$_3$-*m*-Ar), 4.31 (d, ^3J = 3.3 Hz, 1 H, C*H*NH), 6.20-6.47 (m, 1 H, CHN*H*), 6.87 (s, 1 H, H-*p*-Ar), 6.90 (s, 1 H, H-*p*-Ar), 7.00 (s, 2 H, 2 × H-*o*-Ar), 7.14 (s, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 15.6 (q, CH*Me*Me), 21.1 (q, CHMe*Me*), 21.6 (q, 2 C, 2 × *C*H$_3$-*m*-Ar), 21.7 (q, 2 C, 2 × *C*H$_3$-*m*-Ar), 29.7 (d, *C*HMe$_2$), 65.9 (d, CHNH), 89.6 (s, CAr$_2$), 123.4 (d, 2 C, 2 × C-*o*-Ar), 124.0 (d, 2 C, 2 × C-*o*-Ar), 129.3 (d, C-*p*-Ar), 129.9 (d, C-*p*-Ar), 137.6 (s, 2 C, 2 × C-*m*-Ar), 138.0 (s, 2 C, 2 × C-*m*-Ar), 139.3 (s, C-*i*-Ar), 144.2 (s, C-*i*-Ar), 159.1 (s, CO).

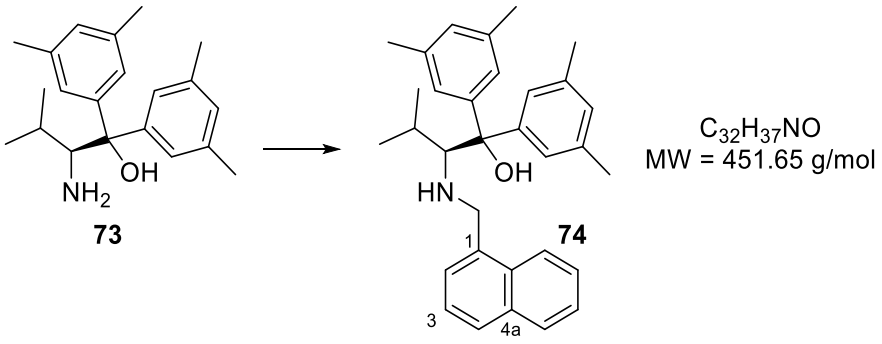
MS (EI, 70 eV): m/z (%) = 337 (3) $[M]^+$, 239 (56) $[C_{17}H_{18}O]^+$, 160 (41), 133 (22), 105 (40) $[C_8H_9]^+$, 91 (64), 43 (100) $[C_3H_7]^+$.

HRMS (EI, 70 eV): calcd for $C_{22}H_{27}O_2N$ $[M]^+$: 337.2036; found: 337.2049;
calcd for $C_{21}{}^{13}CH_{27}O_2N$ $[M]^+$: 338.2070; found: 338.2077.

Chiral HPLC: τ_R (major) = 9.2 min, τ_R (minor) = 11.4 min, [H_2O/MeCN = 50/50 → 0/100, 30 min], Chiralpak AS-RH, 150×4.6.

Specific Rotation: $[\alpha]_D^{25}$ = –212 (c = 0.22, CH_2Cl_2) [99% *ee*].

(*S*)-1,1-Bis(3,5-dimethylphenyl)-3-methyl-2-[(naphthalene-1-ylmethyl)amino]butan-1-ol (74)



According to a modified literature procedure:[112] Acetic acid (138 µL, 145 mg, 2.41 mmol, 1.50 equiv) was added to a solution of 1-naphthaldehyde (262 µL, 301 mg, 1.93 mmol, 1.20 equiv) and valinol **73** (500 mg, 1.61 mmol, 1.00 equiv) in methanol (13.4 mL, 120 mM) at 0 °C. After stirring for 15 minutes, sodium cyanoborohydride (303 mg, 4.82 mmol, 3.00 equiv) was added in one portion and the resulting solution was allowed to warm to room temperature. After 16 hours, the solvent was removed in vacuo and the yellow residue was partitioned between a 1:1 mixture of water and chloroform (40 mL). The layers were separated and the aqueous layer was extracted with chloroform (3 × 20 mL). The combined organic layers were dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. After purification of the residue by column chromatography (silica, cHex/EtOAc = 20/1), valinol **74** (553 mg, 1.22 mmol, 76%) was obtained as a pale yellow solid.

Mp: 137 °C.

TLC: R_f = 0.50 (cHex/EtOAc = 9/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3300 (w, NH), 3041 (w, sp^2-CH), 2945 (m, sp^3-CH), 2909 (m, sp^3-CH), 2862 (m, sp^3-CH), 2824 (m, sp^3-CH), 1597 (m, sp^2-CC), 772 (vs, sp^2-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.72 (d, ^3J = 7.0 Hz, 3 H, CH*Me*Me), 1.01 (d, ^3J = 7.0 Hz, 3 H, CHMe*Me*), 2.02-2.10 (m, 1 H, C*H*Me_2), 2.30 (s, 6 H, 2 × CH_3-*m*-Ar), 2.35 (s,

6 H, 2 × CH_3-*m*-Ar), 3.75 (d, ^3J = 2.0 Hz, 1 H, C*H*NH), 3.79-3.80 (m, 2 H, NHCH_2), 4.72 (br s, 1 H, COH), 6.80 (s, 1 H, H-*p*-Ar), 6.84 (s, 1 H, H-*p*-Ar), 7.22 (s, 2 H, 2 × H-*o*-Ar), 7.26 (d, ^3J = 6.3 Hz, 1 H, H-2), 7.36-7.40 (m, 2 H, H-Napht), 7.44 (*virt.* t, $^3J_1 \approx {}^3J_2$ = 7.5 Hz, 1 H, H-Napht), 7.47 (s, 2 H, 2 × H-*o*-Ar), 7.54 (d, ^3J = 8.4 Hz, 1 H, H-Napht), 7.75 (d, ^3J = 8.2 Hz, 1 H, H-Napht), 7.81 (d, ^3J = 8.0 Hz, 1 H, H-Napht).

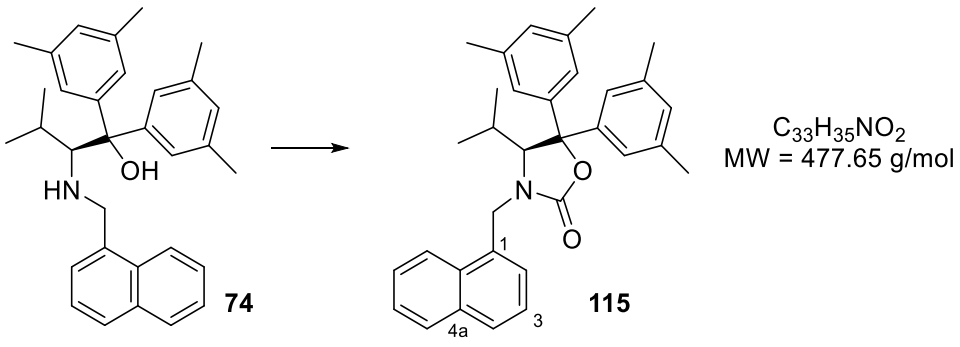
^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 16.3 (q, CH*Me*Me), 21.8 (q, 2 C, 2 × *C*H$_3$-*m*-Ar), 21.9 (q, 2 C, 2 × *C*H$_3$-*m*-Ar), 22.8 (q, CHMe*Me*), 29.0 (d, *C*HMe$_2$), 53.7 (t, NHCH$_2$), 69.4 (d, CHNH), 79.1 (s, COH), 123.5 (d, 2 C, 2 × C-*o*-Ar), 124.2 (d, 2 C, 2 × C-*o*-Ar), 124.6 (d, C-Napht), 125.5 (d, C-Napht), 125.8 (d, C-Napht), 126.2 (d, C-Napht), 126.8 (d, C-2), 128.0 (d, C-*p*-Ar), 128.3 (d, C-*p*-Ar), 128.3 (d, C-Napht), 128.6 (d, C-Napht), 132.0 (s, C-1), 134.0 (s, C-4a), 136.3 (s, C-8a), 137.3 (s, 2 C, 2 × C-*m*-Ar), 137.5 (s, 2 C, 2 × C-*m*-Ar), 145.3 (s, C-*i*-Ar), 149.4 (s, C-*i*-Ar).

MS (EI, 70 eV): m/z (%) = 433 (1) $[M–H_2O]^+$, 294 (4), 212 (5) $[C_{15}H_{18}N]^+$, 156 (19) $[C_{11}H_{10}N]^+$, 141 (65) $[C_{11}H_9]^+$, 128 (100), 115 (18), 105 (15) $[C_8H_9]^+$, 56 (12).

HRMS (EI, 70 eV): calcd for $C_{32}H_{35}N$ $[M–H_2O]^+$: 433.2764; found: 433.2755.

Specific Rotation: $[\alpha]_D^{25}$ = –43.5 (c = 1.15, CH_2Cl_2) [96% *ee*].

(*S*)-5,5-Bis(3,5-dimethylphenyl)-4-isopropyl-3-(naphthalen-1-ylmethyl)oxazolidin-2-one (115)



According to a modified literature procedure:[153] A solution of triphosgene (32.9 mg, 111 μmol, 1.00 equiv) in dichloromethane (2.00 mL, 55.5 mM) was added to a solution of valinol **74** (50.0 mg, 111 μmol, 1.00 equiv) and pyridine (17.8 μL, 17.5 mg, 2.00 equiv) in dichloromethane (2.00 mL, 55.5 mM) at 0 °C. The reaction mixture was allowed to warm to room temperature and was subsequently stirred for 19 hours. The excess triphosgene was quenched with brine (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over sodium sulfate.

After filtration, the solution was concentrated in vacuo. After purification by column chromatography (silica, cHex/EtOAc = 9/1), oxazolidinone **115** (46.6 mg, 976 μmol, 88%, 96% *ee*) was obtained as a colorless solid.

Mp: 200 °C.

TLC: R_f = 0.19 (cHex/EtOAc = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3055 (w, sp^2-CH), 2951 (m, sp^3-CH), 2919 (m, sp^3-CH), 2873 (m, sp^3-CH), 1735 (vs, C=O), 1223 (s, sp^3-CO), 771 (vs, sp^2-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.88 (d, ^3J = 6.7 Hz, 3 H, CH*Me*Me), 1.20 (d, ^3J = 7.3 Hz, 3 H, CHMe*Me*), 1.86-1.90 (m, 1 H, C*H*Me_2), 1.91 (s, 6 H, 2 × CH_3-*m*-Ar), 2.21 (s, 6 H, 2 × CH_3-*m*-Ar), 3.97 (d, ^3J = 1.7 Hz, 1 H, C*H*N), 4.40 (d, ^2J = 14.9 Hz, 1 H, NC*H*H), 5.59 (d, ^2J = 14.9 Hz, 1 H, NCH*H*), 6.42 (s, 1 H, H-*p*-Ar), 6.57 (s, 2 H, 2 × H-*o*-Ar), 6.78 (s, 1 H, H-*p*-Ar), 6.93 (s, 2 H, 2 × H-*o*-Ar), 7.07 (ddd, $^3J_1$ = 8.3 Hz, $^3J_2$ = 6.8 Hz, ^4J = 1.3 Hz, 1 H, H-Napht), 7.26-7.37 (m, 3 H, H-Napht), 7.52 (d, ^3J = 8.6 Hz, 1 H, H-Napht), 7.73 (d, ^3J = 8.2 Hz, 1 H, H-Napht), 7.78 (d, ^3J = 8.2 Hz, 1 H, H-Napht).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 16.1 (q, CH*Me*Me), 21.4 (q, 2 C, 2 × *C*H_3-*m*-Ar), 21.5 (q, 2 C, 2 × *C*H_3-*m*-Ar), 23.3 (q, CHMe*Me*), 30.1 (d, *C*HMe_2), 46.4 (t, NCH_2), 65.8 (d, *C*HN), 88.8 (s, CAr_2), 122.2 (d, 2 C, 2 × C-*o*-Ar), 123.6 (d, 2 C, 2 × C-*o*-Ar), 123.6 (d, C-Napht), 124.5 (d, C-Napht), 125.8 (d, C-Napht), 126.3 (d, C-Napht), 127.9 (d, C-Napht), 128.0 (d, C-Napht), 129.0 (d, C-*p*-Ar), 129.1 (d, C-Napht), 129.5 (d, C-*p*-Ar), 131.2 (s, C-Napht), 131.7 (s, C-Napht), 133.8 (s, C-Napht), 137.3 (s, 2 C, 2 × C-*m*-Ar), 137.6 (s, 2 C, 2 × C-*m*-Ar), 139.1 (s, C-*i*-Ar), 143.9 (s, C-*i*-Ar), 157.3 (s, CO).

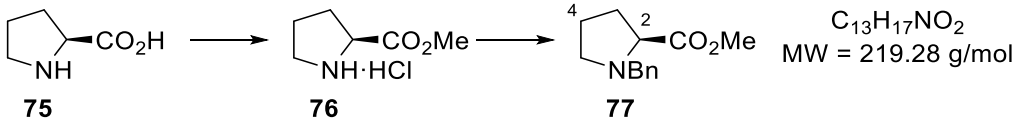
MS (EI, 70 eV): m/z (%) = 477 (1) $[M]^+$, 434 (6) $[M–C_3H_7]^+$, 390 (5), 278 (13) $[C_{21}H_{26}]^+$, 210 (11), 168 (12), 141 (100) $[C_{11}H_9]^+$, 111 (10), 97 (15), 85 (18), 71 (32), 57 (62).

HRMS (EI, 70 eV): calcd for $C_{33}H_{35}O_2N$ $[M]^+$: 477.2662; found: 477.2686.

Chiral HPLC: τ_R (major) = 17.3 min, τ_R (minor) = 18.1 min, [H_2O/MeCN = 50/50 → 0/100, 30 min], Chiralcel OD-RH, 150×4.6.

Specific Rotation: $[\alpha]_D^{25}$ = –77.1 (c = 1.17, CH_2Cl_2) [96% *ee*].

(*S*)-Methyl 1-benzylpyrroldine-2-carboxylate (77)



Esterification: Thionyl chloride (7.61 mL, 12.4 g, 104 mmol, 1.20 equiv) was added dropwise by a syringe pump (0.3 mL/min) to a solution of L-proline (**75**) (10.0 g, 86.9 mmol, 1.00 equiv) in methanol (174 mL, 500 mM) at 0 °C. The reaction solution was allowed to warm to room temperature and was subsequently stirred for three hours. The solvent and the excess of thionyl chloride were removed in vacuo. Residual methanol was removed by azeotropic distillation (toluene). The crude ester **76** was used without further purification in the next step.

Benzylation: Triethylamine (30.1 mL, 22.0 g, 217 mmol, 2.50 equiv) was added to a solution of the crude ester **76** in dichloromethane (80 mL, 1.00 M) at room temperature. After stirring for five minutes, a precipitate was formed which was filtered and washed with small portions of dichloromethane. The filtrate was concentrated and the residue was suspended in diethyl ether (100 mL), filtered, and washed with small portions of diethyl ether. The filtrate was concentrated and the residue was dissolved in diethyl ether (80 mL, 1.00 M), cooled to 0 °C and benzyl bromide (11.4 mL, 16.3 g, 95.5 mmol, 1.10 equiv) was added dropwise. The resulting mixture was allowed to warm to room temperature and was subsequently stirred for 24 hours. The formed precipitate was filtered and washed with small portions of diethyl ether. The filtrate was concentrated and the residue was purified by column chromatography (silica, cHex/EtOAc = 9/1) to provide ester **77** (15.0 g, 68.4 mmol, 79%) as a yellow oil.

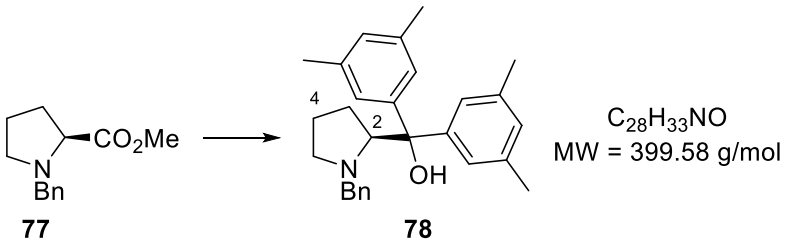
TLC: R_f = 0.32 (P/EtOAc = 4/1) [$KMnO_4$].

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.65-2.03 (m, 3 H, H-3, *H*H-4), 2.04-2.22 (m, 1 H, H*H*-4), 2.32-2.47 (m, 1 H, H-2), 2.99-3.10 (m, 1 H, *H*H-5), 3.20-3.29 (m, 1 H, H*H*-5), 3.57 (d, ^2J = 12.7 Hz, 1 H, C*H*HPh), 3.65 (s, 3 H, CO_2Me), 3.88 (d, ^2J = 12.7 Hz, 1 H, CH*H*Ph), 7.20-7.39 (m, 5 H, 5 × H-Ph).

^{13}C NMR (75.5 MHz, $CDCl_3$, 300 K): δ [ppm] = 23.1 (t, C-4), 29.5 (t, C-3), 51.9 (q, CO_2*Me*), 53.4 (t, C-5), 58.9 (t, *C*H_2Ph), 65.5 (d, C-2), 127.3 (d, 2 C, 2 × C-Ph), 128.3 (d, 2 C, 2 × C-Ph), 129.4 (d, C-Ph), 138.4 (s, C-Ph), 174.7 (s, *C*O_2Me).

The analytical data obtained matched those reported in the literature.[152]

(*S*)-(1-Benzylpyrrolidin-2-yl)bis(3,5-dimethylphenyl)methanol (78)



77 **78**

Following GP1, ester **77** (2.66 g, 12.1 mmol, 1.00 equiv) was converted with 1-bromo-3,5-dimethylbenzene (4.12 mL, 5.61 g, 30.3 mmol, 2.50 equiv), iodine (30.8 mg, 121 µmol, 1.00 mol%) and magnesium turnings (737 mg, 30.3 mmol, 2.50 equiv) within 16 hours. After purification by column chromatography (silica, cHex/EtOAc = 1/0 → 9/1), alcohol **78** (4.61 g, 11.5 mmol, 95%) was obtained as a yellow foam.

Mp: 45 °C.

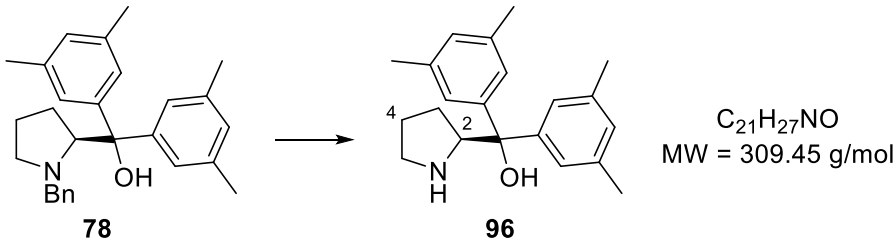
TLC: R_f = 0.49 (P/EtOAc = 9/1) [$KMnO_4$, UV].

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.56-1.70 (m, 2 H, H-4), 1.70-1.85 (m, 1 H, *H*H-3), 1.89-2.05 (m, 1 H, H*H*-3), 2.25 (s, 6 H, 2 × CH_3-*m*-Ar), 2.31 (s, 6 H, 2 × CH_3-*m*-Ar), 2.32-2.40 (m, 1 H, *H*H-5), 2.88-2.95 (m, 1 H, H*H*-5), 3.00 (d, ^2J = 12.7 Hz, 1 H, C*H*HPh), 3.15 (d, ^2J = 12.7 Hz, 1 H, CH*H*Ph), 3.86-3.93 (m, 1 H, H-2), 4.78 (br s, 1 H, COH), 6.72 (s, 1 H, H-*p*-Ar), 6.81 (s, 1 H, H-*p*-Ar), 7.02-7.09 (m, 2 H, 2 × H-*o*-Ph), 7.15-7.23 (m, 3 H, 2 × H-*o*-Ar, H-*p*-Ph), 7.23-7.28 (m, 2 H, 2 × H-*m*-Ph), 7.29 (s, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (75.5 MHz, $CDCl_3$, 300 K): δ [ppm] = 21.7 (q, 2 C, 2 × *C*H_3-*m*-Ar), 21.8 (q, 2 C, 2 × *C*H_3-*m*-Ar), 24.5 (t, C-4), 30.0 (t, C-3), 55.8 (t, C-5), 60.8 (t, *C*H_2Ph), 70.9 (d, C-2), 78.2 (s, COH), 123.6 (d, 2 C, 2 × C-*o*-Ar), 123.6 (d, 2 C, 2 × C-*o*-Ar), 126.9 (d, C-*p*-Ph), 128.0 (d, C-*p*-Ar), 128.1 (d, C-*p*-Ar), 128.2 (d, 2 C, 2 × C-*o*-Ph), 128.8 (d, 2 C, 2 × C-*m*-Ph), 137.4 (s, 2 C, 2 × C-*m*-Ar), 137.5 (s, 2 C, 2 × C-*m*-Ar), 140.1 (s, C-*i*-Ph), 146.6 (s, C-*i*-Ar), 148.0 (s, C-*i*-Ar).

The analytical data obtained matched those reported in the literature.[266]

(*S*)-Bis(3,5-dimethylphenyl)(pyrrolidin-2-yl)methanol (96)



Following GP2, alcohol **78** (4.61 g, 11.5 mmol, 1.00 equiv) was converted with palladium on carbon (461 mg, 10 wt%) under a hydrogen atmosphere (balloon) within 19 hours. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 1/0 → 50/1 → 10/1), the concentrated product was dissolved in hot hexane and filtered. The filtrate was concenctrated and residual hexane was removed by azeotropic distillation (dichloromethane). The residue was dried in vacuo for 48 hours at 60 °C. Prolinol **96** (3.10 g, 10.0 mmol, 87%) was obtained as a pale yellow solid.

Mp: 100 °C.

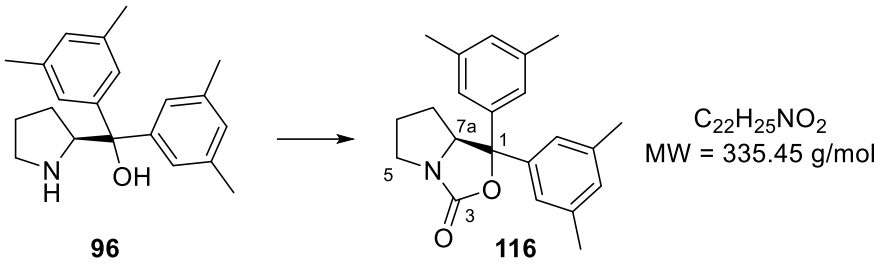
TLC: R_f = 0.15 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.56-1.78 (m, 4 H, H-3, H-4), 2.24 (s, 6 H, 2 × C*H*$_3$-*m*-Ar), 2.26 (s, 6 H, 2 × C*H*$_3$-*m*-Ar), 2.81-2.86 (m, 1 H, *H*H-5), 2.94-2.99 (m, 1 H, H*H*-5), 4.23 (*virt.* t, ^3J = 7.5 Hz, 1 H, H-2), 6.79 (br s, 1 H, H-*p*-Ar), 6.81 (br s, 1 H, H-*p*-Ar), 7.05 (br s, 2 H, 2 × H-*o*-Ar), 7.16 (br s, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 21.6 (q, 2 C, 2 × *C*H$_3$-*m*-Ar), 21.6 (q, 2 C, 2 × *C*H$_3$-*m*-Ar), 27.1 (t, C-4), 28.0 (t, C-3), 48.2 (t, C-5), 65.9 (d, C-2), 79.6 (s, COH), 124.6 (d, 2 C, 2 × C-*o*-Ar), 125.1 (d, 2 C, 2 × C-*o*-Ar), 128.9 (d, C-*p*-Ar), 129.1 (d, C-*p*-Ar), 138.4 (s, 2 C, 2 × C-*m*-Ar), 138.6 (s, 2 C, 2 × C-*m*-Ar), 147.5 (s, C-*i*-Ar), 148.1 (s, C-*i*-Ar).

The analytical data obtained matched those reported in the literature.[267]

(*S*)-1,1-Bis(3,5-dimethylphenyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]-oxazol-3-one (116)



According to a modified literature procedure:[153] A solution of triphosgene (47.9 mg, 162 µmol, 1.00 equiv) in dichloromethane (2.0 mL, 81.0 mM) was added to a solution of prolinol **96** (50.0 mg, 162 µmol, 1.00 equiv) and pyridine (26.0 µL, 25.6 mg, 2.00 equiv) in dichloromethane (2.0 mL, 81.0 mM) at 0 °C. The reaction mixture was allowed to warm to room temperature and was subsequently stirred for 24 hours. The excess triphosgene was quenched with brine (8 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 8 mL). The combined organic layers were dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. After purification by column chromatography (silica, cHex/EtOAc = 9/1), oxazolidinone **116** (51.0 mg, 152 µmol, 94%, 98% *ee*) was obtained as a colorless solid.

Mp: 143 °C.

TLC: R_f = 0.20 (P/EtOAc = 9/1) [$KMnO_4$, UV].

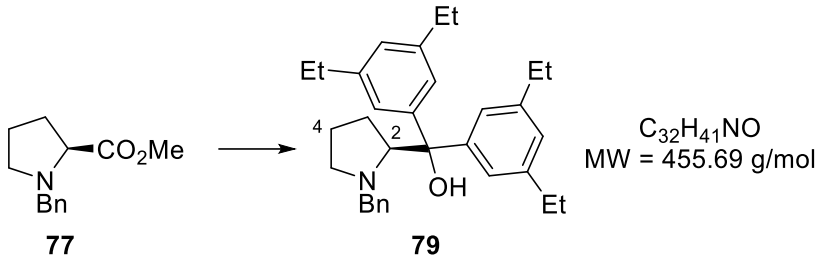
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.06-1.19 (m, 1 H, *H*H-7), 1.67-1.75 (m, 1 H, H*H*-7), 1.79-1.90 (m, 1 H, *H*H-6), 1.91-2.04 (m, 1 H, H*H*-6), 2.29 (s, 6 H, 2 × CH_3-*m*-Ar), 2.31 (s, 6 H, 2 × CH_3-*m*-Ar), 3.23 (ddd, ^2J = 11.5 Hz, $^3J_1$ = 9.5 Hz, $^3J_2$ = 3.7 Hz, 1 H, *H*H-5), 3.72 (*virt.* dt, ^2J = 11.5 Hz, $^3J_1 \approx {}^3J_2$ = 8.1 Hz, 1 H, H*H*-5), 4.50 (dd, $^3J_1$ = 10.6 Hz, $^3J_2$ = 5.5 Hz, 1 H, H-7a), 6.89 (s, 1 H, H-*p*-Ar), 6.93 (s, 1 H, H-*p*-Ar), 6.99 (s, 2 H, 2 × H-*o*-Ar), 7.14 (s, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 21.6 (q, 2 C, 2 × *C*H_3-*m*-Ar), 21.6 (q, 2 C, 2 × *C*H_3-*m*-Ar), 25.0 (t, C-6), 29.1 (t, C-7), 46.2 (t, C-5), 69.3 (d, C-7a), 86.0 (s, C-1), 123.2 (d, 2 C, 2 × C-*o*-Ar), 123.7 (d, 2 C, 2 × C-*o*-Ar), 129.3 (d, C-*p*-Ar), 130.0 (d, C-*p*-Ar), 137.9 (s, 2 C, 2 × C-*m*-Ar), 138.2 (s, 2 C, 2 × C-*m*-Ar), 140.5 (s, C-*i*-Ar), 143.5 (s, C-*i*-Ar), 160.8 (s, C-3).

Chiral HPLC: τ_R (major) = 25.1 min, τ_R (minor) = 28.3 min, [H_2O/MeCN = 50/50 → 0/100, 30 min], Chiralcel, OD-RH, 150×4.6.

The analytical data obtained matched those reported in the literature.[268]

(*S*)-(1-Benzylpyrrolidin-2-yl)bis(3,5-diethylphenyl)methanol (79)



Following GP1, ester **77** (412 mg, 1.88 mmol, 1.00 equiv) was converted with 1-bromo-3,5-diethylbenzene (1.00 g, 4.69 mmol, 2.50 equiv), iodine (4.76 mg, 18.8 µmol, 1.00 mol%) and magnesium turnings (114 mg, 4.69 mmol, 2.50 equiv) within one hour. After purification by column chromatography (silica, cHex/EtOAc = 20/1), alcohol **79** (804 mg, 1.76 mmol, 94%) was obtained as a viscous yellow oil.

TLC: R_f = 0.39 (H/EtOAc = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3360 (br w, OH), 2962 (s, sp^3-CH), 2931 (m, sp^3-CH), 2872 (m, sp^3-CH), 2796 (m, sp^3-CH), 1599 (m, sp^2-CC), 1453 (s, sp^2-CC), 870 (vs), 698 (vs).

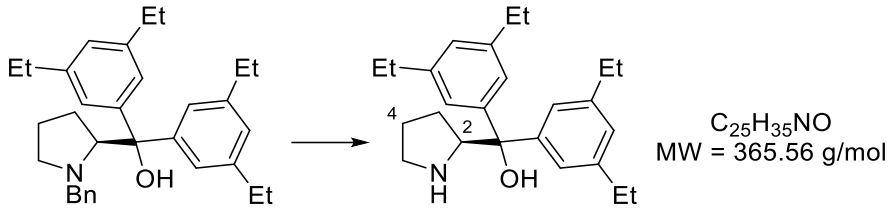
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.16 (t, ^3J = 7.6 Hz, 6 H, 2 × CH_2CH_3-*m*-Ar), 1.22 (t, ^3J = 7.6 Hz, 6 H, 2 × CH_2CH_3-*m*-Ar), 1.57-1.69 (m, 2 H, H-4), 1.75 (*virt.* ddt, ^2J = 12.9 Hz, $^3J_1$ = 8.4 Hz, $^3J_2 \approx {}^3J_3$ = 4.5 Hz, 1 H, *H*H-3), 1.94 (*virt.* dq, ^2J = 12.9 Hz, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 9.0 Hz, 1 H, H*H*-3), 2.35 (*virt.* td, $^2J \approx {}^3J_1$ = 9.5 Hz, $^3J_2$ = 6.8 Hz, 1 H, *H*H-5), 2.53-2.66 (m, 8 H, 4 × CH_2CH_3-*m*-Ar), 2.92 (ddd, ^2J = 9.4 Hz, $^3J_1$ = 6.0 Hz, $^3J_2$ = 3.1 Hz, 1 H, H*H*-5), 3.01 (d, ^2J = 12.7 Hz, 1 H, C*H*HPh), 3.21 (d, ^2J = 12.7 Hz, 1 H, CH*H*Ph), 3.95 (dd, $^3J_1$ = 9.5 Hz, $^3J_2$ = 4.7 Hz, 1 H, H-2), 4.83 (s, 1 H, COH), 6.75 (s, 1 H, H-*p*-Ar), 6.83 (s, 1 H, H-*p*-Ar), 7.00-7.05 (m, 2 H, 2 × H-*o*-Ph), 7.15-7.26 (m, 5 H, 2 × H-*o*-Ar, 2 × H-*m*-Ph, H-*p*-Ph), 7.38 (br s, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 15.8 (q, 2 C, 2 × CH_2CH_3-*m*-Ar), 15.8 (q, 2 C, 2 × CH_2CH_3-*m*-Ar), 24.4 (t, C-4), 29.2 (t, 2 C, 2 × CH_2CH_3-*m*-Ar), 29.2 (t, 2 C, 2 × CH_2CH_3-*m*-Ar), 29.9 (t, C-3), 55.8 (t, C-5), 60.7 (t, CH_2Ph), 71.2 (d, C-2), 78.2 (s, COH), 122.6 (d, 2 C, 2 × C-*o*-Ar), 122.8 (d, 2 C, 2 × C-*o*-Ar), 125.3 (d, C-*p*-Ar), 125.6 (d, C-*p*-Ar), 126.9 (d, C-*p*-Ph), 128.2 (d, 2 C, 2 × C-*m*-Ph), 128.8 (d, 2 C, 2 × C-*o*-Ph), 140.2 (s, C-*i*-Ph), 143.8 (s, 2 C, 2 × C-*m*-Ar), 143.9 (s, 2 C, 2 × C-*m*-Ar), 146.7 (s, C-*i*-Ar), 148.2 (s, C-*i*-Ar).

HRMS (ESI): calcd for $C_{32}H_{42}NO$ $[M+H]^+$: 456.3261; found: 456.3261.

Specific Rotation: $[\alpha]_D^{27}$ = +94.8 (c = 1.24, CH_2Cl_2).

(*S*)-Bis(3,5-diethylphenyl)(pyrrolidin-2-yl)methanol (97)



Following GP2, alcohol **79** (804 mg, 1.76 mmol, 1.00 equiv) was converted with palladium on carbon (80.4 mg, 10 wt%) under a hydrogen atmosphere (balloon) within one hour. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 15/1), prolinol **97** (598 mg, 1.64 mmol, 93%) was obtained as a yellow solid.

Mp: 52 °C.

TLC: R_f = 0.13 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3349 (br w, NH, OH), 2963 (vs, sp^3-CH), 2930 (s, sp^3-CH), 2871 (s, sp^3-CH), 1594 (s, sp^2-CH), 1453 (vs, sp^3-CH), 872 (vs, sp^2-CH), 734 (vs).

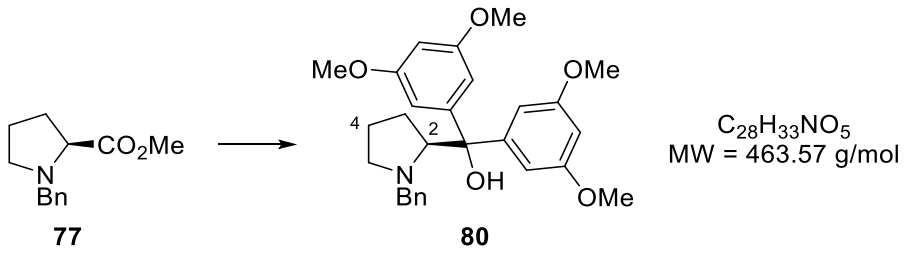
^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.16-1.22 (m, 12 H, 4 × CH_2CH_3-*m*-Ar), 1.55-1.65 (m, 1 H, *H*H-3), 1.65-1.76 (m, 3 H, H*H*-3, H-4), 2.53-2.63 (m, 8 H, 4 × CH_2CH_3-*m*-Ar), 2.79-2.86 (m, 1 H, *H*H-5), 2.92-2.98 (m, 1 H, H*H*-5), 4.20-4.26 (m, 1 H, H-2), 6.84 (t, ^4J = 1.7 Hz, 1 H, H-*p*-Ar), 6.87 (t, ^4J = 1.7 Hz, 1 H, H-*p*-Ar), 7.11 (d, ^4J = 1.7 Hz, 2 H, 2 × H-*o*-Ar), 7.22 (d, ^4J = 1.7 Hz, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 16.3 (q, 4 C, 4 × CH_2CH_3-*m*-Ar), 27.1 (t, C-4), 28.1 (t, C-3), 30.0 (t, 2 C, 2 × CH_2CH_3-*m*-Ar), 30.1 (t, 2 C, 2 × CH_2CH_3-*m*-Ar), 48.2 (t, C-5), 66.0 (d, C-2), 80.0 (s, COH), 123.8 (d, 2 C, 2 × C-*o*-Ar), 124.4 (d, 2 C, 2 × C-*o*-Ar), 126.4 (d, C-*p*-Ar), 126.6 (d, C-*p*-Ar), 145.0 (s, 2 C, 2 × C-*m*-Ar), 145.2 (s, 2 C, 2 × C-*m*-Ar), 147.6 (s, C-*i*-Ar), 148.3 (s, C-*i*-Ar).

HRMS (ESI): calcd for $C_{25}H_{36}NO$ $[M+H]^+$: 366.2791; found: 366.2791.

Specific Rotation: $[\alpha]_D^{26}$ = –60.6 (c = 1.06, CH_2Cl_2).

(*S*)-(1-Benzylpyrrolidin-2-yl)bis(3,5-dimethoxyphenyl)methanol (80)



Following GP1, ester **77** (465 mg, 2.12 mmol, 1.00 equiv) was converted with 1-bromo-3,5-dimethoxybenzene (1.15 g, 5.30 mmol, 2.50 equiv), iodine (5.38 mg, 21.2 μmol, 1.00 mol%) and magnesium turnings (129 mg, 5.30 mmol, 2.50 equiv) within one hour. After purification by column chromatography (silica, cHex/EtOAc = 8/2), prolinol **80** (981 mg, 2.12 mmol, 99%) was obtained as a low-melting amorphous colorless solid.

TLC: R_f = 0.41 (P/EtOAc = 7/3) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3335 (br w, OH), 3086 (w, sp^2-CH), 2998 (w, sp^3-CH), 2940 (m, sp^3-CH), 2836 (w, sp^3-CH), 1594 (vs), 1456 (s, sp^2-CC), 1204 (vs), 1154 (vs, sp^3-CO), 1061 (s).

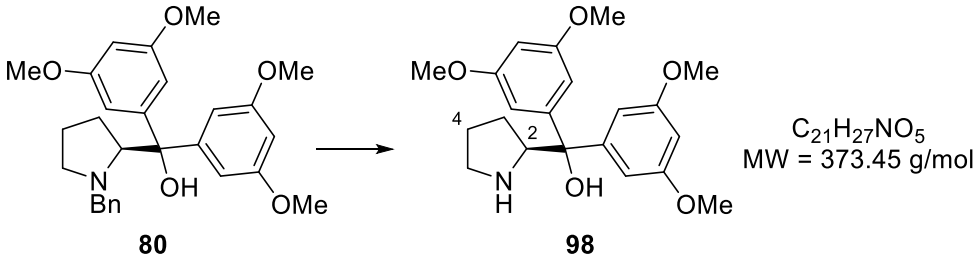
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.58-1.67 (m, 2 H, H-4), 1.71-1.80 (m, 1 H, *H*H-3), 1.98 (*virt.* dq, ^2J = 13.3 Hz, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 9.0 Hz, 1 H, H*H*-3), 2.35 (*virt.* td, $^2J \approx {}^3J_1$ = 9.4 Hz, $^3J_2$ = 7.4 Hz, 1 H, *H*H-5), 2.93 (ddd, ^2J = 9.3 Hz, $^3J_1$ = 5.1 Hz, $^3J_2$ = 3.1 Hz, 1 H, H*H*-5), 3.07 (d, ^2J = 12.8 Hz, 1 H, C*H*HPh), 3.36 (d, ^2J = 12.8 Hz, 1 H, CH*H*Ph), 3.74 (s, 6 H, 2 × OCH_3-*m*-Ar), 3.78 (s, 6 H, 2 × OCH_3-*m*-Ar), 3.85 (dd, $^3J_1$ = 9.5 Hz, $^3J_2$ = 4.9 Hz, 1 H, H-2), 5.00 (s, 1 H, COH), 6.21 (t, ^4J = 2.2 Hz, 1 H, H-*p*-Ar), 6.28 (t, ^4J = 2.3 Hz, 1 H, H-*p*-Ar), 6.74 (d, ^4J = 2.3 Hz, 2 H, 2 × H-*o*-Ar), 6.90 (d, ^4J = 2.2 Hz, 2 H, 2 × H-*o*-Ar), 7.06-7.10 (m, 2 H, 2 × H-*o*-Ph), 7.16-7.21 (m, 1 H, H-*p*-Ph), 7.22-7.26 (m, 2 H, 2 × H-*m*-Ph).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 24.2 (t, C-4), 30.0 (t, C-3), 55.4 (q, 2 C, 2 × O*C*H_3-*m*-Ar), 55.4 (q, 2 C, 2 × O*C*H_3-*m*-Ar), 55.7 (t, C-5), 60.5 (t, *C*H_2Ph), 70.6 (d, C-2), 78.0 (s, COH), 98.1 (d, C-*p*-Ar), 98.2 (d, C-*p*-Ar), 104.2 (d, 2 C, 2 × C-*o*-Ar), 104.4 (d, 2 C, 2 × C-*o*-Ar), 127.0 (d, C-*p*-Ph), 128.3 (d, 2 C, 2 × C-*m*-Ph), 128.7 (d, 2 C, 2 × C-*o*-Ph), 140.0 (s, C-*i*-Ph), 148.9 (s, C-*i*-Ar), 150.7 (s, C-*i*-Ar), 160.5 (s, 2 C, 2 × C-*m*-Ar), 160.6 (s, 2 C, 2 × C-*m*-Ar).

HRMS (ESI): calcd for $C_{28}H_{34}NO_5$ $[M+H]^+$: 464.2431; found: 464.2431.

Specific Rotation: $[\alpha]_D^{25}$ = +57.7 (c = 1.01, CH_2Cl_2).

(*S*)-Bis(3,5-dimethoxyphenyl)(pyrrolidin-2-yl)methanol (98)



Following GP2, ester **80** (972 mg, 2.10 mmol, 1.00 equiv) was converted with palladium on carbon (97.2 mg, 10 wt%) under a hydrogen atmosphere (balloon) within one hour. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 10/1), prolinol **98** (585 mg, 1.57 mmol, 75%) was obtained as a highly viscous yellow oil.

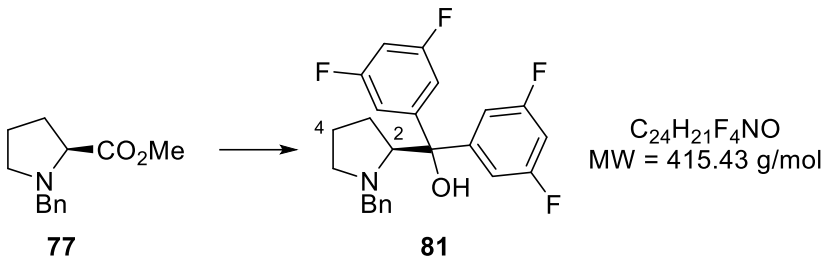
TLC: R_f = 0.05 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$].

^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.59-1.79 (m, 4 H, H-3, H-4), 2.83 (*virt.* dt, ^2J = 10.1 Hz, $^3J_1 \approx {}^3J_2$ = 6.6 Hz, 1 H, *H*H-5), 2.97 (*virt.* dt, ^2J = 10.1 Hz, $^3J_1 \approx {}^3J_2$ = 6.4 Hz, 1 H, H*H*-5), 3.73 (s, 6 H, 2 × OC*H*$_3$-*m*-Ar), 3.74 (s, 6 H, 2 × OC*H*$_3$-*m*-Ar), 4.18 (*virt.* t, $^3J_1 \approx {}^3J_2$ = 7.5 Hz, 1 H, H-2), 6.31 (t, ^4J = 2.3 Hz, 1 H, H-*p*-Ar), 6.32 (t, ^4J = 2.3 Hz, 1 H, H-*p*-Ar), 6.64 (d, ^4J = 2.3 Hz, 2 H, 2 × H-*o*-Ar), 6.74 (d, ^4J = 2.3 Hz, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 27.1 (t, C-4), 27.9 (t, C-3), 48.2 (t, C-5), 55.7 (q, 2 C, 2 × O*C*H$_3$-*m*-Ar), 55.7 (q, 2 C, 2 × O*C*H$_3$-*m*-Ar), 65.8 (d, C-2), 79.8 (s, COH), 99.1 (d, C-*p*-Ar), 99.3 (d, C-*p*-Ar), 105.2 (d, 2 C, 2 × C-*o*-Ar), 105.6 (d, 2 C, 2 × C-*o*-Ar), 149.6 (s, C-*i*-Ar), 150.5 (s, C-*i*-Ar), 162.0 (s, 2 C, 2 × C-*m*-Ar), 162.2 (s, 2 C, 2 × C-*m*-Ar).

The analytical data obtained matched those reported in the literature.[269]

(*S*)-(1-Benzylpyrrolidin-2-yl)bis(3,5-difluorophenyl)methanol (81)



Following GP1, ester **77** (500 mg, 2.28 mmol, 1.00 equiv) was converted with 1-bromo-3,5-difluorobenzene (1.10 g, 5.70 mmol, 2.50 equiv), iodine (5.79 mg, 22.8 µmol, 1.00 mol%) and magnesium turnings (139 mg, 5.70 mmol, 2.50 equiv) within one hour. After purification by

column chromatography (silica, cHex/EtOAc = 1/0 → 30/1), alcohol **81** (862 mg, 2.07 mmol, 91%) was obtained as a viscous colorless oil.

TLC: R_f = 0.53 (P/EtOAc = 9/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3298 (br w, OH), 3090 (w, sp^2-CH), 3030 (w, sp^2-CH), 2972 (w, sp^3-CH), 2876 (w, sp^3-CH), 1618 (s, sp^2-CC), 1594 (s, sp^2-CC), 1452 (s), 1303 (s, sp^2-CF), 1115 (vs, sp^2-CF), 978 (vs, sp^2-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.60-1.70 (m, 3 H, *H*H-3, H-4), 1.88-2.00 (m, 1 H, H*H*-3), 2.42 (*virt.* td, $^2J \approx {}^3J_1$ = 9.2 Hz, $^3J_2$ = 6.8 Hz, 1 H, *H*H-5), 2.95 (*virt.* dt, ^2J = 9.6 Hz, $^3J_1 \approx {}^3J_2$ = 4.9 Hz, 1 H, H*H*-5), 3.15 (d, ^2J = 12.7 Hz, 1 H, C*H*HPh), 3.34 (d, ^2J = 12.7 Hz, 1 H, CH*H*Ph), 3.84 (dd, $^3J_1$ = 9.3 Hz, $^3J_2$ = 4.1 Hz, 1 H, H-2), 5.17 (br s, 1 H, COH), 6.58-6.89 (m, 2 H, 2 × H-*p*-Ar), 7.04-7.12 (m, 4 H, 2 × H-*o*-Ar, 2 × H-*o*-Ph), 7.20-7.30 (m, 5 H, 2 × H-*o*-Ar, 2 × H-*m*-Ph, H-*p*-Ph).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 24.0 (t, C-4), 29.8 (t, C-3), 55.5 (t, C-5), 60.5 (t, *C*H_2Ph), 70.2 (d, C-2), 77.2-77.3 (m, COH)*, 102.1-102.9 (m, 2 C, 2 × C-*p*-Ar), 108.9-109.1 (m, 4 C, 4 × C-*o*-Ar), 127.4 (d, C-*p*-Ph), 128.5 (d, 2 C, 2 × C-*m*-Ph), 128.6 (d, 2 C, 2 × C-*o*-Ph), 139.0 (s, C-*i*-Ph), 149.6 (ts, $^3J_{CF}$ = 8.5 Hz, C-*i*-Ar), 151.8 (ts, $^3J_{CF}$ = 7.5 Hz, C-*i*-Ar), 163.0 (dds, $^1J_{CF}$ = 248 Hz, $^3J_{CF}$ = 12.8 Hz, 2 C, 2 × C-*m*-Ar), 163.2 (dds, $^1J_{CF}$ = 248 Hz, $^3J_{CF}$ = 12.8 Hz, 2 C, 2 × C-*m*-Ar).

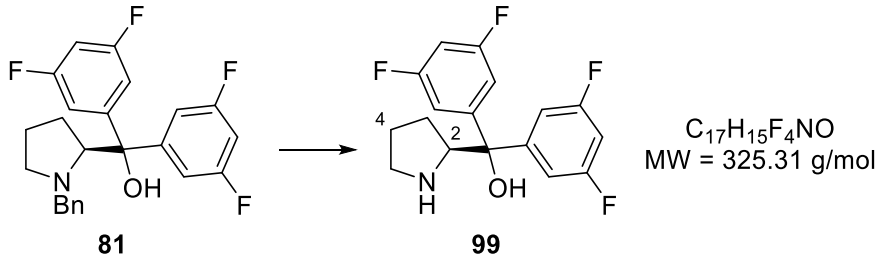
*The ^{13}C signal of COH overlaps with the solvent signal of $CDCl_3$. However, the signal can be located with the help of a HMBC crosspeak with the proton signal of H-2 to assign the ^{13}C signal of COH.

^{19}F NMR (376 MHz, $CDCl_3$, 300 K): δ [ppm] = –109.7-(–109.6) (m, 2 F, 2 × F-*m*-Ar), –109.2-(–109.1) (m, 2 F, 2 × F-*m*-Ar).

HRMS (ESI): calcd for $C_{24}H_{22}F_4NO$ $[M+H]^+$: 416.1632; found: 416.1631.

Specific Rotation: $[\alpha]_D^{26}$ = +43.0 (c = 1.30, CH_2Cl_2).

(*S*)-Bis(3,5-difluorophenyl)(pyrrolidin-2-yl)methanol (99)



Following GP2, alcohol **81** (795 mg, 1.91 mmol, 1.00 equiv) was converted with palladium on carbon (79.5 mg, 10 wt%) under a hydrogen atmosphere (balloon) within 18 hours. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 50/1), prolinol **99** (612 mg, 1.88 mmol, 98%) was obtained as a viscous yellow oil.

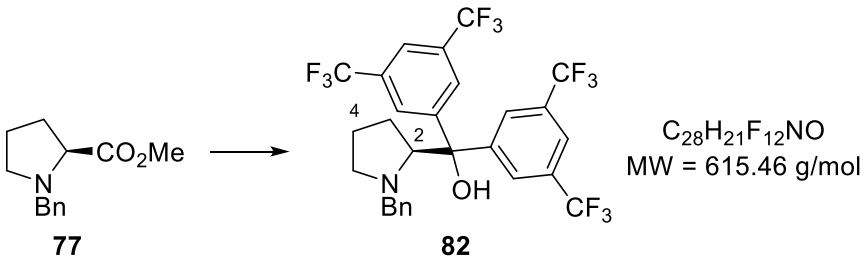
TLC: R_f = 0.09 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$].

^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.54-1.66 (m, 2 H, H-3), 1.70-1.77 (m, 2 H, H-4), 2.86 (*virt.* dt, ^2J = 10.2 Hz, $^3J_1 \approx {}^3J_2$ = 7.0 Hz, 1 H, *H*H-5), 2.96 (*virt.* dt, ^2J = 10.2 Hz, $^3J_1 \approx {}^3J_2$ = 6.3 Hz, 1 H, H*H*-5), 4.21 (*virt.* t, $^3J_1 \approx {}^3J_2$ = 7.7 Hz, 1 H, H-2), 6.74-6.81 (m, 2 H, 2 × H-*p*-Ar), 7.10-7.16 (m, 2 H, 2 × H-*o*-Ar), 7.19-7.24 (m, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 27.2 (t, C-4), 27.8 (t, C-3), 48.3 (t, C-5), 65.3 (d, C-2), 78.8-78.9 (m, COH), 102.9 (td, $^2J_{CF}$ = 25.9 Hz, C-*p*-Ar), 103.0 (td, $^2J_{CF}$ = 25.9 Hz, C-*p*-Ar), 109.8 (ddd, $^2J_{CF}$ = 20.6 Hz, $^4J_{CF}$ = 6.0 Hz, 2 C, 2 × C-*o*-Ar), 110.4 (ddd, $^2J_{CF}$ = 20.6 Hz, $^4J_{CF}$ = 6.0 Hz, 2 C, 2 × C-*o*-Ar), 151.4 (ts, $^3J_{CF}$ = 8.5 Hz, C-*i*-Ar), 152.5 (ts, $^3J_{CF}$ = 8.1 Hz, C-*i*-Ar), 164.4 (dds, $^1J_{CF}$ = 247 Hz, $^3J_{CF}$ = 11.8 Hz, 2 C, 2 × C-*m*-Ar), 164.5 (dds, $^1J_{CF}$ = 247 Hz, $^3J_{CF}$ = 11.8 Hz, 2 C, 2 × C-*m*-Ar).

The analytical data obtained matched those reported in the literature.[270]

(*S*)-(1-Benzylpyrrolidin-2-yl)bis[3,5-bis(trifluoromethyl)phenyl]methanol (82)



Following GP1, ester **77** (500 mg, 2.28 mmol, 1.00 equiv) was converted with 1-bromo-3,5-bis(trifluoromethyl)benzene (1.67 g, 5.70 mmol, 2.50 equiv), iodine (5.79 mg,

22.8 μmol, 1.00 mol%) and magnesium turnings (139 mg, 5.70 mmol, 2.50 equiv) within one hour. After purification by column chromatography (silica, cHex/EtOAc = 1/0 → 30/1), alcohol **82** (1.36 g, 2.21 mmol, 97%) was obtained as a viscous colorless oil.

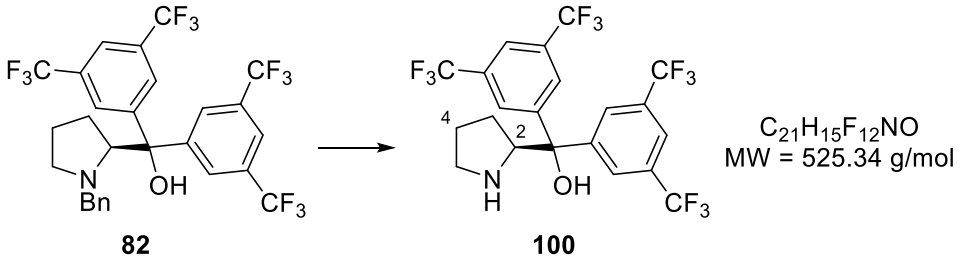
TLC: R_f = 0.59 (P/EtOAc = 9/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.57 (*virt.* ddt, ^2J = 12.9 Hz, $^3J_1$ = 7.6 Hz, $^3J_2 \approx {}^3J_3$ = 5.3 Hz, 1 H, *H*H-3), 1.64-1.76 (m, 2 H, H-4), 1.96 (*virt.* dq, ^2J = 12.9 Hz, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 8.5 Hz, 1 H, H*H*-3), 2.53 (*virt.* td, $^2J \approx {}^3J_1$ = 9.4 Hz, $^3J_2$ = 7.1 Hz, 1 H, *H*H-5), 3.02 (ddd, ^2J = 9.9 Hz, $^3J_1$ = 6.0 Hz, $^3J_2$ = 3.9 Hz, 1 H, H*H*-5), 3.12 (d, ^2J = 12.9 Hz, 1 H, C*H*HPh), 3.21 (d, ^2J = 12.9 Hz, 1 H, CH*H*Ph), 4.09 (dd, $^3J_1$ = 9.1 Hz, $^3J_2$ = 5.1 Hz, 1 H, H-2), 5.52 (br s, 1 H, COH), 6.93-6.99 (m, 2 H, 2 × H-*o*-Ph), 7.19-7.28 (m, 3 H, 2 × H-*m*-Ph, H-*p*-Ph), 7.71-7.73 (m, 1 H, H-*p*-Ar), 7.75-7.78 (m, 1 H, H-*p*-Ar), 8.03-8.06 (m, 2 H, 2 × H-*o*-Ar), 8.18-8.21 (m, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 24.0 (t, C-4), 29.9 (t, C-3), 55.6 (t, C-5), 60.5 (t, *C*H_2Ph), 70.7 (d, C-2), 77.1 (s, COH), 121.0-121.5 (m, 2 C, 2 × C-*p*-Ar), 123.1 (qs, $^1J_{CF}$ = 273 Hz, 2 C, 2 × F_3C-*m*-Ar), 123.2 (qs, $^1J_{CF}$ = 273 Hz, 2 C, 2 × F_3C-*m*-Ar), 125.5-125.8 (m, 2 C, 2 × C-*o*-Ar), 125.8-126.0 (m, 2 C, 2 × C-*o*-Ar), 127.4 (d, C-*p*-Ph), 128.2 (d, 2 C, 2 × C-*o*-Ph), 128.5 (d, 2 C, 2 × C-*m*-Ph), 131.9 (qs, $^2J_{CF}$ = 33.4 Hz, 2 C, 2 × C-*m*-Ar), 132.1 (qs, $^2J_{CF}$ = 33.4 Hz, 2 C, 2 × C-*m*-Ar), 138.2 (s, C-*i*-Ph), 147.7 (s, C-*i*-Ar), 149.6 (s, C-*i*-Ar).

The analytical data obtained matched those reported in the literature.[271]

(*S*)-Bis[3,5-bis(trifluoromethyl)phenyl](pyrrolidin-2-yl)methanol (100)



Following GP2, alcohol **82** (1.33 g, 2.16 mmol, 1.00 equiv) was converted with palladium on carbon (133 mg, 10 wt%) under a hydrogen atmosphere (balloon) within 18 hours. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 1/0 → 30/1), prolinol **100** (1.03 g, 1.96 mmol, 90%) was obtained as a colorless solid.

Mp: 116 °C.

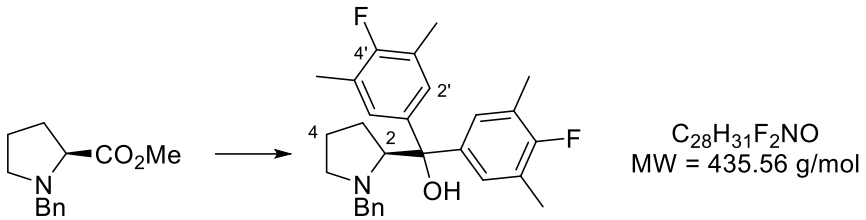
TLC: R_f = 0.68 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$].

^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.54 (*virt.* dq, ^2J = 13.0 Hz, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 7.9 Hz, 1 H, *H*H-3), 1.66 (*virt.* dtd, ^2J = 13.0 Hz, $^3J_1 \approx {}^3J_2$ = 7.7 Hz, $^3J_3$ = 5.4 Hz, 1 H, H*H*-3), 1.70-1.78 (m, 2 H, H-4), 2.86-2.98 (m, 2 H, H-5), 4.48 (*virt.* t, $^3J_1 \approx {}^3J_2$ = 7.7 Hz, 1 H, H-2), 7.82-7.86 (m, 2 H, 2 × H-*p*-Ar), 8.14-8.17 (m, 2 H, 2 × H-*o*-Ar), 8.23-8.26 (m, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 27.3 (t, C-4), 28.0 (t, C-3), 48.4 (t, C-5), 65.5 (d, C-2), 79.0 (s, COH), 121.9-122.2 (m, 2 C, 2 × C-*p*-Ar), 124.8 (qs, $^1J_{CF}$ = 272 Hz, 2 C, 2 × F_3C-*m*-Ar), 124.8 (qs, $^1J_{CF}$ = 272 Hz, 2 C, 2 × F_3C-*m*-Ar), 127.5-127.6 (m, 2 C, 2 × C-*o*-Ar), 127.9-128.0 (m, 2 C, 2 × C-*o*-Ar), 132.8 (qs, $^2J_{CF}$ = 33.2 Hz, 2 C, 2 × C-*m*-Ar), 132.8 (qs, $^2J_{CF}$ = 33.2 Hz, 2 C, 2 × C-*m*-Ar), 149.9 (s, C-*i*-Ar), 150.7 (s, C-*i*-Ar).

The analytical data obtained matched those reported in the literature.[272]

(*S*)-(1-Benzylpyrrolidin-2-yl)bis(4-fluoro-3,5-dimethylphenyl)methanol (83)



Following GP1, ester **77** (432 mg, 1.97 mmol, 1.00 equiv) was converted with 5-bromo-2-fluoro-1,3-dimethylbenzene (1.00 g, 4.92 mmol, 2.50 equiv), iodine (5.00 mg, 19.7 μmol, 1.00 mol%) and magnesium turnings (120 mg, 4.92 mmol, 2.50 equiv) within one hour. After purification by column chromatography (silica, cHex/EtOAc = 20/1), alcohol **83** (831 mg, 1.91 mmol, 97%) was obtained as a viscous yellow oil.

TLC: R_f = 0.31 (P/EtOAc = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3321 (br w, OH), 3029 (w, sp^2-CH), 2923 (w, sp^3-CH), 2867 (w, sp^3-CH), 2803 (w, sp^3-CH), 1487 (vs, sp^2-CC), 1205 (s, sp^2-CF), 1130 (vs, sp^2-CF), 728 (vs).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.59-1.67 (m, 2 H, H-4), 1.69-1.77 (m, 1 H, *H*H-3), 1.95 (*virt.* dq, ^2J = 13.0 Hz, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 9.0 Hz, 1 H, H*H*-3), 2.19 (d, $^4J_{HF}$ = 2.0 Hz, 6 H, 2 × CH_3-*m*-Ar), 2.25 (d, $^4J_{HF}$ = 2.0 Hz, 6 H, 2 × CH_3-*m*-Ar), 2.33-2.40 (m, 1 H, *H*H-5), 2.93 (ddd, ^2J = 9.2 Hz, $^3J_1$ = 5.5 Hz, $^3J_2$ = 3.7 Hz, 1 H, H*H*-5), 3.04 (d, ^2J = 12.7 Hz, 1 H, C*H*HPh), 3.20 (d, ^2J = 12.7 Hz, 1 H, CH*H*Ph), 3.84 (dd, $^3J_1$ = 9.5 Hz, $^3J_2$ = 4.5 Hz, 1 H, H-2),

4.82 (br s, 1 H, COH), 7.03-7.07 (m, 2 H, 2 × H-*o*-Ph), 7.15-7.18 (m, 2 H, 2 × H-*o*-Ar), 7.18-7.29 (m, 5 H, 2 × H-*o*-Ar, 2 × H-*m*-Ph, H-*p*-Ph).

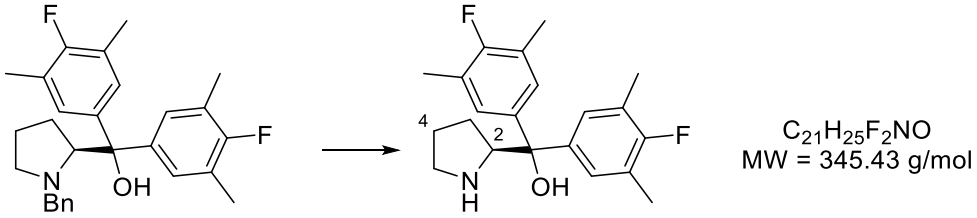
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 15.1 (d, $^3J_{CF}$ = 7.5 Hz, 2 C, 2 × *C*H$_3$-*m*-Ar), 15.1 (d, $^3J_{CF}$ = 7.5 Hz, 2 C, 2 × *C*H$_3$-*m*-Ar), 24.4 (t, C-4), 30.0 (t, C-3), 55.8 (t, C-5), 60.8 (t, *C*H$_2$Ph), 70.7 (d, C-2), 77.5 (s, COH), 124.0 (ds, $^2J_{CF}$ = 18.0 Hz, 2 C, 2 × C-*m*-Ar), 124.0 (ds, $^2J_{CF}$ = 18.0 Hz, 2 C, 2 × C-*m*-Ar), 126.1 (dd, $^3J_{CF}$ = 7.9 Hz, 2 C, 2 × C-*o*-Ar), 126.1 (dd, $^3J_{CF}$ = 7.9 Hz, 2 C, 2 × C-*o*-Ar), 127.0 (d, C-*p*-Ph), 128.3 (d, 2 C, 2 × C-*m*-Ph), 128.6 (d, 2 C, 2 × C-*o*-Ph), 139.8 (s, C-*i*-Ph), 141.6 (ds, $^4J_{CF}$ = 4.1 Hz, C-*i*-Ar), 142.8 (ds, $^4J_{CF}$ = 3.7 Hz, C-*i*-Ar), 158.6 (ds, $^1J_{CF}$ = 243 Hz, C-*p*-Ar), 158.6 (ds, $^1J_{CF}$ = 243 Hz, C-*p*-Ar).

^{19}F NMR (376 MHz, $CDCl_3$, 298 K): δ [ppm] = –126.0-(–125.8) (m, 1 F, F-*p*-Ar), –125.7-(–125.6) (m, 1 F, F-*p*-Ar).

HRMS (ESI): calcd for $C_{28}H_{32}F_2NO$ $[M+H]^+$: 436.2446; found: 436.2445.

Specific Rotation: $[\alpha]_D^{25}$ = +95.7 (c = 1.34, CH_2Cl_2).

(*S*)-Bis(4-fluoro-3,5-dimethylphenyl)(pyrrolidin-2-yl)methanol (101)



83 **101**

Following GP2, alcohol **83** (831 mg, 1.91 mmol, 1.00 equiv) was converted with palladium on carbon (83.1 mg, 10 wt%) under a hydrogen atmosphere (balloon) within one hour. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 9/1), prolinol **101** (514 mg, 1.49 mmol, 78%) was obtained as a highly viscous yellow oil.

TLC: R_f = 0.07 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3359 (br w, OH, NH), 2923 (m, sp^3-CH), 2869 (m, sp^3-CH), 1486 (vs, sp^2-CC), 1204 (s, sp^2-CF), 1131 (vs, sp^2-CF), 721 (vs), 683 (vs).

^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.53-1.68 (m, 2 H, H-3), 1.68-1.76 (m, 2 H, H-4), 2.18 (d, $^4J_{HF}$ = 2.2 Hz, 6 H, 2 × C*H*$_3$-*m*-Ar), 2.20 (d, $^4J_{HF}$ = 2.2 Hz, 6 H, 2 × C*H*$_3$-*m*-Ar), 2.83 (*virt.* dt, ^2J = 10.1 Hz, $^3J_1 \approx {}^3J_2$ = 6.6 Hz, 1 H, *H*H-5), 2.96 (*virt.* dt, ^2J = 10.1 Hz,

$^3J_1 \approx {}^3J_2$ = 6.4 Hz, 1 H, H*H*-5), 4.17 (*virt.* t, $^3J_1 \approx {}^3J_2$ = 7.6 Hz, 1 H, H-2), 7.10 (d, $^4J_{HF}$ = 6.9 Hz, 2 H, 2 × H-*o*-Ar), 7.20 (d, $^4J_{HF}$ = 6.9 Hz, 2 H, 2 × H-*o*-Ar).

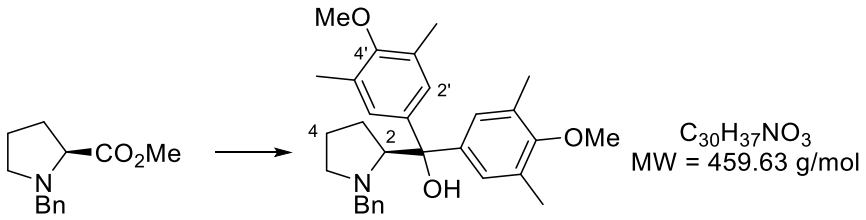
^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 14.8 (dq, $^3J_{CF}$ = 4.1 Hz, 2 C, 2 × *C*H$_3$-*m*-Ar), 14.8 (dq, $^3J_{CF}$ = 4.1 Hz, 2 C, 2 × *C*H$_3$-*m*-Ar), 27.1 (t, C-4), 28.0 (t, C-3), 48.2 (t, C-5), 65.8 (d, C-2), 78.9 (s, COH), 124.6 (ds, $^2J_{CF}$ = 20.1 Hz, 2 C, 2 × C-*m*-Ar), 124.8 (ds, $^2J_{CF}$ = 20.1 Hz, 2 C, 2 × C-*m*-Ar), 127.4 (dd, $^3J_{CF}$ = 4.8 Hz, 2 C, 2 × C-*o*-Ar), 128.0 (dd, $^3J_{CF}$ = 4.8 Hz, 2 C, 2 × C-*o*-Ar), 142.8 (ds, $^4J_{CF}$ = 4.0 Hz, C-*i*-Ar), 143.4 (ds, $^4J_{CF}$ = 4.0 Hz, C-*i*-Ar), 159.7 (ds, $^1J_{CF}$ = 242 Hz, C-*p*-Ar), 159.9 (ds, $^1J_{CF}$ = 242 Hz, C-*p*-Ar).

^{19}F NMR (376 MHz, CD_3OD, 298 K): δ [ppm] = –125.9-(–125.7) (m, 2 F, 2 × F-*p*-Ar).

HRMS (ESI): calcd for $C_{21}H_{26}F_2NO$ $[M+H]^+$: 346.1977; found: 346.1976.

Specific Rotation: $[\alpha]_D^{27}$ = –82.0 (c = 1.02, CH_2Cl_2).

(*S*)-(1-Benzylpyrrolidin-2-yl)bis(4-methoxy-3,5-dimethylphenyl)methanol (84)



77 **84**

Following GP1, ester **77** (500 mg, 2.28 mmol, 1.00 equiv) was converted with 5-bromo-2-methoxy-1,3-dimethylbenzene (1.23 g, 5.70 mmol, 2.50 equiv), iodine (5.79 mg, 22.8 μmol, 1.00 mol%) and magnesium turnings (139 mg, 5.70 mmol, 2.50 equiv) within one hour. After purification by column chromatography (silica, cHex/EtOAc = 20/1 → 9/1), alcohol **84** (1.02 g, 2.23 mmol, 98%) was obtained as a viscous yellow oil.

TLC: R_f = 0.07 (P/EtOAc = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3359 (br w, OH), 3028 (w, sp^2-CH), 2945 (m, sp^3-CH), 2823 (w, sp^3-CH), 1483 (vs, sp^2-CC), 1223 (vs), 1133 (vs, sp^3-CO), 1014 (vs), 732 (s, sp^2-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.57-1.68 (m, 2 H, H-4), 1.69-1.78 (m, 1 H, *H*H-3), 1.93 (*virt.* dq, ^2J = 13.1 Hz, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 9.1 Hz, 1 H, H*H*-3), 2.21 (s, 6 H, 2 × C*H*$_3$-*m*-Ar), 2.28 (s, 6 H, 2 × C*H*$_3$-*m*-Ar), 2.32-2.38 (m, 1 H, *H*H-5), 2.90-2.96 (m, 1 H, H*H*-5), 3.02 (d, ^2J = 12.8 Hz, 1 H, C*H*HPh), 3.14 (d, ^2J = 12.8 Hz, 1 H, CH*H*Ph), 3.59 (s, 3 H, OC*H*$_3$-*p*-Ar), 3.68 (s, 3 H, OC*H*$_3$-*p*-Ar), 3.83 (dd, $^3J_1$ = 9.5 Hz, $^3J_2$ = 4.4 Hz, 1 H, H-2), 4.74

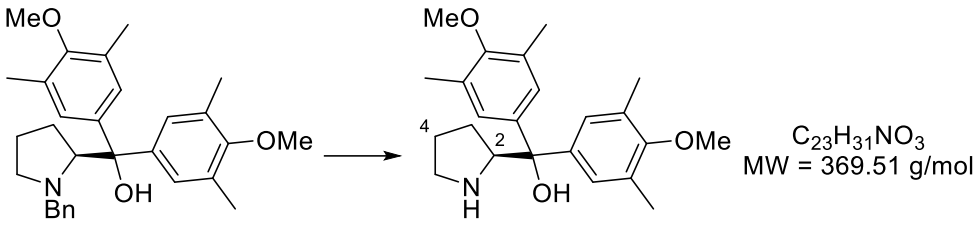
(br s, 1 H, COH), 7.00-7.05 (m, 2 H, 2 × H-*o*-Ph), 7.16-7.20 (m, 3 H, 2 × H-*o*-Ar, H-*p*-Ph), 7.21-7.25 (m, 2 H, 2 × H-*m*-Ph), 7.27 (s, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 16.5 (q, 2 C, 2 × *C*H_3-*m*-Ar), 16.6 (q, 2 C, 2 × *C*H_3-*m*-Ar), 24.5 (t, C-4), 30.0 (t, C-3), 55.9 (t, C-5), 59.7 (q, O*C*H_3-*p*-Ar), 59.8 (q, O*C*H_3-*p*-Ar), 60.8 (t, *C*H_2Ph), 71.1 (d, C-2), 77.7 (s, COH), 126.2 (d, 2 C, 2 × C-*o*-Ar), 126.2 (d, 2 C, 2 × C-*o*-Ar), 126.9 (d, C-*p*-Ph), 128.2 (d, 2 C, 2 × C-*m*-Ph), 128.7 (d, 2 C, 2 × C-*o*-Ph), 130.2 (s, 4 C, 4 × C-*m*-Ar), 140.0 (s, C-*i*-Ph), 141.9 (s, C-*i*-Ar), 143.2 (s, C-*i*-Ar), 155.3 (s, C-*p*-Ar), 155.5 (s, C-*p*-Ar).

HRMS (ESI): calcd for $C_{30}H_{38}NO_3$ $[M+H]^+$: 460.2846; found: 460.2844.

Specific Rotation: $[\alpha]_D^{25}$ = +74.3 (c = 1.37, CH_2Cl_2).

(*S*)-Bis(4-methoxy-3,5-dimethylphenyl)(pyrrolidin-2-yl)methanol (102)



Following GP2, alcohol **84** (1.01 g, 2.20 mmol, 1.00 equiv) was converted with palladium on carbon (101 mg, 10 wt%) under a hydrogen atmosphere (balloon) within one hour. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 9/1), prolinol **102** (647 mg, 1.75 mmol, 80%) was obtained as a yellow solid.

Mp: decomp. >150 °C.

TLC: R_f = 0.07 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$].

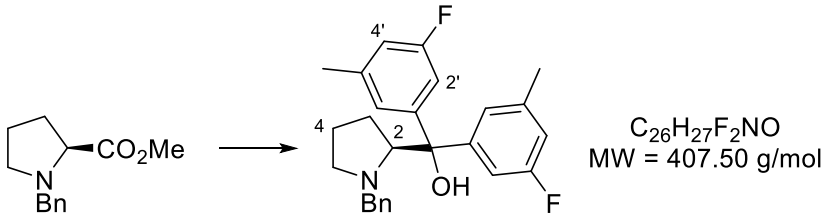
^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.74-1.89 (m, 4 H, H-3, H-4), 2.23 (s, 6 H, 2 × C*H*$_3$-*m*-Ar), 2.24 (s, 6 H, 2 × C*H*$_3$-*m*-Ar), 2.95 (*virt.* dt, ^2J = 10.7 Hz, $^3J_1 \approx {}^3J_2$ = 6.8 Hz, 1 H, *H*H-5), 3.07 (*virt.* dt, ^2J = 10.7 Hz, $^3J_1 \approx {}^3J_2$ = 6.3 Hz, 1 H, H*H*-5), 3.66 (s, 3 H, OC*H*$_3$-*p*-Ar), 3.66 (s, 3 H, OC*H*$_3$-*p*-Ar), 4.38 (*virt.* t, $^3J_1 \approx {}^3J_2$ = 7.6 Hz, 1 H, H-2), 7.10 (s, 2 H, 2 × H-*o*-Ar), 7.20 (s, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 16.4 (q, 2 C, 2 × *C*H_3-*m*-Ar), 16.5 (q, 2 C, 2 × *C*H_3-*m*-Ar), 26.5 (t, C-4), 27.7 (t, C-3), 48.0 (t, C-5), 60.0 (q, 2 C, 2 × O*C*H_3-*p*-Ar), 66.6 (d, C-2), 78.7 (s, COH), 127.3 (d, 2 C, 2 × C-*o*-Ar), 127.5 (d, 2 C, 2 × C-*o*-Ar), 131.4 (s, 2 C,

2 × C-*m*-Ar), 131.6 (s, 2 C, 2 × C-*m*-Ar), 142.4 (s, C-*i*-Ar), 142.6 (s, C-*i*-Ar), 156.9 (s, C-*p*-Ar), 157.0 (s, C-*p*-Ar).

The analytical data obtained matched those reported in the literature.[273]

(*S*)-(1-Benzylpyrrolidin-2-yl)bis(3-fluoro-5-methylphenyl)methanol (85)



Following GP1, ester **77** (232 mg, 1.06 mmol, 1.00 equiv) was converted with 1-bromo-3-fluoro-5-methylbenzene (500 mg, 2.65 mmol, 2.50 equiv), iodine (2.69 mg, 10.6 µmol, 1.00 mol%) and magnesium turnings (64.3 mg, 2.65 mmol, 2.50 equiv) within one hour. After purification by column chromatography (silica, cHex/EtOAc = 30/1), prolinol **85** (352 mg, 865 µmol, 82%) was obtained as a viscous yellow oil.

TLC: R_f = 0.46 (P/EtOAc = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3330 (br w, OH), 3029 (w, sp^2-CH), 2923 (m, sp^3-CH), 2855 (w, sp^3-CH), 2807 (w, sp^3-CH), 1615 (s, sp^2-CC), 1592 (s, sp^2-CC), 1452 (s, sp^3-CH), 1286 (s, sp^2-CF), 745 (s, sp^2-CF).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.60-1.74 (m, 3 H, *H*H-3, H-4), 1.95 (*virt.* dq, ^2J = 12.4 Hz, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 8.8 Hz, 1 H, H*H*-3), 2.29 (s, 3 H, CH_3-5'-Ar), 2.33 (s, 3 H, CH_3-5'-Ar), 2.34-2.44 (m, 1 H, *H*H-5), 2.93 (*virt.* dt, ^2J = 9.7 Hz, $^3J_1 \approx {}^3J_2$ = 4.4 Hz, 1 H, H*H*-5), 3.07 (d, ^2J = 12.7 Hz, 1 H, C*H*HPh), 3.25 (d, ^2J = 12.7 Hz, 1 H, CH*H*Ph), 3.85 (dd, $^3J_1$ = 9.5 Hz, $^3J_2$ = 4.5 Hz, 1 H, H-2), 4.98 (br s, 1 H, COH), 6.63 (d, $^3J_{HF}$ = 9.2 Hz, 1 H, H-4'-Ar), 6.70 (d, $^3J_{HF}$ = 9.3 Hz, 1 H, H-4'-Ar), 7.02-7.09 (m, 3 H, H-2'-Ar, 2 × H-*o*-Ph), 7.14 (s, 1 H, H-6'-Ar), 7.17-7.28 (m, 4 H, H-2'-Ar, 2 × H-*m*-Ph, H-*p*-Ph), 7.29 (s, 1 H, H-6'-Ar).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 21.8 (dq, $^4J_{CF}$ = 1.8 Hz, *C*H_3-5'-Ar), 21.8 (dq, $^4J_{CF}$ = 1.7 Hz, *C*H_3-5'-Ar), 24.3 (t, C-4), 29.9 (t, C-3), 55.7 (t, C-5), 60.6 (t, *C*H_2Ph), 70.5 (d, C-2), 77.6 (*virt.* ts, $^4J_{CF,1} \approx {}^4J_{CF,2}$ = 2.2 Hz, COH)*, 109.9 (dd, $^2J_{CF}$ = 20.2 Hz, C-2'-Ar), 110.1 (dd, $^2J_{CF}$ = 20.3 Hz, C-2'-Ar), 114.2 (dd, $^2J_{CF}$ = 21.0 Hz, C-4'-Ar), 114.3 (dd, $^2J_{CF}$ = 21.1 Hz, C-4'-Ar), 122.0 (dd, $^4J_{CF}$ = 2.4 Hz, C-6'-Ar), 122.1 (dd, $^4J_{CF}$ = 2.2 Hz, C-6'-Ar), 127.1 (d, C-*p*-Ph), 128.4 (d, 2 C, 2 × C-*m*-Ph), 128.7 (d, 2 C, 2 × C-*o*-Ph), 139.6 (s, C-*i*-Ph), 140.2 (ds,

$^{3}J_{CF}$ = 8.0 Hz, C-5'-Ar), 140.3 (ds, $^{3}J_{CF}$ = 7.8 Hz, C-5'-Ar), 148.3 (ds, $^{3}J_{CF}$ = 7.5 Hz, C-1'-Ar), 150.3 (ds, $^{3}J_{CF}$ = 6.6 Hz, C-1'-Ar), 162.8 (ds, $^{1}J_{CF}$ = 244 Hz, C-3'-Ar), 163.0 (ds, $^{1}J_{CF}$ = 245 Hz, C-3'-Ar).

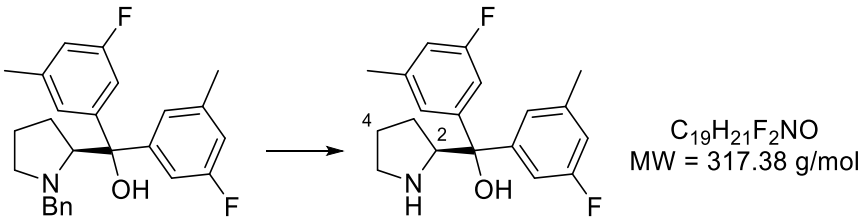
*The ^{13}C signal of COH overlaps with the solvent signal of $CDCl_3$. However, the signal can be located with the help of a HMBC crosspeak with the proton signal of H-2 to assign the ^{13}C signal of COH.

^{19}F NMR (376 MHz, $CDCl_3$, 300 K): δ [ppm] = –114.7 (*virt.* t, $^{3}J_{HF,1} \approx {}^{3}J_{HF,2}$ = 9.9 Hz, 1 F, F-3'-Ar), –114.4 (*virt.* t, $^{3}J_{HF,1} \approx {}^{3}J_{HF,2}$ = 9.9 Hz, 1 F, F-3'-Ar).

HRMS (ESI): calcd for $C_{26}H_{28}F_2NO$ $[M+H]^+$: 408.2133; found: 408.2132.

Specific Rotation: $[\alpha]_D^{25}$ = +69.5 (c = 0.95, CH_2Cl_2).

(*S*)-Bis(3-fluoro-5-methylphenyl)(pyrrolidin-2-yl)methanol (103)



Following GP2, alcohol **85** (346 mg, 849 μmol, 1.00 equiv) was converted with palladium on carbon (34.6 mg, 10 wt%) under a hydrogen atmosphere (balloon) within one hour. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 20/1), prolinol **103** (223 mg, 703 μmol, 83%) was obtained as a yellow solid.

Mp: 83 °C.

TLC: R_f = 0.19 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3368 (br w, NH, OH), 2973 (w, sp^3-CH), 2949 (w, sp^3-CH), 2921 (w, sp^3-CH), 2873 (w, sp^3-CH), 1614 (s, sp^2-CC), 1594 (vs, sp^2-CC), 1450 (s), 1283 (vs, sp^2-CF), 847 (vs).

^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.54-1.67 (m, 2 H, H-3), 1.69-1.76 (m, 2 H, H-4), 2.30 (s, 3 H, C*H*$_3$-5'-Ar), 2.32 (s, 3 H, C*H*$_3$-5'-Ar), 2.84 (*virt.* dt, ^{2}J = 10.1 Hz, $^{3}J_1 \approx {}^{3}J_2$ = 6.8 Hz, 1 H, *H*H-5), 2.96 (*virt.* dt, ^{2}J = 10.1 Hz, $^{3}J_1 \approx {}^{3}J_2$ = 6.3 Hz, 1 H, H*H*-5), 4.20 (*virt.* t, $^{3}J_1 \approx {}^{3}J_2$ = 7.7 Hz, 1 H, H-2), 6.70-6.76 (m, 2 H, H-4'-Ar), 7.03 (dddd, $^{3}J_{HF}$ = 10.5 Hz, $^{4}J_1$ = 2.4 Hz, $^{4}J_2$ = 1.6 Hz, ^{5}J = 0.6 Hz, 1 H, H-2'-Ar), 7.08 (*virt.* td, $^{4}J_1 \approx {}^{4}J_2$ = 1.6 Hz,

$^{5}J_{HF}$ = 0.8 Hz, 1 H, H-6'-Ar), 7.10 (dddd, $^{3}J_{HF}$ = 10.5 Hz, $^{4}J_{1}$ = 2.4 Hz, $^{4}J_{2}$ = 1.6 Hz, ^{5}J = 0.6 Hz, 1 H, H-2'-Ar), 7.20 (*virt.* td, $^{4}J_{1} \approx {}^{4}J_{2}$ = 1.6 Hz, $^{5}J_{HF}$ = 0.8 Hz, 1 H, H-6'-Ar).

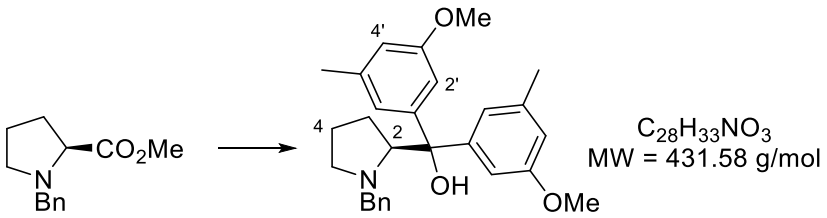
^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 21.5 (dq, $^{4}J_{CF}$ = 1.9 Hz, *C*H$_3$-5'-Ar), 21.5 (dq, $^{4}J_{CF}$ = 1.9 Hz, *C*H$_3$-5'-Ar), 27.2 (t, C-4), 27.9 (t, C-3), 48.3 (t, C-5), 65.5 (d, C-2), 79.1 (*virt.* t, $^{4}J_{CF,1} \approx {}^{4}J_{CF,2}$ = 1.7 Hz, COH), 110.7 (dd, $^{2}J_{CF}$ = 23.2 Hz, C-2'-Ar), 111.3 (dd, $^{2}J_{CF}$ = 23.2 Hz, C-2'-Ar), 114.8 (dd, $^{2}J_{CF}$ = 21.4 Hz, C-4'-Ar), 114.9 (dd, $^{2}J_{CF}$ = 21.4 Hz, C-4'-Ar), 123.2 (dd, $^{4}J_{CF}$ = 2.4 Hz, C-6'-Ar), 123.7 (dd, $^{4}J_{CF}$ = 2.4 Hz, C-6'-Ar), 141.4 (ds, $^{3}J_{CF}$ = 8.0 Hz, C-5'-Ar), 141.6 (ds, $^{3}J_{CF}$ = 8.0 Hz, C-5'-Ar), 149.9 (ds, $^{3}J_{CF}$ = 7.3 Hz, C-1'-Ar), 150.7 (ds, $^{3}J_{CF}$ = 7.0 Hz, C-1'-Ar), 164.1 (ds, $^{1}J_{CF}$ = 243 Hz, C-3'-Ar), 164.2 (ds, $^{1}J_{CF}$ = 243 Hz, C-3'-Ar).

^{19}F NMR (376 MHz, CD_3OD, 298 K): δ [ppm] = –114.7-(–114.6) (m, 1 F, F-3'-Ar), –114.5-(–114.4) (m, 1 F, F-3'-Ar).

HRMS (ESI): calcd for $C_{19}H_{22}F_2NO$ $[M+H]^+$: 318.1664; found: 318.1663.

Specific Rotation: $[\alpha]_D^{26}$ = –100 (c = 1.06, CH_2Cl_2).

(*S*)-(1-Benzylpyrrolidin-2-yl)bis(3-methoxy-5-methylphenyl)methanol (86)



Following GP1, ester **77** (436 mg, 1.99 mmol, 1.00 equiv) was converted with 1-bromo-3-methoxy-5-methylbenzene (1.00 g, 4.97 mmol, 2.50 equiv), iodine (5.05 mg, 19.9 μmol, 1.00 mol%) and magnesium turnings (121 mg, 4.97 mmol, 2.50 equiv) within one hour. After purification by column chromatography (silica, cHex/EtOAc = 15/1), alcohol **86** (821 mg, 1.90 mmol, 96%) was obtained as a viscous yellow oil.

TLC: R_f = 0.21 (P/EtOAc = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3343 (br w, OH), 3062 (w, sp^2-CH), 3027 (w, sp^2-CH), 2950 (m, sp^3-CH), 2835 (w, sp^3-CH), 2804 (w, sp^3-CH), 1595 (vs), 1455 (s, sp^2-CC), 1288 (vs), 1153 (s, sp^3-CO).

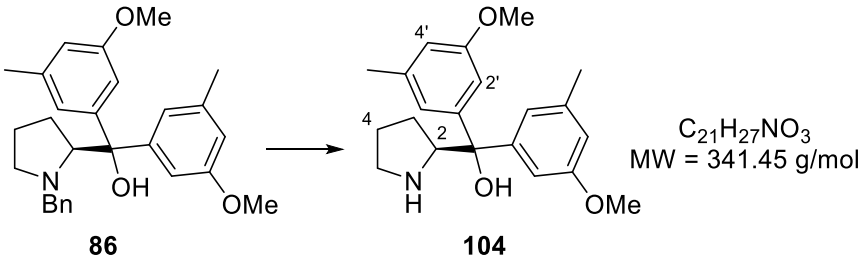
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.57-1.68 (m, 2 H, H-4), 1.72-1.80 (m, 1 H, *H*H-3), 1.97 (*virt.* dq, ^2J = 13.2 Hz, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 9.1 Hz, 1 H, H*H*-3), 2.27 (s, 3 H, CH_3-5'-Ar), 2.31 (s, 3 H, CH_3-5'-Ar), 2.32-2.39 (m, 1 H, *H*H-5), 2.88-2.94 (m, 1 H, H*H*-5), 3.03 (d, ^2J = 12.7 Hz, 1 H, C*H*HPh), 3.26 (d, ^2J = 12.7 Hz, 1 H, CH*H*Ph), 3.73 (s, 3 H, OCH_3-3'-Ar), 3.78 (s, 3 H, OCH_3-3'-Ar), 3.87 (dd, $^3J_1$ = 9.5 Hz, $^3J_2$ = 4.6 Hz, 1 H, H-2), 4.91 (s, 1 H, COH), 6.45 (br s, 1 H, H-Ar), 6.52 (br s, 1 H, H-Ar), 6.93 (br s, 1 H, H-Ar), 6.98 (br s, 1 H, H-Ar), 7.04-7.09 (m, 3 H, H-Ar, 2 × H-*o*-Ph), 7.11 (br s, 1 H, H-Ar), 7.16-7.21 (m, 1 H, H-*p*-Ph), 7.21-7.26 (m, 2 H, 2 × H-*m*-Ph).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.0 (q, *C*H_3-5'-Ar), 22.1 (q, *C*H_3-5'-Ar), 24.3 (t, C-4), 30.0 (t, C-3), 55.3 (q, O*C*H_3-3'-Ar), 55.3 (q, O*C*H_3-3'-Ar), 55.8 (t, C-5), 60.6 (t, *C*H_2Ph), 70.7 (d, C-2), 78.0 (s, COH), 109.1 (d, C-Ar), 109.2 (d, C-Ar), 112.3 (d, C-Ar), 112.4 (d, C-Ar), 119.1 (d, C-Ar), 119.1 (d, C-Ar), 126.9 (d, C-*p*-Ph), 128.2 (d, 2 C, 2 × C-*m*-Ph), 128.8 (d, 2 C, 2 × C-*o*-Ph), 139.1 (s, C-5'-Ar), 139.1 (s, C-5'-Ar), 140.0 (s, C-*i*-Ph), 147.9 (s, C-1'-Ar), 149.6 (s, C-1'-Ar), 159.3 (s, C-3'-Ar), 159.5 (s, C-3'-Ar).

HRMS (ESI): calcd for $C_{28}H_{34}NO_3$ $[M+H]^+$: 432.2533; found: 432.2533.

Specific Rotation: $[\alpha]_D^{25}$ = +84.4 (c = 0.71, CH_2Cl_2).

(*S*)-Bis(3-methoxy-5-methylphenyl)(pyrrolidin-2-yl)methanol (104)



Following GP2, alcohol **86** (808 mg, 1.87 mmol, 1.00 equiv) was converted with palladium on carbon (80.8 mg, 10 wt%) under a hydrogen atmosphere (balloon) within one hour. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 15/1), prolinol **104** (593 mg, 1.74 mmol, 93%) was obtained as a highly viscous yellow oil.

TLC: R_f = 0.13 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3350 (br w, NH, OH), 2941 (m, sp^3-CH), 2869 (m, sp^3-CH), 2835 (m, sp^3-CH), 1592 (vs), 1454 (s, sp^3-CH), 834 (s, sp^2-CH).

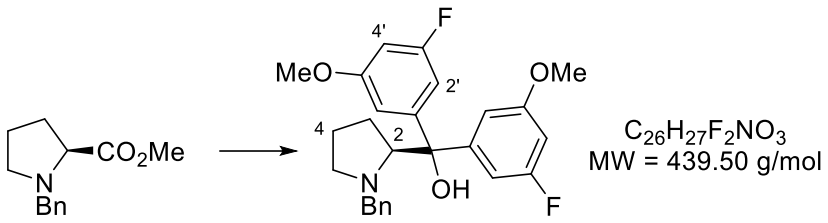
^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.58-1.78 (m, 4 H, H-3, H-4), 2.27 (s, 3 H, C*H*$_3$-5'-Ar), 2.29 (s, 3 H, C*H*$_3$-5'-Ar), 2.81-2.88 (m, 1 H, *H*H-5), 2.95-3.01 (m, 1 H, H*H*-5), 3.73 (s, 3 H, OC*H*$_3$-3'-Ar), 3.74 (s, 3 H, OC*H*$_3$-3'-Ar), 4.19-4.24 (m, 1 H, H-2), 6.55-6.57 (m, 1 H, H-Ar), 6.57-6.59 (m, 1 H, H-Ar), 6.83-6.87 (m, 2 H, H-Ar), 6.92-6.95 (m, 1 H, H-Ar), 6.95-6.97 (m, 1 H, H-Ar).

^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 21.8 (q, *C*H$_3$-5'-Ar), 21.9 (q, *C*H$_3$-5'-Ar), 27.0 (t, C-4), 27.9 (t, C-3), 48.2 (t, C-5), 55.5 (q, O*C*H$_3$-3'-Ar), 55.6 (q, O*C*H$_3$-3'-Ar), 65.9 (d, C-2), 79.6 (s, COH), 110.0 (d, C-Ar), 110.5 (d, C-Ar), 113.4 (d, C-Ar), 113.6 (d, C-Ar), 120.0 (d, C-Ar), 120.4 (d, C-Ar), 140.0 (s, C-5'-Ar), 140.2 (s, C-5'-Ar), 148.8 (s, C-1'-Ar), 149.5 (s, C-1'-Ar), 160.9 (s, C-3'-Ar), 161.1 (s, C-3'-Ar).

HRMS (ESI): calcd for $C_{21}H_{28}NO_3$ $[M+H]^+$: 342.2064; found: 342.2063.

Specific Rotation: $[\alpha]_D^{26} = -72.9$ (c = 1.37, CH_2Cl_2).

(*S*)-(1-Benzylpyrrolidin-2-yl)bis(3-fluoro-5-methoxyphenyl)methanol (87)



Following GP1, ester **77** (500 mg, 2.28 mmol, 1.00 equiv) was converted with 1-bromo-3-fluoro-5-methoxybenzene (1.17 g, 5.70 mmol, 2.50 equiv), iodine (5.79 mg, 22.8 μmol, 1.00 mol%) and magnesium turnings (139 mg, 5.70 mmol, 2.50 equiv) within one hour. After purification by column chromatography (silica, cHex/EtOAc = 20/1 → 10/1), alcohol **87** (876 mg, 1.99 mmol, 88%) was obtained as a yellow, viscous oil.

TLC: R_f = 0.22 (P/EtOAc = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3319 (br w, OH), 3089 (w, sp^2-CH), 2941 (m, sp^3-CH), 2873 (w, sp^3-CH), 2837 (w, sp^3-CH), 1611 (vs, sp^2-CC), 1591 (vs, sp^2-CC), 1453 (s, sp^3-CO), 1429 (vs, sp^3-CO), 743 (vs, sp^2-CF).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.59-1.75 (m, 3 H, *H*H-3, H-4), 1.96 (*virt.* dq, ^2J = 12.5 Hz, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 8.8 Hz, 1 H, H*H*-3), 2.38 (*virt.* q, $^2J \approx {}^3J_1 \approx {}^3J_2$ = 8.4 Hz, 1 H, *H*H-5), 2.93 (*virt.* dt, ^2J = 9.1 Hz, $^3J_1 \approx {}^3J_2$ = 4.2 Hz, 1 H, H*H*-5), 3.10 (d, ^2J = 12.7 Hz, 1 H,

C*H*HPh), 3.35 (d, ^{2}J = 12.7 Hz, 1 H, CH*H*Ph), 3.74 (s, 3 H, OCH_3-5'-Ar), 3.78 (s, 3 H, OCH_3-5'-Ar), 3.83 (dd, $^{3}J_1$ = 9.4 Hz, $^{3}J_2$ = 4.7 Hz, 1 H, H-2), 5.05 (br s, 1 H, COH), 6.38 (*virt.* dt, $^{3}J_{HF}$ = 10.3 Hz, $^{4}J_1 \approx {}^{4}J_2$ = 2.3 Hz, 1 H, H-4'-Ar), 6.44 (*virt.* dt, $^{3}J_{HF}$ = 10.5 Hz, $^{4}J_1 \approx {}^{4}J_2$ = 2.3 Hz, 1 H, H-4'-Ar), 6.86 (*virt.* dt, $^{3}J_{HF}$ = 9.9 Hz, $^{4}J_1 \approx {}^{4}J_2$ = 1.9 Hz, 1 H, H-2'-Ar), 6.92 (*virt.* t, $^{4}J_1 \approx {}^{4}J_2$ = 1.9 Hz, 1 H, H-6'-Ar), 7.02 (*virt.* dt, $^{3}J_{HF}$ = 10.0 Hz, $^{4}J_1 \approx {}^{4}J_2$ = 1.9 Hz, 1 H, H-2'-Ar), 7.05-7.10 (m, 3 H, H-6'-Ar, 2 × H-*o*-Ph), 7.18-7.23 (m, 1 H, H-*p*-Ph), 7.23-7.28 (m, 2 H, 2 × H-*m*-Ph).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 24.1 (t, C-4), 29.9 (t, C-3), 55.6 (q, OCH_3-5'-Ar)*, 55.6 (q, OCH_3-5'-Ar)*, 55.7 (t, C-5)*, 60.5 (t, CH_2Ph), 70.3 (d, C-2), 77.6 (*virt.* ts, $^{4}J_{CF,1} \approx {}^{4}J_{CF,2}$ = 2.2 Hz, COH), 99.5 (dd, $^{2}J_{CF}$ = 25.2 Hz, C-4'-Ar), 99.6 (dd, $^{2}J_{CF}$ = 25.5 Hz, C-4'-Ar), 105.2 (dd, $^{2}J_{CF}$ = 23.1 Hz, C-2'-Ar), 105.3 (dd, $^{2}J_{CF}$ = 23.1 Hz, C-2'-Ar), 107.8 (dd, $^{4}J_{CF}$ = 2.6 Hz, C-6'-Ar), 107.9 (dd, $^{4}J_{CF}$ = 2.5 Hz, C-6'-Ar), 127.1 (d, C-*p*-Ph), 128.4 (d, 2 C, 2 × C-*m*-Ph), 128.7 (d, 2 C, 2 × C-*o*-Ph), 139.5 (s, C-*i*-Ph), 149.2 (ds, $^{3}J_{CF}$ = 8.9 Hz, C-1'-Ar), 151.2 (ds, $^{3}J_{CF}$ = 8.0 Hz, C-1'-Ar), 160.7 (ds, $^{3}J_{CF}$ = 11.3 Hz, C-5'-Ar), 160.8 (ds, $^{3}J_{CF}$ = 11.2 Hz, C-5'-Ar), 163.5 (ds, $^{1}J_{CF}$ = 244 Hz, C-3'-Ar), 163.7 (ds, $^{1}J_{CF}$ = 245 Hz, C-3'-Ar).

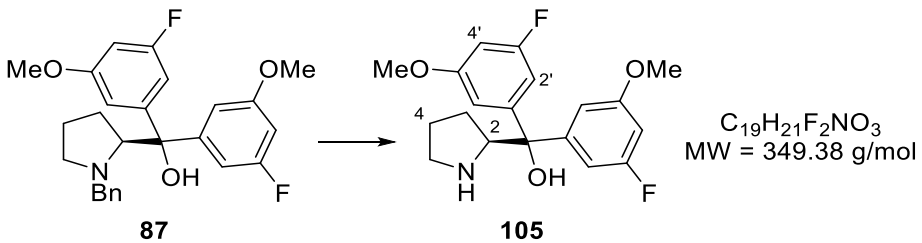
*Assignment of signals is interconvertible.

^{19}F NMR (376 MHz, $CDCl_3$, 300 K): δ [ppm] = –111.9 (*virt.* t, $^{3}J_{HF,1} \approx {}^{3}J_{HF,2}$ = 10.2 Hz, 1 F, F-3'-Ar), –111.6 (*virt.* t, $^{3}J_{HF,1} \approx {}^{3}J_{HF,2}$ = 10.2 Hz, 1 F, F-3'-Ar).

HRMS (ESI): calcd for $C_{26}H_{28}F_2NO_3$ $[M+H]^+$: 440.2032; found: 440.2030.

Specific Rotation: $[\alpha]_D^{26}$ = +51.1 (c = 1.18, CH_2Cl_2).

(*S*)-Bis(3-fluoro-5-methoxyphenyl)(pyrrolidin-2-yl)methanol (105)



87 **105**

Following GP2, alcohol **87** (859 mg, 1.95 mmol, 1.00 equiv) was converted with palladium on carbon (85.9 mg, 10 wt%) under a hydrogen atmosphere (balloon) within one hour. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 10/1), prolinol **105** (560 mg, 1.60 mmol, 82%) was obtained as a highly viscous yellow oil.

TLC: R_f = 0.21 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3357 (br w, NH, OH), 3093 (w, sp^2-CH), 2944 (w, sp^3-CH), 2873 (w, sp^3-CH), 2839 (w, sp^3-CH), 1610 (vs, sp^2-CC), 1590 (vs, sp^2-CC), 1453 (vs), 1428 (vs).

^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.56-1.68 (m, 2 H, H-3), 1.68-1.77 (m, 2 H, H-4), 2.84 (*virt.* dt, ^2J = 10.1 Hz, $^3J_1 \approx {}^3J_2$ = 6.8 Hz, 1 H, *H*H-5), 2.96 (*virt.* dt, ^2J = 10.1 Hz, $^3J_1 \approx {}^3J_2$ = 6.3 Hz, 1 H, H*H*-5), 3.76 (s, 3 H, OC*H*$_3$-5'-Ar), 3.77 (s, 3 H, OC*H*$_3$-5'-Ar), 4.17 (*virt.* t, $^3J_1 \approx {}^3J_2$ = 7.7 Hz, 1 H, H-2), 6.49-6.55 (m, 2 H, 2 × H-4'-Ar), 6.81 (ddd, $^3J_{HF}$ = 10.2 Hz, $^4J_1$ = 2.4 Hz, $^4J_2$ = 1.5 Hz, 1 H, H-2'-Ar), 6.87 (*virt.* t, $^4J_1 \approx {}^4J_2$ = 2.0 Hz, 1 H, H-6'-Ar), 6.91 (ddd, $^3J_{HF}$ = 10.2 Hz, $^4J_1$ = 2.4 Hz, $^4J_2$ = 1.5 Hz, 1 H, H-2'-Ar), 6.97 (*virt.* t, $^4J_1 \approx {}^4J_2$ = 2.0 Hz, 1 H, H-6'-Ar).

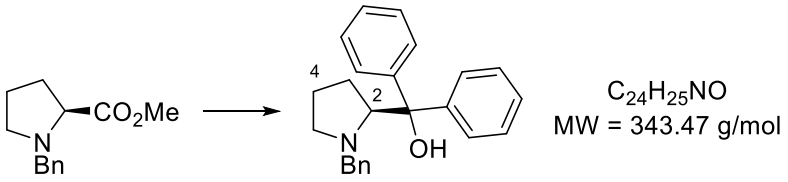
^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 27.1 (t, C-4), 27.9 (t, C-3), 48.3 (t, C-5), 56.0 (q, OCH_3-5'-Ar), 56.0 (q, OCH_3-5'-Ar), 65.5 (d, C-2), 79.3 (*virt.* ts, $^4J_{CF,1} \approx {}^4J_{CF,2}$ = 2.3 Hz, COH), 100.4 (dd, $^2J_{CF}$ = 25.5 Hz, C-4'-Ar), 100.6 (dd, $^2J_{CF}$ = 25.5 Hz, C-4'-Ar), 105.8 (dd, $^2J_{CF}$ = 23.6 Hz, C-2'-Ar), 106.4 (dd, $^2J_{CF}$ = 23.6 Hz, C-2'-Ar), 108.8 (dd, $^4J_{CF}$ = 2.5 Hz, C-6'-Ar), 109.3 (dd, $^4J_{CF}$ = 2.5 Hz, C-6'-Ar), 150.5 (ds, $^3J_{CF}$ = 8.9 Hz, C-1'-Ar), 151.5 (ds, $^3J_{CF}$ = 8.5 Hz, C-1'-Ar), 162.3 (ds, $^3J_{CF}$ = 11.3 Hz, C-5'-Ar), 162.4 (ds, $^3J_{CF}$ = 11.3 Hz, C-5'-Ar), 164.8 (ds, $^1J_{CF}$ = 243 Hz, C-3'-Ar), 165.0 (ds, $^1J_{CF}$ = 243 Hz, C-3'-Ar).

^{19}F NMR (376 MHz, CD_3OD, 298 K): δ [ppm] = –112.1 (*virt.* t, $^3J_{HF,1} \approx {}^3J_{HF,2}$ = 10.4 Hz, 1 F, F-3'-Ar), –111.9 (*virt.* t, $^3J_{HF,1} \approx {}^3J_{HF,2}$ = 10.2 Hz, 1 F, F-3'-Ar).

HRMS (ESI): calcd for $C_{19}H_{22}F_2NO_3$ $[M+H]^+$: 350.1562; found: 350.1561.

Specific Rotation: $[\alpha]_D^{26}$ = –61.7 (c = 1.33, CH_2Cl_2).

(*S*)-(1-Benzylpyrrolidin-2-yl)diphenylmethanol (88)



77 **88**

Following GP1, ester **77** (500 mg, 2.28 mmol, 1.00 equiv) was converted with bromobenzene (895 mg, 5.70 mmol, 2.50 equiv), iodine (5.79 mg, 22.8 μmol, 1.00 mol%) and magnesium turnings (139 mg, 5.70 mmol, 2.50 equiv) within one hour. After purification by column

chromatography (silica, cHex/EtOAc = 20/1 → 10/1), alcohol **88** (722 mg, 2.10 mmol, 92%) was obtained as a colorless solid.

Mp: 115 °C.

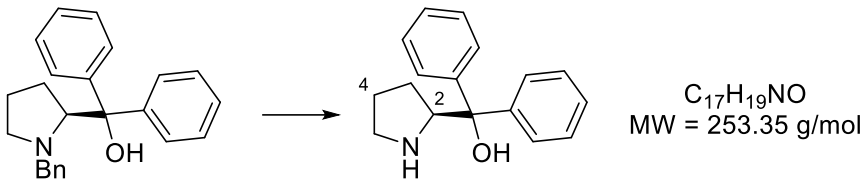
TLC: R_f = 0.39 (P/EtOAc = 9/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.57-1.71 (m, 2 H, H-4), 1.73-1.81 (m, 1 H, *H*H-3), 1.97 (*virt.* dq, ^2J = 13.2 Hz, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 9.0 Hz, 1 H, H*H*-3), 2.36 (*virt.* td, $^2J \approx {}^3J_1$ = 9.5 Hz, $^3J_2$ = 7.1 Hz, 1 H, *H*H-5), 2.89-2.96 (m, 1 H, H*H*-5), 3.03 (d, ^2J = 12.6 Hz, 1 H, C*H*HPh), 3.24 (d, ^2J = 12.6 Hz, 1 H, CH*H*Ph), 3.98 (dd, $^3J_1$ = 9.4 Hz, $^3J_2$ = 4.6 Hz, 1 H, H-2), 4.94 (br s, 1 H, COH), 7.03-7.06 (m, 2 H, 2 × H-*o*-Ph), 7.08-7.12 (m, 1 H, H-*p*-Ar), 7.14-7.32 (m, 8 H, 4 × H-*m*-Ar, H-*p*-Ar, 2 × H-*m*-Ph, H-*p*-Ph), 7.57-7.60 (m, 2 H, 2 × H-*o*-Ar), 7.71-7.75 (m, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 24.3 (t, C-4), 30.0 (t, C-3), 55.7 (t, C-5), 60.7 (t, *C*H_2Ph), 70.8 (d, C-2), 78.1 (s, COH), 125.7 (d, 2 C, 2 × C-*o*-Ar), 125.7 (d, 2 C, 2 × C-*o*-Ar), 126.4 (d, C-*p*-Ar), 126.5 (d, C-*p*-Ar), 127.0 (d, C-*p*-Ph), 128.2 (d, 2 C, 2 × C-*m*-Ar), 128.2 (d, 2 C, 2 × C-*m*-Ar), 128.3 (d, 2 C, 2 × C-*m*-Ph), 128.7 (d, 2 C, 2 × C-*o*-Ph), 139.8 (s, C-*i*-Ph), 146.8 (s, C-*i*-Ar), 148.2 (s, C-*i*-Ar).

The analytical data obtained matched those reported in the literature.[152]

(*S*)-Diphenyl(pyrrolidin-2-yl)methanol (106)



88 **106**

Following GP2, alcohol **88** (709 mg, 2.06 mmol, 1.00 equiv) was converted with palladium on carbon (70.9 mg, 10 wt%) under a hydrogen atmosphere (balloon) within one hour. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 10/1), prolinol **106** (464 mg, 1.83 mmol, 89%) was obtained as a colorless solid.

Mp: 60 °C.

TLC: R_f = 0.09 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$].

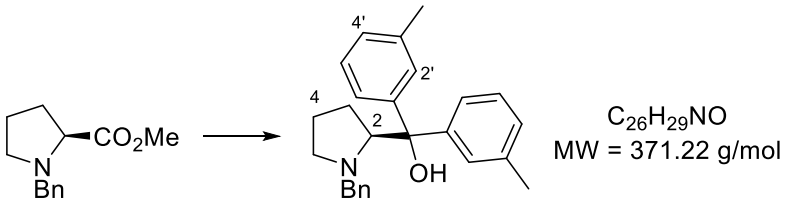
^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.56-1.67 (m, 1 H, *H*H-3), 1.67-1.78 (m, 3 H, H*H*-3, H-4), 2.82 (m, 1 H, *H*H-5), 2.95-3.02 (m, 1 H, H*H*-5), 4.26-4.33 (m, 1 H, H-2), 7.12-7.20

(m, 2 H, 2 × H-*p*-Ph), 7.23-7.32 (m, 4 H, 4 × H-*m*-Ph), 7.44-7.49 (m, 2 H, 2 × H-*o*-Ph), 7.55-7.60 (m, 2 H, 2 × H-*o*-Ph).

^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 27.1 (t, C-4), 27.9 (t, C-3), 48.2 (t, C-5), 65.9 (d, C-2), 79.6 (s, COH), 126.8 (d, 2 C, 2 × C-*o*-Ph), 127.3 (d, 2 C, 2 × C-*o*-Ph), 127.5 (d, C-*p*-Ph), 127.7 (d, C-*p*-Ph), 129.0 (d, 2 C, 2 × C-*m*-Ph), 129.2 (d, 2 C, 2 × C-*m*-Ph), 147.5 (s, C-*i*-Ph), 148.2 (s, C-*i*-Ph).

The analytical data obtained matched those reported in the literature.[274]

(*S*)-(1-Benzylpyrrolidin-2-yl)di-*m*-tolylmethanol (89)



Following GP1, ester **77** (500 mg, 2.28 mmol, 1.00 equiv) was converted with 1-bromo-3-methylbenzene (975 mg, 5.70 mmol, 2.50 equiv), iodine (5.79 mg, 22.8 µmol, 1.00 mol%) and magnesium turnings (139 mg, 5.70 mmol, 2.50 equiv) within one hour. After purification by column chromatography (silica, cHex/EtOAc = 30/1), alcohol **89** (821 mg, 2.21 mmol, 97%) was obtained as a viscous yellow oil.

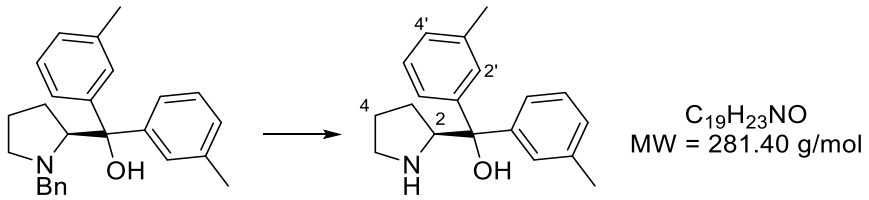
TLC: R_f = 0.37 (P/EtOAc = 9/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.58-1.68 (m, 2 H, H-4), 1.69-1.81 (m, 1 H, *H*H-3), 1.93-2.08 (m, 1 H, H*H*-3), 2.27 (s, 3 H, CH_3-3'-Ar), 2.31 (s, 3 H, CH_3-3'-Ar), 2.33-2.42 (m, 1 H, *H*H-5), 2.83-2.95 (m, 1 H, H*H*-5), 3.04 (d, ^2J = 12.3 Hz, 1 H, C*H*HPh), 3.16 (d, ^2J = 12.3 Hz, 1 H, CH*H*Ph), 3.90-4.14 (m, 1 H, H-2), 6.92 (d, ^3J = 7.5 Hz, 1 H, H-4'-Ar), 6.98 (d, ^3J = 7.5 Hz, 1 H, H-4'-Ar), 7.02-7.06 (m, 2 H, 2 × H-*o*-Ph), 7.10-7.23 (m, 5 H, 2 × H-5'-Ar, 2 × H-*m*-Ph, H-*p*-Ph), 7.36 (d, ^2J = 8.0 Hz, 1 H, H-6'-Ar), 7.40 (br s, 1 H, H-2'-Ar), 7.44 (d, ^3J = 8.5 Hz, 1 H, H-6'-Ar), 7.55 (br s, 1 H, H-2'-Ar).

^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 21.7 (q, 2 C, 2 × *C*H_3-3'-Ar), 25.3 (t, C-4), 30.7 (t, C-3), 56.6 (t, C-5), 61.9 (t, *C*H_2Ph), 72.0 (d, C-2), 79.9 (s, COH), 124.2 (d, C-6'-Ar), 124.4 (d, C-6'-Ar), 127.7 (d, C-2'-Ar), 127.8 (d, C-2'-Ar), 128.0 (d, 3 C, 2 × C-4'-Ar, C-*p*-Ph), 128.8 (d, C-5'-Ar), 128.9 (d, C-5'-Ar), 129.1 (d, 2 C, 2 × C-*m*-Ph), 129.5 (d, 2 C, 2 × C-*o*-Ph), 138.6 (s, C-3'-Ar), 138.6 (s, C-3'-Ar), 141.2 (s, C-*i*-Ph), 147.9 (s, C-1'-Ar), 149.2 (s, C-1'-Ar).

The analytical data obtained matched those reported in the literature.[266]

(*S*)-Pyrrolidin-2-yldi-*m*-tolylmethanol (107)



89 **107**

Following GP2, alcohol **89** (809 g, 2.18 mmol, 1.00 equiv) was converted with palladium on carbon (80.9 mg, 10 wt%) under a hydrogen atmosphere (balloon) within one hour. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 20/1 → 10/1), prolinol **107** (481 mg, 1.71 mmol, 78%) was obtained as a low-melting amorphous colorless solid.

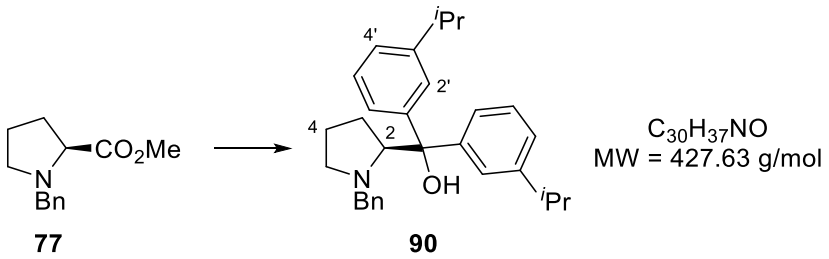
TLC: R_f = 0.11 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$].

^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.55-1.65 (m, 1 H, *H*H-3), 1.65-1.77 (m, 3 H, H*H*-3, H-4), 2.28 (s, 3 H, C*H*$_3$-3'-Ar), 2.30 (s, 3 H, C*H*$_3$-3'-Ar), 2.81-2.87 (m, 1 H, *H*H-5), 2.93-3.00 (m, 1 H, H*H*-5), 4.22-4.28 (m, 1 H, H-2), 6.95-7.01 (m, 2 H, 2 × H-4'-Ar), 7.13 (*virt.* t, $^3J_1 \approx {}^3J_2$ = 7.7 Hz, 1 H, H-5'-Ar), 7.17 (*virt.* t, $^3J_1 \approx {}^3J_2$ = 7.7 Hz, 1 H, H-5'-Ar), 7.22-7.25 (m, 1 H, H-6'-Ar), 7.28 (*virt.* t, $^4J_1 \approx {}^4J_2$ = 1.8 Hz, 1 H, H-2'-Ar), 7.33-7.36 (m, 1 H, H-6'-Ar), 7.38 (*virt.* t, $^4J_1 \approx {}^4J_2$ = 1.8 Hz, 1 H, H-2'-Ar).

^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 21.7 (q, *C*H$_3$-3'-Ar), 21.7 (q, *C*H$_3$-3'-Ar), 27.1 (t, C-4), 28.0 (t, C-3), 48.2 (t, C-5), 65.8 (d, C-2), 79.7 (s, COH), 123.9 (d, C-6'-Ar), 124.4 (d, C-6'-Ar), 127.4 (d, C-2'-Ar), 128.0 (d, C-2'-Ar), 128.1 (d, C-4'-Ar), 128.3 (d, C-4'-Ar), 128.8 (d, C-5'-Ar), 129.1 (d, C-5'-Ar), 138.6 (s, C-3'-Ar), 138.8 (s, C-3'-Ar), 147.6 (s, C-1'-Ar), 148.2 (s, C-1'-Ar).

The analytical data obtained matched those reported in the literature.[266]

(*S*)-(1-Benzylpyrrolidin-2-yl)bis(3-isopropylphenyl)methanol (90)



Following GP1, ester **77** (441 mg, 2.01 mmol, 1.00 equiv) was converted with 1-bromo-3-isopropylbenzene (1.00 g, 5.02 mmol, 2.50 equiv), iodine (5.10 mg, 20.1 µmol, 1.00 mol%) and magnesium turnings (122 mg, 5.02 mmol, 2.50 equiv) within one hour. After purification by column chromatography (silica, cHex/EtOAc = 1/0→ 20/1), alcohol **90** (812 mg, 1.90 mmol, 95%) was obtained as a viscous yellow oil.

TLC: R_f = 0.30 (P/EtOAc = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3347 (br w, OH), 3027 (w, sp^2-CH), 2959 (vs, sp^3-CH), 2869 (m, sp^3-CH), 2800 (m, sp^3-CH), 700 (vs, sp^2-CH).

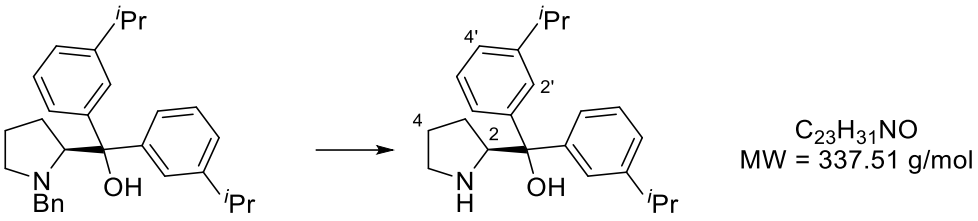
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.18 (d, ^3J = 6.9 Hz, 3 H, CHC*H*$_3$CH$_3$-3'-Ar), 1.20 (d, ^3J = 6.9 Hz, 3 H, CHCH$_3$C*H*$_3$-3'-Ar), 1.25 (d, ^3J = 6.9 Hz, 3 H, CHC*H*$_3$CH$_3$-3'-Ar), 1.25 (d, ^3J = 6.9 Hz, 3 H, CHCH$_3$C*H*$_3$-3'-Ar), 1.57-1.71 (m, 2 H, H-4), 1.71-1.80 (m, 1 H, *H*H-3), 1.95 (*virt.* dq, ^2J = 13.1 Hz, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 9.0 Hz, 1 H, H*H*-3), 2.36 (*virt.* td, $^2J \approx {}^3J_1$ = 9.5 Hz, $^3J_2$ = 6.9 Hz, 1 H, *H*H-5), 2.82-2.97 (m, 3 H, H*H*-5, 2 × C*H*Me$_2$-3'-Ar), 3.03 (d, ^2J = 12.7 Hz, 1 H, C*H*HPh), 3.22 (d, ^2J = 12.7 Hz, 1 H, CH*H*Ph), 3.98 (dd, $^3J_1$ = 9.4 Hz, $^3J_2$ = 4.7 Hz, 1 H, H-2), 4.91 (br s, 1 H, COH), 6.96 (*virt.* dt, ^3J = 7.5 Hz, $^4J_1 \approx {}^4J_2$ = 1.3 Hz, 1 H, H-4'-Ar), 7.01-7.05 (m, 3 H, H-4'-Ar, 2 × H-*o*-Ph), 7.15-7.24 (m, 5 H, 2 × H-5'-Ar, 2 × H-*m*-Ph, H-*p*-Ph), 7.38-7.42 (m, 1 H, H-6'-Ar), 7.46 (*virt.* t, $^4J_1 \approx {}^4J_2$ = 1.8 Hz, 1 H, H-2'-Ar), 7.48 (ddd, ^3J = 7.9 Hz, $^4J_1$ = 1.9 Hz, $^4J_2$ = 1.2 Hz, 1 H, H-6'-Ar), 7.67 (*virt.* t, $^4J_1 \approx {}^4J_2$ = 1.9 Hz, 1 H, H-2'-Ar).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 24.1 (q, CH*C*H$_3$CH$_3$-3'-Ar), 24.2 (q, CHCH$_3$*C*H$_3$-3'-Ar), 24.2 (q, CH*C*H$_3$CH$_3$-3'-Ar), 24.2 (q, CHCH$_3$*C*H$_3$-3'-Ar), 24.4 (t, C-4), 29.9 (t, C-3), 34.4 (d, *C*HMe$_2$-3'-Ar), 34.5 (d, *C*HMe$_2$-3'-Ar), 55.8 (t, C-5), 60.7 (t, *C*H$_2$Ph), 71.1 (d, C-2), 78.2 (s, COH), 123.2 (d, C-6'-Ar), 123.6 (d, C-6'-Ar), 123.8 (d, C-2'-Ar), 123.9 (d, C-2'-Ar), 124.2 (d, C-4'-Ar), 124.4 (d, C-4'-Ar), 126.9 (d, C-*p*-Ph), 128.0 (d, C-5'-Ar), 128.1 (d, C-5'-Ar), 128.2 (d, 2 C, 2 × C-*m*-Ph), 128.7 (d, 2 C, 2 × C-*o*-Ph), 140.0 (s, C-*i*-Ph), 146.7 (s, C-1'-Ar), 148.1 (s, C-1'-Ar), 148.5 (s, C-3'-Ar), 148.7 (s, C-3'-Ar).

HRMS (ESI): calcd for $C_{30}H_{38}NO$ $[M+H]^+$: 428.2948; found: 428.2947.

Specific Rotation: $[\alpha]_D^{25} = +79.8$ (c = 1.18, CH_2Cl_2).

(*S*)-Bis(3-isopropylphenyl)(pyrrolidin-2-yl)methanol (108)



90 **108**

Following GP2, alcohol **90** (790 mg, 1.85 mmol, 1.00 equiv) was converted with palladium on carbon (79.0 mg, 10 wt%) under a hydrogen atmosphere (balloon) within two hours. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 30/1 → 10/1), prolinol **108** (563 mg, 1.67 mmol, 90%) was obtained as a low-melting amorphous yellow solid.

TLC: R_f = 0.17 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3352 (br w, NH, OH), 2958 (s, sp^3-CH), 2869 (m, sp^3-CH), 1601 (m), 703 (vs, sp^2-CH).

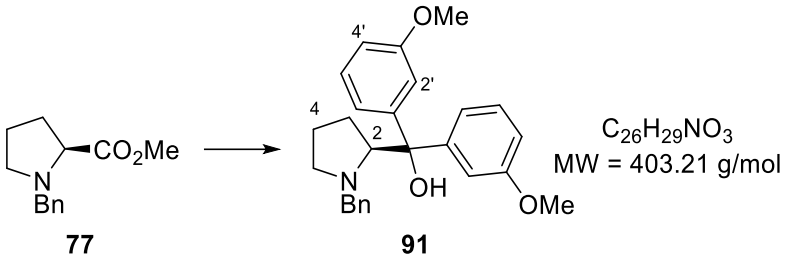
^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.19-1.24 [m, 12 H, 2 × CH(C*H*$_3$)$_2$-3'-Ar], 1.59-1.69 (m, 1 H, *H*H-3), 1.69-1.79 (m, 3 H, H*H*-3, H-4), 2.80-2.92 [m, 3 H, *H*H-5, 2 × C*H*(CH$_3$)$_2$-3'-Ar], 2.95-3.02 (m, 1 H, H*H*-5), 4.26-4.32 (m, 1 H, H-2), 7.02-7.09 (m, 2 H, 2 × H-4'-Ar), 7.15-7.27 (m, 3 H, 2 × H-5'-Ar, H-6'-Ar), 7.35-7.39 (m, 2 H, H-2'-Ar, H-6'-Ar), 7.44-7.47 (m, 1 H, H-2'-Ar).

^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 24.4 (q, CH*C*H$_3$CH$_3$-3'-Ar), 24.5 (q, CHCH$_3$*C*H$_3$-3'-Ar), 24.5 (q, CH*C*H$_3$CH$_3$-3'-Ar), 24.6 (q, CHCH$_3$*C*H$_3$-3'-Ar), 27.0 (t, C-4), 28.0 (t, C-3), 35.5 (d, *C*HMe$_2$-3'-Ar), 35.6 (d, *C*HMe$_2$-3'-Ar), 48.2 (t, C-5), 66.1 (d, C-2), 79.9 (s, COH), 124.5 (d, C-6'-Ar), 124.8 (d, C-6'-Ar), 125.0 (d, C-2'-Ar), 125.4 (d, C-2'-Ar), 125.6 (d, C-4'-Ar), 125.6 (d, C-4'-Ar), 128.9 (d, C-5'-Ar), 129.2 (d, C-5'-Ar), 147.4 (s, C-1'-Ar), 148.1 (s, C-1'-Ar), 149.7 (s, C-3'-Ar), 149.9 (s, C-3'-Ar).

HRMS (ESI): calcd for $C_{23}H_{32}NO$ $[M+H]^+$: 338.2478; found: 338.2478.

Specific Rotation: $[\alpha]_D^{27} = -71.3$ (c = 1.35, CH_2Cl_2).

(*S*)-(1-Benzylpyrrolidin-2-yl)bis(3-methoxyphenyl)methanol (91)



Following GP1, ester **77** (500 mg, 2.28 mmol, 1.00 equiv) was converted with 1-bromo-3-methoxybenzene (1.07 g, 5.70 mmol, 2.50 equiv), iodine (5.79 mg, 22.8 µmol, 1.00 mol%) and magnesium turnings (139 mg, 5.70 mmol, 2.50 equiv) within one hour. After purification by column chromatography (silica, cHex/EtOAc = 20/1 → 9/1), alcohol **91** (888 mg, 2.20 mmol, 96%) was obtained as a viscous yellow oil.

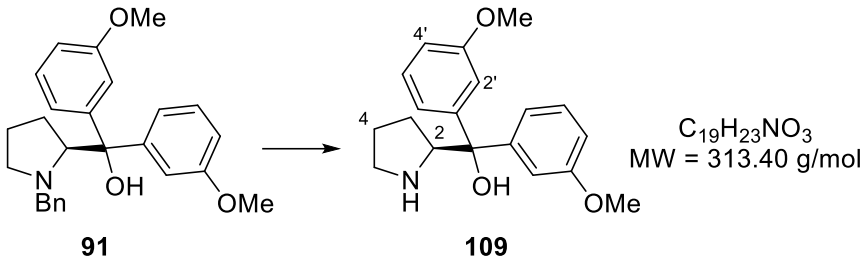
TLC: R_f = 0.14 (P/EtOAc = 9/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.57-1.67 (m, 2 H, H-4), 1.67-1.77 (m, 1 H, *H*H-3), 1.95-2.07 (m, 1 H, H*H*-3), 2.27-2.46 (m, 1 H, *H*H-5), 2.83-2.95 (m, 1 H, H*H*-5), 3.07 (d, ^2J = 12.9 Hz, 1 H, C*H*HPh), 3.23 (d, ^2J = 12.9 Hz, 1 H, CH*H*Ph), 3.73 (s, 3 H, OCH_3-3'-Ar), 3.76 (s, 3 H, OCH_3-3'-Ar), 3.95-4.09 (m, 1 H, H-2), 6.68 (ddd, ^3J = 8.1 Hz, $^4J_1$ = 2.6 Hz, $^4J_2$ = 1.0 Hz, 1 H, H-4'-Ar), 6.73 (ddd, ^3J = 7.9 Hz, $^4J_1$ = 2.5 Hz, $^4J_2$ = 1.4 Hz, 1 H, H-4'-Ar), 7.03-7.07 (m, 2 H, 2 × H-Ph), 7.13-7.23 (m, 7 H, H-2'-Ar, 2 × H-5'-Ar, H-6'-Ar, 3 × H-Ph), 7.26 (ddd, ^3J = 7.9 Hz, $^4J_1$ = 1.8 Hz, $^4J_2$ = 1.0 Hz, 1 H, H-6'-Ar), 7.34 (dd, $^4J_1$ = 2.5 Hz, $^4J_2$ = 1.8 Hz, 1 H, H-2'-Ar).

^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 25.2 (t, C-4), 30.7 (t, C-3), 55.6 (q, O*C*H$_3$-3'-Ar), 55.6 (q, O*C*H$_3$-3'-Ar), 56.6 (t, C-5), 61.9 (t, *C*H$_2$Ph), 71.9 (d, C-2), 79.7 (s, COH), 112.6 (d, C-4'-Ar), 112.6 (d, C-4'-Ar), 113.1 (d, C-2'-Ar), 113.2 (d, C-2'-Ar), 119.4 (d, C-6'-Ar), 119.7 (d, C-6'-Ar), 127.8 (d, C-*p*-Ph), 129.1 (d, 2 C, 2 × C-Ph), 129.6 (d, 2 C, 2 × C-Ph), 129.9 (d, C-5'-Ar), 130.0 (d, C-5'-Ar), 141.1 (s, C-*i*-Ph), 149.4 (s, C-1'-Ar), 150.8 (s, C-1'-Ar), 160.9 (s, C-3'-Ar), 161.0 (s, C-3'-Ar).

The analytical data obtained matched those reported in the literature.[266]

(*S*)-Bis(3-methoxyphenyl)(pyrrolidin-2-yl)methanol (109)



Following GP2, alcohol **91** (872 mg, 2.16 mmol, 1.00 equiv) was converted with palladium on carbon (87.2 mg, 10 wt%) under a hydrogen atmosphere (balloon) within one hour. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 15/1 → 10/1), prolinol **109** (517 mg, 1.65 mmol, 76%) was obtained as a low-melting amorphous colorless solid.

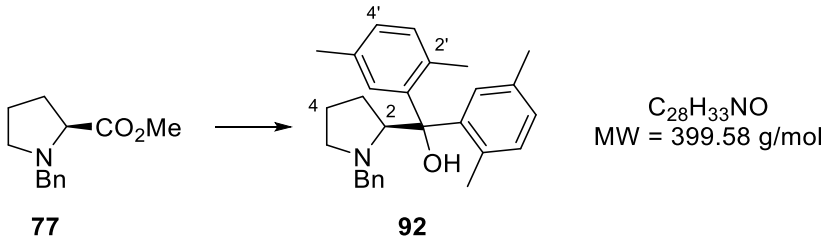
TLC: R_f = 0.09 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.56-1.66 (m, 1 H, *H*H-3), 1.66-1.77 (m, 3 H, H*H*-3, H-4), 2.80-2.87 (m, 1 H, *H*H-5), 2.93-3.00 (m, 1 H, H*H*-5), 3.74 (s, 3 H, OC*H*$_3$-3'-Ar), 3.75 (s, 3 H, OC*H*$_3$-3'-Ar), 4.19-4.26 (m, 1 H, H-2), 6.70-6.76 (m, 2 H, 2 × H-4'-Ar), 7.01 (ddd, ^3J = 7.8 Hz, $^4J_1$ = 1.7 Hz, $^4J_2$ = 1.0 Hz, 1 H, H-6'-Ar), 7.07 (dd, $^4J_1$ = 2.6 Hz, $^4J_2$ = 1.7 Hz, 1 H, H-2'-Ar), 7.12-7.23 (m, 4 H, H-2'-Ar, 2 × H-5'-Ar, H-6'-Ar).

^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 27.1 (t, C-4), 28.0 (t, C-3), 48.2 (t, C-5), 55.6 (q, O*C*H$_3$-3'-Ar), 55.6 (q, O*C*H$_3$-3'-Ar), 65.8 (d, C-2), 79.6 (s, COH), 112.6 (d, C-4'-Ar), 112.8 (d, C-2'-Ar), 112.9 (d, C-4'-Ar), 113.4 (d, C-2'-Ar), 119.2 (d, C-6'-Ar), 119.6 (d, C-6'-Ar), 129.9 (d, C-5'-Ar), 130.1 (d, C-5'-Ar), 149.1 (s, C-1'-Ar), 149.9 (s, C-1'-Ar), 160.9 (s, C-3'-Ar), 161.1 (s, C-3'-Ar).

The analytical data obtained matched those reported in the literature.[266]

(*S*)-(1-Benzylpyrrolidin-2-yl)bis(2,5-dimethylphenyl)methanol (92)



Following GP1, ester **77** (500 mg, 2.28 mmol, 1.00 equiv) was converted with 1-bromo-2,5-dimethylbenzene (1.05 g, 5.70 mmol, 2.50 equiv), iodine (5.79 mg, 22.8 μmol, 1.00 mol%) and magnesium turnings (139 mg, 5.70 mmol, 2.50 equiv) within one hour at

100 °C. After purification by column chromatography (silica, cHex/EtOAc = 1/0→ 50/1), alcohol **92** (766 mg, 1.92 mmol, 84%) was obtained as a pale yellow solid.

Mp: 113 °C.

TLC: R_f = 0.20 (P/EtOAc = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3370 (br w, OH), 3024 (w, sp^2-CH), 2922 (m, sp^3-CH), 2883 (w, sp^3-CH), 2792 (w, sp^3-CH), 1493 (s), 1451 (s), 808 (vs, sp^2-CH), 697 (vs, sp^2-CH).

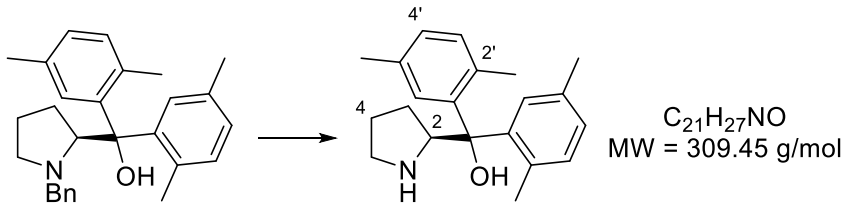
^{1}H NMR (400 MHz, $CDCl_3$, 328 K): δ [ppm] = 1.59-1.76 (m, 2 H, H-4), 2.07 (s, 3 H, C*H*$_3$-2'-Ar), 2.15 (s, 3 H, C*H*$_3$-2'-Ar), 2.17-2.24 (m, 2 H, H-3), 2.27 (s, 3 H, C*H*$_3$-5'-Ar), 2.29-2.34 (m, 1 H, *H*H-5), 2.36 (s, 3 H, C*H*$_3$-5'-Ar), 2.88-3.05 (m, 3 H, H*H*-5, C*H*$_2$Ph), 3.95 (dd, $^3J_1$ = 8.7 Hz, $^3J_2$ = 4.5 Hz, 1 H, H-2), 4.43 (br s, 1 H, COH), 6.77-6.85 (m, 2 H, H-3'-Ar, H-4'-Ar), 6.88-6.96 (m, 2 H, H-3'-Ar, H-4'-Ar), 6.99-7.10 (m, 2 H, 2 × H-*o*-Ph), 7.12-7.25 (m, 3 H, 2 × H-*m*-Ph, H-*p*-Ph), 7.29 (s, 1 H, H-6'-Ar), 7.72 (s, 1 H, H-6'-Ar).

^{13}C NMR (101 MHz, $CDCl_3$, 328 K): δ [ppm] = 21.3 (q, *C*H$_3$-2'-Ar), 21.3 (q, *C*H$_3$-5'-Ar), 21.5 (q, *C*H$_3$-5'-Ar), 22.3 (q, *C*H$_3$-2'-Ar), 25.1 (t, C-4), 31.2 (t, C-3), 56.1 (t, C-5), 61.1 (t, *C*H$_2$Ph), 69.0 (d, C-2), 81.4 (s, COH), 126.8 (d, C-*p*-Ph), 127.6 (d, C-4'-Ar), 127.7 (d, C-4'-Ar), 128.1 (d, 2 C, 2 × C-*m*-Ph), 128.7 (d, 2 C, 2 × C-*o*-Ph), 129.6 (d, C-6'-Ar), 130.6 (d, C-6'-Ar), 132.3 (d, C-3'-Ar), 132.4 (s, C-2'-Ar), 132.6 (d, C-3'-Ar), 132.8 (s, C-5'-Ar), 134.3 (s, C-5'-Ar), 136.0 (s, C-2'-Ar), 140.1 (s, C-*i*-Ph), 141.4 (s, C-1'-Ar), 143.5 (s, C-1'-Ar).

HRMS (ESI): calcd for $C_{28}H_{34}NO$ $[M+H]^+$: 400.2635; found: 400.2634.

Specific Rotation: $[\alpha]_D^{26}$ = +233 (c = 1.37, CH_2Cl_2).

(*S*)-Bis(2,5-dimethylphenyl)(pyrrolidin-2-yl)methanol (110)



92 **110**

Following GP2, alcohol **92** (746 mg, 1.87 mmol, 1.00 equiv) was converted with palladium on carbon (74.6 mg, 10 wt%) under a hydrogen atmosphere (balloon) within two hours. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 1/0 → 50/1→ 10/1), prolinol **110** (528 mg, 1.71 mmol, 91%) was obtained as a colorless solid.

Mp: decomp. >150 °C.

TLC: R_f = 0.11 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3306 (br w, NH, OH), 2922 (m, sp^3-CH), 2869 (m, sp^3-CH), 2734 (m, sp^3-CH), 1495 (m, sp^3-CH), 802 (vs, sp^2-CH).

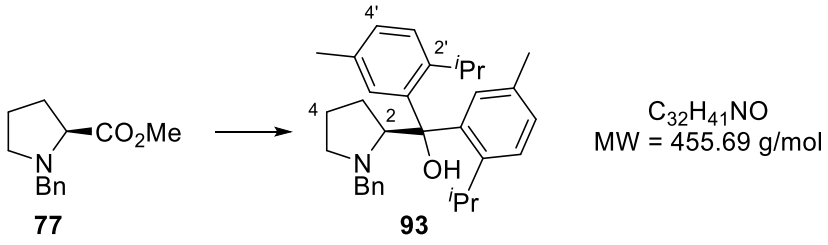
^{1}H NMR (400 MHz, CD_3OD, 328 K): δ [ppm] = 1.48-1.65 (m, 1 H, *H*H-3), 1.69-1.86 (m, 3 H, H*H*-3, H-4), 1.91 (s, 6 H, 2 × C*H*$_3$-2'-Ar), 2.30 (s, 3 H, C*H*$_3$-5'-Ar), 2.35 (s, 3 H, C*H*$_3$-5'-Ar), 2.95-3.09 (m, 2 H, H-5), 4.34-4.44 (m, 1 H, H-2), 6.82-6.99 (m, 4 H, 2 × H-3'-Ar, 2 × H-4'-Ar), 7.52 (br s, 1 H, H-6'-Ar), 7.58 (br s, 1 H, H-6'-Ar).

^{13}C NMR (101 MHz, CD_3OD, 328 K): δ [ppm] = 21.2 (q, 2 C, 2 × *C*H$_3$-5'-Ar), 21.4 (q, *C*H$_3$-2'-Ar), 21.5 (q, *C*H$_3$-2'-Ar), 26.7 (t, C-4), 29.0 (t, C-3), 48.0 (t, C-5), 64.5 (d, C-2), 80.7 (s, COH), 128.5 (d, C-4'-Ar), 128.8 (d, C-4'-Ar), 129.5 (d, C-6'-Ar), 130.0 (d, C-6'-Ar), 133.1 (d, C-3'-Ar), 133.7 (d, C-3'-Ar), 134.0 (s, C-1'-Ar), 135.1 (s, C-5'-Ar), 135.5 (s, C-5'-Ar), 135.5 (s, C-1'-Ar), 143.3 (s, C-2'-Ar), 144.0 (s, C-2'-Ar).

HRMS (ESI): calcd for $C_{21}H_{28}NO$ $[M+H]^+$: 310.2165; found: 310.2165.

Specific Rotation: $[\alpha]_D^{27}$ = –70.1 (c = 1.14, MeOH).

(*S*)-(1-Benzylpyrrolidin-2-yl)bis(2-isopropyl-5-methylphenyl)methanol (93)



Following GP1, ester **77** (412 mg, 1.88 mmol, 1.00 equiv) was converted with 2-bromo-1-isopropyl-4-methylbenzene (1.00 g, 4.69 mmol, 2.50 equiv), iodine (4.76 mg, 18.8 µmol, 1.00 mol%) and magnesium turnings (114 mg, 4.69 mmol, 2.50 equiv) within three hours at 100 °C. After purification by column chromatography (silica, cHex/EtOAc = 1/0→ 50/1), alcohol **93** (711 mg, 1.56 mmol, 83%) was obtained as a pale viscous yellow oil.

TLC: R_f = 0.38 (P/EtOAc = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3398 (br w, OH), 3025 (w, sp^2-CH), 2957 (s, sp^3-CH), 2925 (m, sp^3-CH), 2868 (w, sp^3-CH), 1454 (s, sp^3-CH), 818 (vs, sp^2-CH), 697 (vs, sp^2-CH).

^{1}H NMR (400 MHz, $CDCl_3$, 328 K): δ [ppm] = 1.05-1.31 [m, 12 H, 2 × CH(C*H*$_3$)$_2$-2'-Ar], 1.58-1.77 (m, 2 H, H-4), 1.93-2.52 (m, 9 H, H-3, *H*H-5, 2 × C*H*$_3$-5'-Ar), 2.74-3.45 (m, 5 H, H*H*-5, 2 × C*H*Me$_2$-2'-Ar, C*H*$_2$Ph), 3.81-4.10 (m, 1 H, H-2), 4.54 (br s, 1 H, COH), 6.79-7.03 (m, 4 H, 2 × H-3'-Ar, 2 × H-4'-Ar), 7.03-7.11 (m, 2 H, 2 × H-*o*-Ph), 7.11-7.24 (m, 3 H, 2 × H-*m*-Ph, H-*p*-Ph), 7.33-7.41 (m, 1 H, H-6'-Ar), 7.76-7.95 (m, 1 H, H-6'-Ar).

^{13}C NMR (101 MHz, $CDCl_3$, 328 K): δ [ppm] = 21.2 (q, *C*H$_3$-5'-Ar), 22.2 (q, *C*H$_3$-5'-Ar), 23.6 (q, CH*C*H$_3$CH$_3$-2'-Ar), 24.2 (q, CHCH$_3$*C*H$_3$-2'-Ar), 24.2 (q, CH*C*H$_3$CH$_3$-2'-Ar), 24.5 (q, CHCH$_3$*C*H$_3$-2'-Ar), 25.0 (t, C-4), 31.2 (t, C-3), 34.1 (d, *C*HMe$_2$-2'-Ar), 34.2 (d, *C*HMe$_2$-2'-Ar), 56.0 (t, C-5), 61.0 (t, *C*H$_2$Ph), 68.7 (d, C-2), 81.5 (s, COH), 124.8 (d, C-4'-Ar), 124.9 (d, C-4'-Ar), 126.8 (d, C-*p*-Ph), 127.2 (d, C-6'-Ar), 128.1 (d, 2 C, 2 × C-*m*-Ph), 128.2 (d, C-6'-Ar), 128.7 (d, 2 C, 2 × C-*o*-Ph), 132.4 (d, C-3'-Ar), 132.6 (d, C-3'-Ar), 136.4 (s, 2 C, 2 × C-1'-Ar)*, 140.0 (s, C-*i*-Ph), 141.1 (s, C-5'-Ar)**, 143.4 (s, C-5'-Ar), 143.7 (s, C-2'-Ar), 145.2 (s, C-2'-Ar).

Only signals of the major rotamer are assigned.

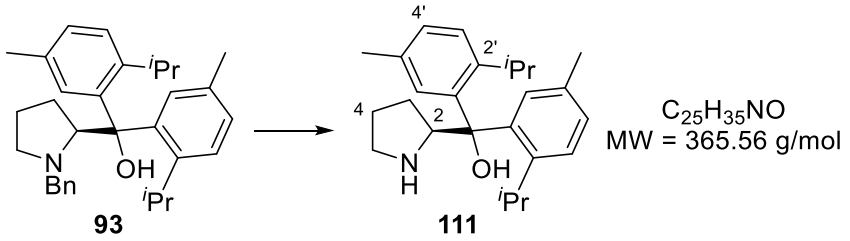
*The ^{13}C signal intensity of C-1'-Ar was insufficient for an appropriate assignment. However, the signal can be located with the help of a HMBC crosspeak with the proton signal of H-6-Ar to assign the ^{13}C signal of C-1'-Ar.

**The ^{13}C signal intensity of C-5'-Ar was insufficient for an appropriate assignment. However, the signal can be located with the help of a HMBC crosspeak with the proton signal of *C*H$_3$-5'-Ar to assign the ^{13}C signal of C-5'-Ar.

HRMS (ESI): calcd for $C_{32}H_{42}NO$ $[M+H]^+$: 456.3261; found: 456.3259.

Specific Rotation: $[\alpha]_D^{25}$ = +209 (c = 1.40, CH_2Cl_2).

(*S*)-Bis(2-isopropyl-5-methylphenyl)(pyrrolidin-2-yl)methanol (111)



Following GP2, alcohol **93** (698 mg, 1.53 mmol, 1.00 equiv) was converted with palladium on carbon (69.8 mg, 10 wt%) under a hydrogen atmosphere (balloon) within two hours. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 1/0 → 100/1→ 10/1), prolinol **111** (528 mg, 1.50 mmol, 98%) was obtained as a highly viscous yellow oil.

TLC: R_f = 0.20 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3336 (br w, NH, OH), 2956 (s, sp^3-CH), 2926 (m, sp^3-CH), 2867 (m, sp^3-CH), 1493 (m, sp^2-CC), 1457 (m, sp^2-CC), 818 (vs, sp^2-CH).

^{1}H NMR (400 MHz, CD_3OD, 333 K): δ [ppm] = 0.22-1.03 (m, 3 H, CHC*H*$_3$CH$_3$-2'-Ar), 1.13-1.34 [m, 9 H, CHCH$_3$C*H*$_3$-2'-Ar, CH(C*H*$_3$)$_2$-2'-Ar], 1.56-2.42 (m, 10 H, H-3, H-4, 2 × C*H*$_3$-5'-Ar), 2.80-3.60 (m, 4 H, H-5, 2 × C*H*Me$_2$-2'-Ar), 4.31-4.45 (m, 1 H, H-2), 6.82-7.16 (m, 4 H, 2 × H-3'-Ar, 2 × H-4'-Ar), 7.41-7.80 (m, 2 H, 2 × H-6'-Ar).

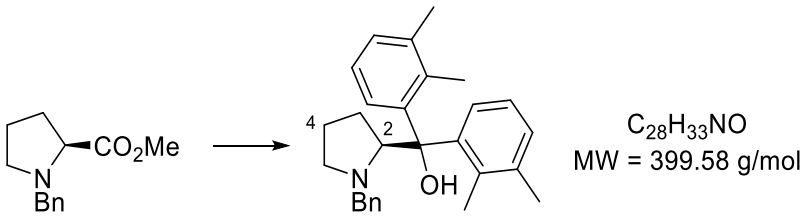
^{13}C NMR (101 MHz, CD_3OD, 333 K): δ [ppm] = 21.4 (q, *C*H$_3$-5'-Ar), 21.4 (q, *C*H$_3$-5'-Ar), 24.4 (q, CH*C*H$_3$CH$_3$-2'-Ar), 24.4 (q, CHCH$_3$*C*H$_3$-2'-Ar), 24.4 (q, CH*C*H$_3$CH$_3$-2'-Ar), 24.5 (q, CHCH$_3$*C*H$_3$-2'-Ar), 26.8 (t, C-4), 29.0 (t, C-3), 35.1 (d, *C*HMe$_2$-2'-Ar), 35.1 (d, *C*HMe$_2$-2'-Ar), 48.0 (t, C-5), 64.4 (d, C-2), 81.0 (s, COH), 125.8 (d, C-4'-Ar), 127.5 (d, C-6'-Ar), 127.7 (d, C-6'-Ar), 129.3 (d, C-4'-Ar), 133.2 (d, C-3'-Ar), 133.8 (d, C-3'-Ar), 134.6 (s, C-5'-Ar), 135.8 (s, C-5'-Ar), 143.2 (s, C-1'-Ar), 144.0 (s, C-1'-Ar), 146.2 (s, C-2'-Ar), 146.7 (s, C-2'-Ar).

Only signals of the major rotamer are assigned.

HRMS (ESI): calcd for $C_{25}H_{36}NO$ $[M+H]^+$: 366.2791; found: 366.2791.

Specific Rotation: $[\alpha]_D^{27}$ = –159 (c = 1.06, CH_2Cl_2).

(*S*)-(1-Benzylpyrrolidin-2-yl)bis(2,3-dimethylphenyl)methanol (94)



77 **94**

Following GP1, ester **77** (5.00 g, 22.8 mmol, 1.00 equiv) was converted with 1-bromo-2,3-dimethylbenzene (7.64 mL, 10.6 g, 57.0 mmol, 2.50 equiv), iodine (57.9 mg, 228 µmol, 1.00 mol%) and magnesium turnings (1.39 g, 57.0 mmol, 2.50 equiv) within 72 hours. After purification by column chromatography (silica, Hex/EtOAc = 1/0 → 20/1 → 10/1), alcohol **94** (7.00 g, 17.5 mmol, 77%) was obtained as a yellow viscous oil.

TLC: R_f = 0.44 (Hex/EtOAc = 8/2) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3409 (br w, OH), 3060 (w, sp^2-CH), 3027 (w, sp^2-CH), 2944 (m, sp^3-CH), 2912 (m, sp^3-CH), 2796 (w, sp^3-CH), 1736 (w), 1453 (s, sp^3-CH), 779 (vs, sp^2-CH), 735 (vs, sp^2-CH).

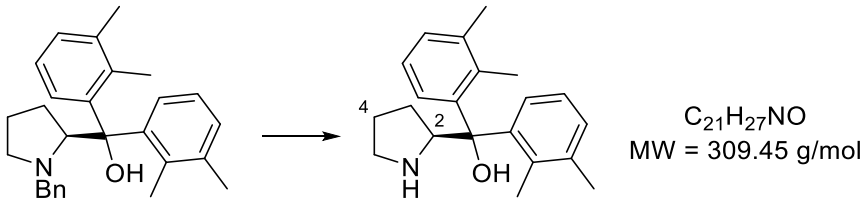
^{1}H NMR (400 MHz, CD_3OD, 328 K): δ [ppm] = 1.58-1.73 (m, 2 H, H-4), 1.97 (br s, 3 H, C*H*$_3$-*o*-Ar), 2.00 (s, 3 H, C*H*$_3$-*o*-Ar), 2.11 (s, 3 H, C*H*$_3$-*m*-Ar), 2.15 (s, 3 H, C*H*$_3$-*m*-Ar), 2.17-2.36 (m, 3 H, H-3, *H*H-5), 2.86-2.92 (m, 1 H, H*H*-5), 2.97 (br s, 2 H, C*H*$_2$Ph), 4.00 (dd, $^3J_1$ = 8.7 Hz, $^3J_2$ = 4.2 Hz, 1 H, H-2), 6.95-6.99 (m, 1 H, H-*p*-Ar), 7.01-7.09 (m, 5 H, 2 × H-*m*-Ar, H-*p*-Ar, 2 × H-*o*-Ph), 7.09-7.20 (m, 3 H, 2 × H-*m*-Ph, H-*p*-Ph), 7.44-7.50 (m, 1 H, H-*o*-Ar), 7.78-7.92 (m, 1 H, H-*o*-Ar).

^{13}C NMR (101 MHz, CD_3OD, 328 K): δ [ppm] = 17.3 (q, *C*H$_3$-*o*-Ar), 17.6 (q, *C*H$_3$-*o*-Ar), 21.1 (q, *C*H$_3$-*m*-Ar), 21.2 (q, *C*H$_3$-*m*-Ar), 25.7 (t, C-4), 32.1 (t, C-3), 56.7 (t, C-5), 62.2 (t, *C*H$_2$Ph), 70.9 (d, C-2), 83.2 (s, COH), 124.4 (d, C-*m*-Ar), 125.5 (d, C-*m*-Ar), 127.6 (d, C-*p*-Ph), 128.1 (d, C-*o*-Ar), 128.8 (d, 2 C, 2 × C-*m*-Ph), 129.1 (d, C-*o*-Ar), 129.7 (d, C-*p*-Ar), 129.7 (d, 2 C, 2 × C-*o*-Ph), 129.8 (d, C-*p*-Ar), 135.3 (s, C-*o*-Ar), 138.6 (s, C-*m*-Ar), 138.8 (s, C-*o*-Ar), 139.4 (s, C-*m*-Ar), 141.0 (s, C-*i*-Ph), 143.6 (s, C-*i*-Ar), 145.4 (s, C-*i*-Ar).

HRMS (ESI): calcd for $C_{28}H_{34}NO$ $[M+H]^+$: 400.2635; found: 400.2634.

Specific Rotation: $[\alpha]_D^{25}$ = +175 (c = 1.06, CH_2Cl_2) [>99.99% *ee*].

(*S*)-Bis(2,3-dimethylphenyl)(pyrrolidin-2-yl)methanol (112)



Following GP2, alcohol **94** (7.00 g, 17.5 mmol, 1.00 equiv) was converted with palladium on carbon (700 mg, 10 wt%) under a hydrogen atmosphere (balloon) within five hours. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 1/0 → 100/1 → 50/1→ 10/1, short), (silica, Hex/EtOAc/AcOH = 10/1/0 → 0/10/1, short) and (silica, CH_2Cl_2/MeOH/NH_3(conc.) = 1/0/0 → 100/1/0 → 50/1/0→ 10/1/0.1, long) [*n.b.*: The product should be purified in small portions of ca. 500 mg], the concentrated product was dissolved in hot hexane and filtered. The filtrate was concentrated and residual hexane was removed by azeotropic distillation (dichloromethane). The residue was dried in vacuo for 48 hours at 60 °C. Prolinol **112** (4.10 g, 13.2 mmol, 76%) was obtained as a pale yellow solid [*n.b.*: Cooling with liquid nitrogen in vacuo assists pulverization of the product].

Mp: 83 °C.

TLC: R_f = 0.07 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3347 (w, NH, OH), 2946 (m, sp^3-CH), 2872 (m, sp^3-CH), 1456 (m, sp^3-CH), 744 (vs, sp^2-CH).

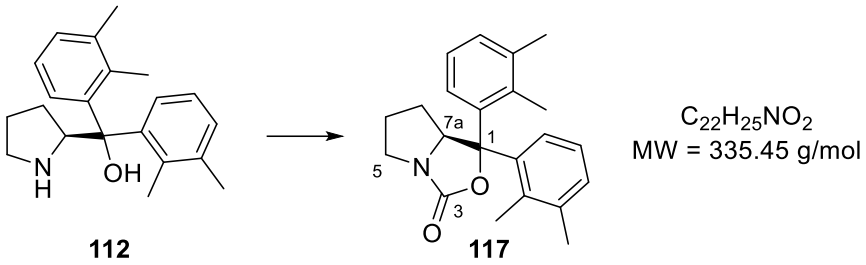
^{1}H NMR (400 MHz, CD_3OD, 328 K): δ [ppm] = 1.36 (br s, 1 H, *H*H-3), 1.59-1.78 (m, 3 H, H*H*-3, H-4), 1.83-1.91 (m, 6 H, 2 × CH_3-*o*-Ar), 2.14 (s, 6 H, 2 × CH_3-*m*-Ar), 2.89-3.02 (m, 2 H, H-5), 4.31 (*virt.* t, ^3J = 7.1 Hz, 1 H, H-2), 6.98-7.13 (m, 4 H, 2 × H-*m*-Ar, 2 × H-*p*-Ar), 7.58-7.73 (m, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (101 MHz, CD_3OD, 328 K): δ [ppm] = 17.1 (q, *C*H_3-*o*-Ar), 17.1 (q, *C*H_3-*o*-Ar), 21.1 (q, *C*H_3-*m*-Ar), 21.1 (q, *C*H_3-*m*-Ar), 26.9 (t, C-4), 29.4 (t, C-3), 47.9 (t, C-5), 64.9 (d, C-2), 81.1 (s, COH), 125.2 (d, C-*m*-Ar), 125.4 (d, C-*m*-Ar), 126.9 (d, C-*o*-Ar), 127.4 (d, C-*o*-Ar), 129.6 (d, C-*p*-Ar), 129.9 (d, C-*p*-Ar), 135.4 (s, C-*o*-Ar), 137.4 (s, C-*o*-Ar), 138.8 (s, C-*m*-Ar), 139.6 (s, C-*m*-Ar), 144.6 (s, C-*i*-Ar), 145.2 (s, C-*i*-Ar).

HRMS (ESI): calcd for $C_{21}H_{28}NO$ $[M+H]^+$: 310.2165; found: 310.2165.

Specific Rotation: $[\alpha]_D^{25}$ = –155 (c = 1.15, CH_2Cl_2) [>99.99% *ee*].

(*S*)-1,1-Bis(2,3-dimethylphenyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]-oxazol-3-one (117)



According to a modified literature procedure:[153] A solution of triphosgene (19.2 mg, 64.6 μmol, 1.00 equiv) in dichloromethane (1.0 mL, 64.6 mM) was added to a solution of prolinol **112** (20.0 mg, 64.6 μmol, 1.00 equiv) and pyridine (10.4 μL, 10.2 mg, 2.00 equiv) in dichloromethane (1.0 mL, 64.6 mM) at 0 °C. The reaction mixture was allowed to warm to room temperature and was subsequently stirred for 24 hours. The excess triphosgene was quenched with brine (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over sodium sulfate After filtration, the solution was concentrated in vacuo. After purification by column chromatography (silica, P/Et_2O = 7/3), oxazolidinone **117** (21.1 mg, 62.9 μmol, 97%, >99.99% *ee*) was obtained as a colorless solid.

Mp: 210 °C.

TLC: R_f = 0.25 (P/Et_2O = 1/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2974 (w, sp^3-CH), 2946 (w, sp^3-CH), 2909 (w, sp^3-CH), 2880 (w, sp^3-CH), 1747 (vs, C=O), 1456 (m, sp^3-CH), 789 (s, sp^2-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.04-1.13 (m, 1 H, *H*H-7), 1.26 (dddd, ^2J = 12.3 Hz, $^3J_1$ = 6.8 Hz, $^3J_2$ = 5.3 Hz, $^3J_3$ = 1.5 Hz, 1 H, H*H*-7), 1.69 (s, 3 H, CH_3-Ar), 1.79 (s, 3 H, CH_3-Ar), 1.80-1.88 (m, 1 H, *H*H-6), 1.95-2.03 (m, 1 H, H*H*-6), 2.18 (s, 6 H, 2 × CH_3-Ar), 3.33 (ddd, ^2J = 11.6 Hz, $^3J_1$ = 9.9 Hz, $^3J_2$ = 3.3 Hz, 1 H, *H*H-5), 3.77 (*virt.* dt, ^2J = 11.6 Hz, $^3J \approx {}^3J$ = 8.4 Hz, 1 H, H*H*-5), 4.86 (dd, $^3J_1$ = 10.8 Hz, $^3J_2$ = 5.3 Hz, 1 H, H-7a), 7.08-7.12 (m, 1 H, H-Ar), 7.13-7.17 (m, 3 H, 3 × H-Ar), 7.58-7.63 (m, 1 H, H-Ar), 7.72 (dd, ^3J = 7.9 Hz, ^4J = 1.7 Hz, 1 H, H-Ar).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 16.8 (q, *C*H_3-Ar), 17.2 (q, *C*H_3-Ar), 20.9 (q, *C*H_3-Ar), 21.3 (q, *C*H_3-Ar), 24.5 (t, C-6), 28.3 (t, C-7), 46.6 (t, C-5), 66.4 (d, C-7a), 86.2 (s, C-1), 124.0 (d, C-Ar), 124.7 (d, C-Ar), 125.1 (d, C-Ar), 125.2 (d, C-Ar), 129.5 (d, C-Ar), 130.6

(d, C-Ar), 131.7 (s, C-Ar), 137.4 (s, C-Ar), 137.8 (s, C-Ar), 138.8 (s, C-Ar), 139.0 (s, C-Ar), 140.0 (s, C-Ar), 161.1 (s, C-3).

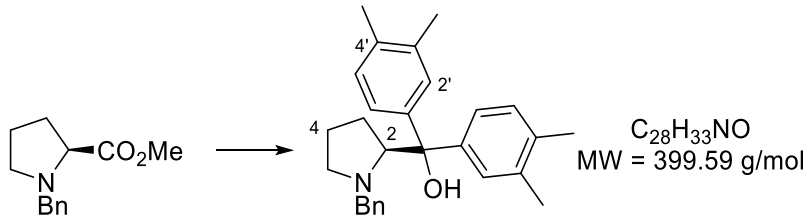
MS (EI, 70 eV): m/z (%) = 335 (7) $[M]^+$, 291 (25), 276 (38), 223 (48) $[C_{17}H_{19}]^+$, 207 (100), 192 (26), 172 (13), 133 (7), 70 (22), 59 (16).

HRMS (EI, 70 eV): calcd for $C_{22}H_{25}NO_2$ $[M]^+$: 335.1880; found: 335.1882;
calcd for $C_{21}{}^{13}CH_{25}NO_2$ $[M]^+$: 336.1913; found: 336.1919.

Chiral HPLC: τ_R (major) = 19.9 min, τ_R (minor) = 24.5 min, [H_2O/MeCN = 80/20 → 0/100, 30 min], Chiralcel, OD-RH, 150×4.6.

Specific Rotation: $[\alpha]_D^{25}$ = –448 (c = 1.31, CH_2Cl_2) [>99.99% *ee*].

(*S*)-(1-Benzylpyrrolidin-2-yl)bis(3,4-dimethylphenyl)methanol (95)



77 **95**

Following GP1, ester **77** (500 mg, 2.28 mmol, 1.00 equiv) was converted with 1-bromo-3,4-dimethylbenzene (1.05 g, 5.70 mmol, 2.50 equiv), iodine (5.79 mg, 22.8 µmol, 1.00 mol%) and magnesium turnings (139 mg, 5.70 mmol, 2.50 equiv) within one hour. After purification by column chromatography (silica, cHex/EtOAc = 1/0 → 20/1), alcohol **95** (818 mg, 2.05 mmol, 90%) was obtained as a viscous yellow oil.

TLC: R_f = 0.49 (P/EtOAc = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3340 (br w, OH), 3025 (m, sp^2-CH), 2965 (s, sp^3-CH), 2920 (vs, sp^3-CH), 2870 (m, sp^3-CH), 2800 (m, sp^3-CH), 1496 (vs, sp^2-CC), 1451 (vs, sp^3-CC), 1121 (vs, sp^3-CO), 731 (vs, sp^2-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.57-1.68 (m, 2 H, H-4), 1.72-1.79 (m, 1 H, *H*H-3), 1.94 (*virt.* dq, ^2J = 13.2 Hz, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 9.1 Hz, 1 H, H*H*-3), 2.11 (s, 3 H, CH_3-4'-Ar), 2.18 (s, 3 H, CH_3-4'-Ar), 2.19 (s, 3 H, CH_3-3'-Ar), 2.22 (s, 3 H, CH_3-3'-Ar), 2.34 (*virt.* td, $^2J \approx {}^3J_1$ = 9.5 Hz, $^3J_2$ = 7.0 Hz, 1 H, *H*H-5), 2.87-2.92 (m, 1 H, H*H*-5), 3.00 (d, ^2J = 12.6 Hz, 1 H, C*H*HPh), 3.25 (d, ^2J = 12.6 Hz, 1 H, CH*H*Ph), 3.90 (dd, $^3J_1$ = 9.5 Hz, $^3J_2$ = 4.7 Hz, 1 H, H-2), 4.87 (s, 1 H, COH), 7.00 (d, ^3J = 7.9 Hz, 1 H, H-5'-Ar), 7.03-7.08 (m,

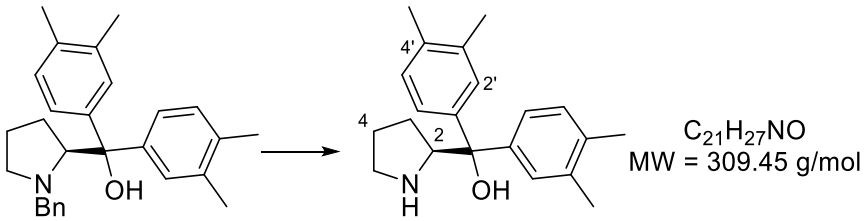
3 H, H-5'-Ar, 2 × H-*o*-Ph), 7.16-7.21 (m, 1 H, H-*p*-Ph), 7.21-7.27 (m, 3 H, H-6'-Ar, 2 × H-*m*-Ph), 7.34 (d, ^4J = 2.0 Hz, 1 H, H-2'-Ar), 7.38 (dd, ^3J = 7.9 Hz, ^4J = 2.0 Hz, 1 H, H-6'-Ar), 7.46-7.47 (m, 1 H, H-2'-Ar).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 19.4 (q, *C*H_3-4'-Ar), 19.5 (q, *C*H_3-4'-Ar), 20.2 (q, *C*H_3-3'-Ar), 20.3 (q, *C*H_3-3'-Ar), 24.3 (t, C-4), 30.0 (t, C-3), 55.7 (t, C-5), 60.8 (t, *C*H_2Ph), 70.7 (d, C-2), 77.8 (s, COH), 122.9 (d, C-6'-Ar), 123.1 (d, C-6'-Ar), 126.8 (d, C-2'-Ar), 126.9 (d, C-2'-Ar), 126.9 (d, C-*p*-Ph), 128.2 (d, 2 C, 2 × C-*m*-Ph), 128.9 (d, 2 C, 2 × C-*o*-Ph), 129.3 (d, C-5'-Ar), 129.6 (d, C-5'-Ar), 134.4 (s, C-4'-Ar), 134.4 (s, C-4'-Ar), 136.2 (s, C-3'-Ar), 136.3 (s, C-3'-Ar), 140.1 (s, C-*i*-Ph), 144.6 (s, C-1'-Ar), 145.8 (s, C-1'-Ar).

HRMS (ESI): calcd for $C_{28}H_{34}NO$ $[M+H]^+$: 400.2635; found: 400.2634.

Specific Rotation: $[\alpha]_D^{25}$ = +90.3 (c = 0.98, CH_2Cl_2).

(*S*)-Bis(3,4-dimethylphenyl)(pyrrolidin-2-yl)methanol (113)



Following GP2, alcohol **95** (811 mg, 2.03 mmol, 1.00 equiv) was converted with palladium on carbon (81.1 mg, 10 wt%) under a hydrogen atmosphere (balloon) within one hour. After purification by column chromatography (silica, CH_2Cl_2/MeOH = 10/1), prolinol **113** (462 mg, 1.49 mmol, 74%) was obtained as a low-melting amorphous yellow solid.

TLC: R_f = 0.12 (CH_2Cl_2/MeOH = 9/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3338 (br w, NH, OH), 2966 (m, sp^3-CH), 2939 (m, sp^3-CH), 2917 (m, sp^3-CH), 2868 (m, sp^3-CH), 1500 (s, sp^3-CC), 798 (vs, sp^2-CH).

^{1}H NMR (500 MHz, CD_3OD, 298 K): δ [ppm] = 1.61-1.71 (m, 1 H, *H*H-3), 1.71-1.81 (m, 3 H, H*H*-3, H-4), 2.19 (s, 3 H, C*H*$_3$-4'-Ar), 2.20 (s, 3 H, C*H*$_3$-4'-Ar), 2.21 (s, 3 H, C*H*$_3$-3'-Ar), 2.23 (s, 3 H, C*H*$_3$-3'-Ar), 2.84-2.91 (m, 1 H, *H*H-5), 2.97-3.04 (m, 1 H, H*H*-5), 4.25-4.30 (m, 1 H, H-2), 7.01 (d, ^3J = 8.0 Hz, 1 H, H-5'-Ar), 7.05 (d, ^3J = 8.0 Hz, 1 H, H-5'-Ar), 7.14 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1 H, H-6'-Ar), 7.19 (d, ^4J = 2.0 Hz, 1 H, H-2'-Ar), 7.24 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1 H, H-6'-Ar), 7.29 (d, ^4J = 2.0 Hz, 1 H, H-2'-Ar).

^{13}C NMR (126 MHz, CD_3OD, 300 K): δ [ppm] = 19.3 (q, 2 C, 2 × *C*H_3-4'-Ar), 20.1 (q, *C*H_3-3'-Ar), 20.1 (q, *C*H_3-3'-Ar), 26.9 (t, C-4), 27.9 (t, C-3), 48.1 (t, C-5), 66.3 (d, C-2), 79.3 (s, COH), 124.3 (d, C-6'-Ar), 124.6 (d, C-6'-Ar), 128.0 (d, C-2'-Ar), 128.5 (d, C-2'-Ar), 130.1 (d, C-5'-Ar), 130.3 (d, C-5'-Ar), 135.7 (s, C-4'-Ar), 135.9 (s, C-4'-Ar), 137.0 (s, C-3'-Ar), 137.3 (s, C-3'-Ar), 145.0 (s, C-1'-Ar), 145.4 (s, C-1'-Ar).

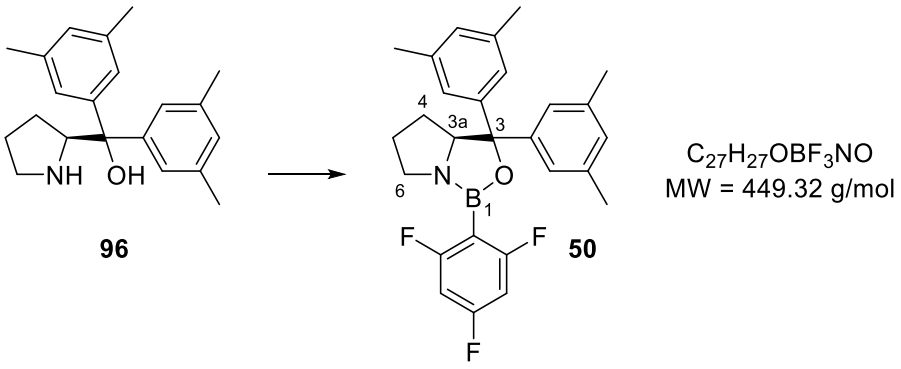
HRMS (ESI): calcd for $C_{21}H_{28}NO$ $[M+H]^+$: 310.2165; found: 310.2165.

Specific Rotation: $[\alpha]_D^{27}$ = –22.8 (c = 1.40, MeOH).

6.3.3 Synthesis and Activation of the Oxazaborolidine Catalyst

6.3.3.1 Synthesis of the Oxazaborolidine-Catalyst

(*S*)-3,3-bis(3,5-dimethylphenyl)-1-(2,4,6-trifluorophenyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole (50)



Following GP3, prolinol **96** (1.00 equiv) and 2,4,6-trifluorophenylboronic acid (1.00 equiv) were converted to the oxazaborolidine **50** (quant).

Mp: 160 °C.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2960 (w, sp^3-CH), 2918 (w, sp^3-CH), 2871 (w, sp^3-CH), 1628 (m, sp^2-CC), 1591 (s, sp^2-CC), 1413 (s, sp^3-CH), 1105 (vs, sp^2-CF), 998 (vs).

^{1}H NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 0.99-1.08 (m, 1 H, *H*H-4), 1.42-1.54 (m, 3 H, H*H*-4, H-5), 2.12 (s, 6 H, 2 × C*H*$_3$-*m*-Ar), 2.19 (s, 6 H, 2 × C*H*$_3$-*m*-Ar), 3.04 (*virt.* dt, ^2J = 10.5 Hz, $^3J_1 \approx {}^3J_2$ = 6.9 Hz, 1 H, *H*H-6), 3.14 (*virt.* dt, ^2J = 10.5 Hz, $^3J_1 \approx {}^3J_2$ = 6.7 Hz, 1 H, H*H*-6), 4.56 (dd, $^3J_1$ = 9.9 Hz, $^3J_2$ = 5.0 Hz, 1 H, H-3a), 6.25-6.30 (m, 2 H, 2 × H-*m*-Ar^F), 6.74 (br s, 2 H, 2 × H-*p*-Ar), 7.43 (s, 2 H, 2 × H-*o*-Ar), 7.49 (s, 2 H, 2 × H-*o*-Ar).

^{13}C NMR (126 MHz, C_6D_6, 300 K): δ [ppm] = 21.6 (q, 2 C, 2 × *C*H$_3$-*m*-Ar), 21.7 (q, 2 C, 2 × *C*H$_3$-*m*-Ar), 26.7 (t, C-5), 30.9 (t, C-4), 43.4 (t, C-6), 73.4 (d, C-3a), 89.4 (s, C-3), 100.0-100.5 (m, 2 C, 2 × C-*m*-Ar^F), 103.9-105.0 (m, C-*i*-Ar^F)*, 124.6 (d, 2 C, 2 × C-*o*-Ar), 124.8 (d, 2 C, 2 × C-*o*-Ar), 128.7 (d, C-*p*-Ar), 129.3 (d, C-*p*-Ar), 137.4 (s, 2 C, 2 × C-*m*-Ar), 137.7 (s, 2 C, 2 × C-*m*-Ar), 144.6 (s, C-*i*-Ar), 147.9 (s, C-*i*-Ar), 163.8 (dts, $^1J_{CF}$ = 249 Hz, $^3J_{CF}$ = 15.5 Hz, C-*p*-Ar^F), 167.1 (ddds, $^1J_{CF}$ = 249 Hz, $^3J_{CF,1}$ = 16.6 Hz, $^3J_{CF,2}$ = 14.9 Hz, 2 C, 2 × C-*o*-Ar^F).

*The ^{13}C signal intensity of C-*i*-Ar^F was insufficient for an appropriate assignment of its multiplicity due to multiple C-B and C-F couplings. However, the signal can be located with the help of a HMBC crosspeak with the proton signal of H-*m*-Ar^F to assign the ^{13}C signal of C-*i*-Ar^F.

^{19}F NMR (471 MHz, C_6D_6, 300 K): δ [ppm] = –105.6 (*virt.* quint, $^3J_{HF} \approx {}^4J_{FF}$ = 8.7 Hz, 1 F, F-*p*-Ar^F), –96.8 (*virt.* t, $^3J_{HF} \approx {}^4J_{FF}$ = 7.8 Hz, 2 F, 2 × F-*o*-Ar^F).

^{11}B NMR (128 MHz, C_6D_6, 300 K): δ [ppm] = 30.2 (br s, 1 B, NBO).

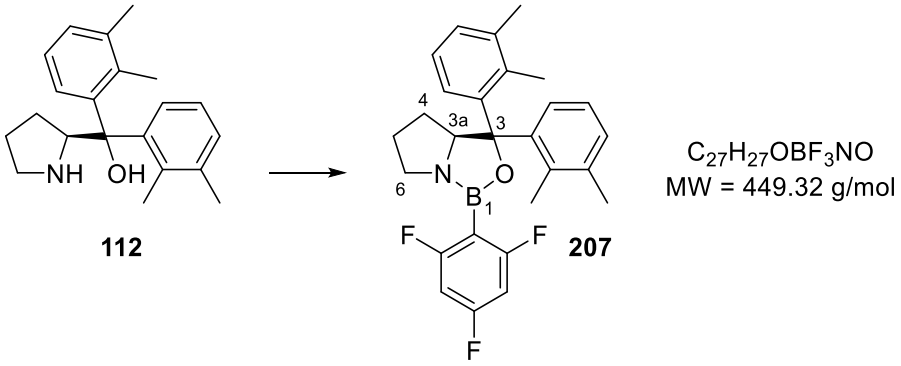
MS (EI, 70 eV): m/z (%) = 449 (67) $[M]^+$, 380 (44) $[M–C_4H_7N]^+$, 365 (49), 291 (10) $[M–C_6H_2BF_3O]^+$, 267 (14), 223 (25), 207 (73), 192 (21), 133 (23), 91 (65), 70 (100) $[C_4H_8N]^+$.

HRMS (EI, 70 eV): calcd for $C_{27}H_{27}ON^{11}BF_3$ $[M]^+$: 449.2132; found: 449.2130;
calcd for $C_{26}{}^{13}CH_{27}ON^{11}BF_3$ $[M]^+$: 450.2166; found: 450.2167.

[*N.b.*: The sample was measured in an NMR tube with J Young valve under inert gas using dry benzene-d_6.]

The analytical data obtained matched those reported in the literature.[123]

(*S*)-3,3-bis(2,3-dimethylphenyl)-1-(2,4,6-trifluorophenyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole (207)



Following GP3, prolinol **112** (1.00 equiv) and 2,4,6-trifluorophenylboronic acid (1.00 equiv) were converted to the oxazaborolidine **207** (quant).

Mp: 168 °C.

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2963 (m, sp^3-CH), 1628 (s, sp^2-CC), 1590 (s, sp^2-CC), 1412 (s, sp^3-CH), 1104 (vs, sp^2-CF), 997 (vs), 785 (vs).

^1H NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 0.86-0.96 (m, 1 H, *H*H-4), 0.98-1.06 (m, 1 H, H*H*-4), 1.35-1.45 (m, 2 H, H-5), 1.70 (s, 3 H, C*H*$_3$-*o*-Ar), 1.92 (s, 3 H, C*H*$_3$-*m*-Ar), 1.98 (s, 3 H,

C*H*$_3$-*m*-Ar), 2.08 (s, 3 H, C*H*$_3$-*o*-Ar), 3.15 (*virt.* td, $^2J \approx {}^3J_1$ = 10.2 Hz, $^3J_2$ = 5.3 Hz, 1 H, *H*H-6), 3.20-3.27 (m, 1 H, H*H*-6), 4.71 (dd, $^3J_1$ = 10.3 Hz, $^3J_2$ = 5.1 Hz, 1 H, H-3a), 6.16-6.22 (m, 2 H, 2 × H-*m*-Ar^F), 6.99-7.04 (m, 2 H, 2 × H-*p*-Ar), 7.13 (*virt.* t, $^3J_1 \approx {}^3J_2$ = 7.7 Hz, 1 H, H-*m*-Ar), 7.26 (*virt.* t, $^3J_1 \approx {}^3J_2$ = 7.7 Hz, 1 H, H-*m*-Ar), 7.78 (d, ^3J = 8.1 Hz, 1 H, H-*o*-Ar), 8.37 (d, ^3J = 7.9 Hz, 1 H, H-*o*-Ar).

^{13}C NMR (126 MHz, C_6D_6, 300 K): δ [ppm] = 17.4 (q, *C*H$_3$-*o*-Ar), 17.6 (q, *C*H$_3$-*o*-Ar), 20.8 (q, *C*H$_3$-*m*-Ar), 21.2 (q, *C*H$_3$-*m*-Ar), 25.1 (t, C-5), 30.3 (t, C-4), 44.1 (t, C-6), 70.0 (d, C-3a), 88.8 (s, C-3), 99.9-100.5 (m, 2 C, 2 × C-*m*-Ar^F), 103.6-104.9 (m, C-*i*-Ar^F)*, 124.2 (d, C-*o*-Ar), 125.5 (d, C-*m*-Ar), 125.6 (d, C-*m*-Ar), 125.9 (d, C-*o*-Ar), 129.1 (d, C-*p*-Ar), 129.9 (d, C-*p*-Ar), 131.8 (s, C-*i*-Ar), 137.3 (s, C-*i*-Ar), 137.3 (s, C-*m*-Ar), 138.7 (s, C-*m*-Ar), 143.4 (s, C-*o*-Ar), 144.2 (s, C-*o*-Ar), 164.9 (dts, $^1J_{CF}$ = 250 Hz, $^3J_{CF}$ = 15.4 Hz, C-*p*-Ar^F), 167.1 (ddds, $^1J_{CF}$ = 250 Hz, $^3J_{CF,1}$ = 16.7 Hz, $^3J_{CF,2}$ = 15.0 Hz, 2 C, 2 × C-*o*-Ar^F).

*The ^{13}C signal intensity of C-*i*-Ar^F was insufficient for an appropriate assignment of its multiplicity due to multiple C-B and C-F couplings. However, the signal can be located with the help of a HMBC crosspeak with the proton signal of H-*m*-Ar^F to assign the ^{13}C signal of C-*i*-Ar^F.

^{19}F NMR (376 MHz, C_6D_6, 300 K): δ [ppm] = –105.7 (*virt.* quint, $^3J_{HF} \approx {}^4J_{FF}$ = 8.8 Hz, 1 F, F-*p*-Ar^F), –96.9 (*virt.* t, $^3J_{HF} \approx {}^4J_{FF}$ = 8.0 Hz, 2 F, 2 × F-*o*-Ar^F).

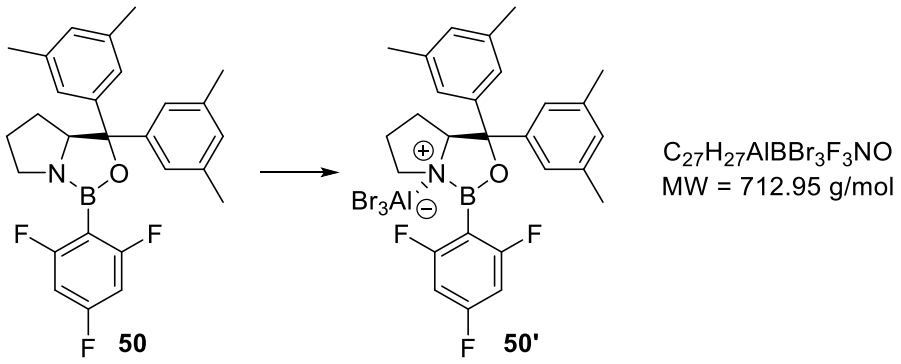
^{11}B NMR (128 MHz, C_6D_6, 300 K): δ [ppm] = 29.7 (br s, 1 B, NBO).

MS (EI, 70 eV): m/z (%) = 449 (10) $[M]^+$, 434 (1) $[M–CH_3]^+$, 365 (24), 276 (8), 223 (16), 207 (31), 192 (24), 133 (13), 111 (8), 97 (24), 83 (100).

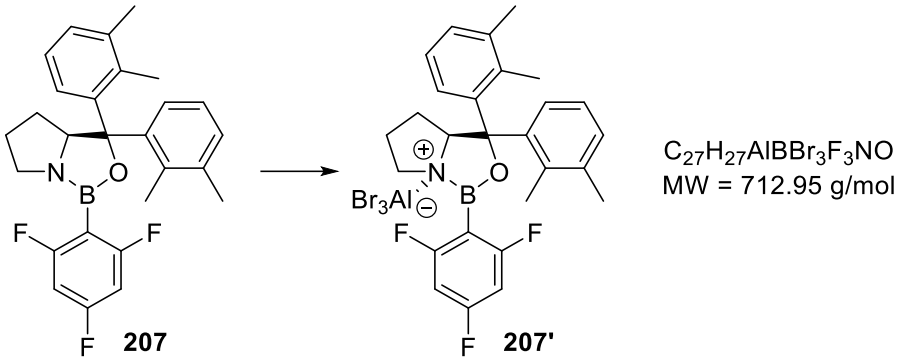
HRMS (EI, 70 eV): calcd for $C_{27}H_{27}ON^{11}BF_3$ $[M]^+$: 449.2132; found: 449.2133;
calcd for $C_{26}{}^{13}CH_{27}ON^{11}BF_3$ $[M]^+$: 450.2166; found: 450.2170.

[*N.b.*: The sample was measured in an NMR tube with J Young valve under inert gas using dry benzene-d_6.]

6.3.3.2 Activation of the Oxazaborolidine-Catalyst



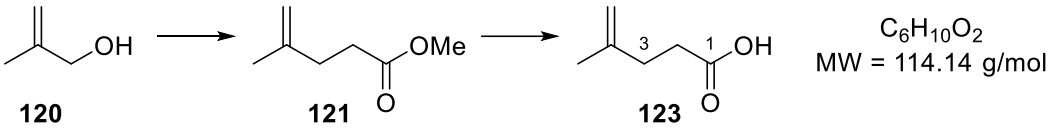
Following GP4, oxazaborolidine **50** (1.00 equiv) was converted with a solution of aluminum bromide (1.00 M in dibromomethane, 1.00 equiv) to the activated catalyst **50'** (quant).



Following GP4, oxazaborolidine **207** (1.00 equiv) was converted with a solution of aluminum bromide (1.00 M in dibromomethane, 1.00 equiv) to the activated catalyst **207'** (quant).

6.3.4 Synthesis of Alkene Side-Chains

4-Methylpent-4-enoic acid (123)



According to a modified literature procedure:[155]

Johnson-Claisen Rearrangement: A solution of alcohol **120** (3.00 g, 3.52 mL, 41.6 mmol, 1.00 equiv) in trimethyl orthoacetate (13.9 g, 14.7 mL, 116 mmol, 2.78 equiv) was acidified with propionic acid (216 mg, 217 µL, 2.91 mmol, 0.07 equiv). The reaction mixture was stirred in a round-bottom flask which was equipped with a *Dean-Stark* apparatus and heated at reflux at 150 °C. After three hours, no further condensation of methanol was observed and the reaction mixture was allowed to cool to room temperature. The excess of trimethyl orthoacetate was hydrolyzed by addition of aqueous hydrochloric acid solution (1.00 M, 10 mL) and stirring for 30 minutes. The mixture was diluted with diethyl ether (20 mL) and the organic layer was washed with aqueous hydrochloric acid solution (1.00 M, 10 mL), saturated aqueous sodium hydrogen carbonate solution (2 × 10 mL), and brine (10 mL). After drying of the organic layer over sodium sulfate, filtration, and removal of the solvent in vacuo, the crude product **121** was used in the next step without further purification. The crude product **121** consisted of a mixture of the title compound **121** and the acylated starting material **122** which was inseparable. In order to facilitate a separation, the crude product **121** was subjected to saponification conditions which enabled the isolation of the corresponding acid **123**.

Saponification: A solution of the crude product **121** and lithium hydroxide monohydrate (3.49 g, 83.2 mmol, 2.00 equiv) in a 3:1 mixture of methanol and water (20 mL, 2.00 M) was stirred for one hour at 100 °C. The reaction mixture was allowed to cool to room temperature and was subsequently partitioned between aqueous hydrochloric acid solution (1.00 M, 30 mL) and diethyl ether (30 mL). The basic aqueous layer was extracted with diethyl ether (10 × 30 mL) in order to remove the released starting material **120**. The aqueous layer was acidified with aqueous hydrochloric acid (12.0 M) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried with brine (20 mL) and over sodium sulfate. After filtration and removal of the solvent in vacuo, acid **123** (2.54 g, 22.3 mmol, 53% over two steps) was obtained as a colorless oil.

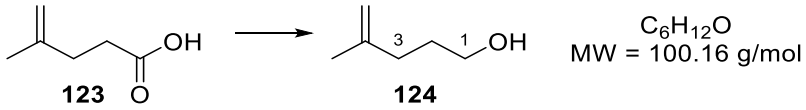
TLC: R_f = 0.17 (CH_2Cl_2/Et_2O = 9/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.75 (br s, 3 H, Me-4), 2.32-2.37 (m, 2 H, H-3), 2.49-2.54 (m, 2 H, H-2), 4.71 (br s, 1 H, *H*H-5), 4.77 (br s, 1 H, H*H*-5), 11.26 (br s, 1 H, CO_2H).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.7 (q, Me-4), 32.4 (t, C-2), 32.4 (t, C-3), 110.7 (t, C-5), 143.9 (s, C-4), 179.4 (s, C-1).

The analytical data obtained matched those reported in the literature.[275]

4-Methylpent-4-en-1-ol (124)



According to a modified literature procedure:[156]

A solution of acid **123** (2.54 g, 22.3 mmol, 1.00 equiv) in tetrahydrofuran (27 mL, 840 mM) was added to a suspension of lithiumaluminum hydride (1.69 g, 44.5 mmol, 2.00 equiv) in tetrahydrofuran (31 mL, 1.45 M) at 0 °C. The reaction mixture was allowed to warm to room temperature and was subsequently stirred for one hour. After cooling to 0 °C, methanol was added dropwise to quench the excess of lithiumaluminum hydride. When no further gas evolution was observed, aqueous hydrochloric acid solution (1.00 M, 40 mL) was added and the resulting mixture was stirred for 15 minutes. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The organic layers were combined, dried with brine (50 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. Purification of the residue by column chromatography (silica, P/Et_2O = 1/0 → 2/1) afforded alcohol **124** (1.61 g, 16.1 mmol, 72%) as a colorless oil.

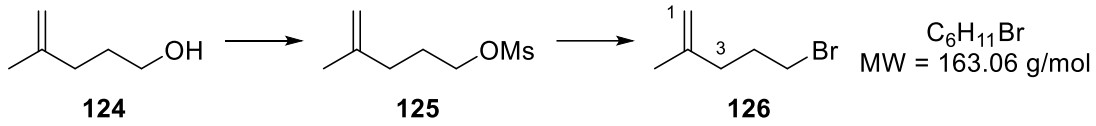
TLC: R_f = 0.22 (P/Et_2O = 3/2) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.34 (t, ^3J = 5.4 Hz, 1 H, OH-1), 1.69-1.76 (m, 5 H, H-2, Me-4), 2.10 (td, ^3J = 7.5 Hz, ^4J = 1.2 Hz, 2 H, H-3), 3.66 (td, $^3J_1$ = 6.4 Hz, $^3J_2$ = 5.4 Hz, 2 H, H-1), 4.71-4.74 (m, 2 H, H-5).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.5 (q, Me-4), 30.6 (t, C-2), 34.3 (t, C-3), 62.9 (t, C-1), 110.4 (t, C-5), 145.7 (s, C-4).

The analytical data obtained matched those reported in the literature.[276]

5-Bromo-2-methylpent-1-ene (126)



According to a modified literature procedure:[157]

Mesylation: Mesyl chloride (1.87 mL, 2.76 g, 24.1 mmol, 1.50 equiv) was added dropwise to a solution of alcohol **124** (1.61 g, 16.1 mmol, 1.00 equiv) and triethylamine (6.72 mL, 4.88 g, 48.2 mmol, 3.00 equiv) in dichloromethane (9.5 mL, 1.70 M) at 0 °C. The reaction mixture was allowed to warm to room temperature and was subsequently stirred for two hours. [*N.b.*: Reaction monitoring by TLC was conducted by using a pentane-dichloromethane eluent, other typical mixtures could not lead to a distinction between the alcohol **124** and the mesylated product **125**.] Aqueous hydrochloric acid solution (1.00 M, 40 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL). The organic layers were combined, washed with saturated aqueous sodium hydrogen carbonate solution (30 mL) and dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. The orange crude product **125** was used in the next step without further purification.

Bromination: Dry lithium bromide (1.40 g, 16.1 mmol, 1.00 equiv) was added to a solution of the crude mesylated alcohol **125** in freshly distilled acetone (30 mL, 540 mM) and then the resulting mixture was heated at reflux for 17 hours. After the reaction mixture was allowed to cool to room temperature, the solvent was removed in vacuo and the crude product **126** was partitioned between a 1:1 mixture of saturated aqueous ammonium chloride solution and diethyl ether (100 mL). The aqueous layer was extracted with diethyl ether (3 × 40 mL). The organic layers were combined and dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. The residue was purified by column chromatography (silica, P) to provide alkenyl bromide **126** (1.43 g, 8.77 mmol, 55% over two steps) as a colorless oil.

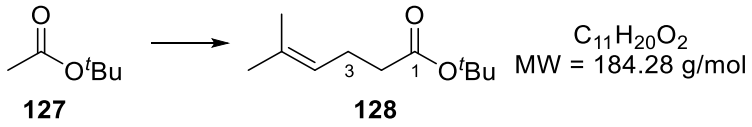
TLC: R_f = 0.44 (P) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.73 (br s, 3 H, Me-2), 1.96-2.03 (m, 2 H, H-4), 2.14-2.19 (m, 2 H, H-3), 3.41 (t, ^3J = 6.7 Hz, 2 H, H-5), 4.71-4.73 (m, 1 H, *H*H-1), 4.76-4.78 (m, 1 H, H*H*-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.5 (q, Me-2), 30.7 (t, C-4), 33.5 (t, C-5), 36.2 (t, C-3), 111.2 (t, C-1), 144.1 (s, C-2).

The analytical data obtained matched those reported in the literature.[276]

***tert*-Butyl 5-methylhex-4-enoate (128)**



127 **128**

According to a literature procedure:[158] A solution of *n*-butyllithium (2.50 M in hexane, 16.4 mL, 41.1 mmol, 1.75 equiv) was added to a solution of diisopropylamine (6.41 mL, 4.63 g, 45.8 mmol, 1.95 equiv) in tetrahydrofuran (55 mL, 840 mM) at –78 °C. The mixture was allowed to warm to 0 °C, stirred for ten minutes, and cooled back to –78 °C. A solution of ester **127** (5.83 mL, 5.05 g, 43.5 mmol, 1.85 equiv) in tetrahydrofuran (15.6 mL, 2.78 M) was added to the freshly prepared lithiumdiisopropylamide solution and the resulting reaction mixture was stirred for 40 minutes. A solution of 1-bromo-3-methylbut-2-ene (2.71 mL, 3.50 g, 23.5 mmol, 1.00 equiv) and DMPU (7.81 mL, 8.28 g, 64.6 mmol, 2.75 equiv) in tetrahydrofuran (43 mL, 545 mM) was added dropwise to the enolate solution at –78 °C and the resulting mixture was stirred for two hours. Saturated aqueous ammonium chloride solution (100 mL) was added to the reaction solution and the resulting emulsion was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The organic layers were combined, dried with brine (2 × 50 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. The product was purified by column chromatography (silica, P/Et_2O = 100/1) affording ester **128** (3.82 g, 20.7 mmol, 88%) as a colorless oil.

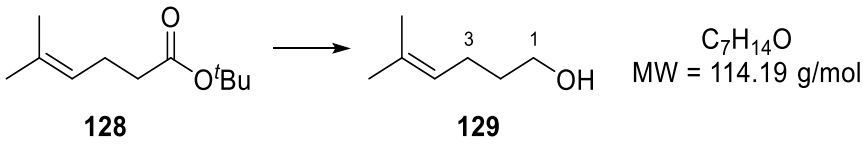
TLC: R_f = 0.63 (P/Et_2O = 9/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.44 (s, 9 H, CO_2CMe_3), 1.62 (br s, 3 H, Me-5), 1.68 (br s, 3 H, Me-5), 2.20-2.30 (m, 4 H, H-2, H-3), 5.06-5.11 (m, 1 H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 17.9 (q, Me-5), 24.0 (t, C-3), 25.8 (q, Me-5), 28.3 (q, 3 C, $CO_2C\mathit{Me}_3$), 35.9 (t, C-2), 80.1 (s, $CO_2\mathit{C}Me_3$), 122.9 (d, C-4), 132.8 (s, C-5), 173.0 (s, $\mathit{C}O_2CMe_3$).

The analytical data obtained matched those reported in the literature.[158]

5-Methylhex-4-en-1-ol (129)



128 **129**

According to a modified literature procedure:[156] A solution of ester **128** (3.50 g, 19.0 mmol, 1.00 equiv) in tetrahydrofuran (23 mL, 840 mM) was added to a suspension of lithiumaluminum hydride (721 mg, 19.0 mmol, 1.00 equiv) in tetrahydrofuran (13 mL, 1.45 M) at 0 °C. The reaction mixture was allowed to warm to room temperature and was subsequently stirred for 30 minutes. After cooling to 0 °C, methanol was added dropwise to quench the excess of lithiumaluminum hydride. When no further gas evolution was observed, aqueous hydrochloric acid solution (1.00 M, 40 mL) was added and the resulting mixture was stirred for 15 minutes. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The organic layers were combined, dried with brine (20 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. Purification of the residue by column chromatography (silica, P/Et_2O = 3/1) furnished alcohol **129** (1.99 g, 17.4 mmol, 92%) as a colorless oil.

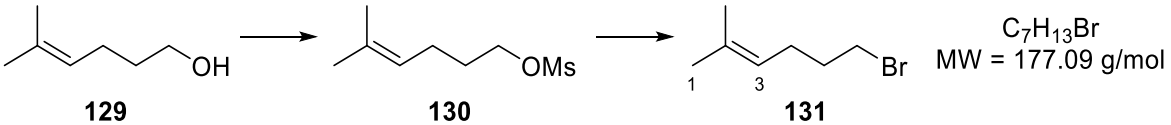
TLC: R_f = 0.33 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.30 (t, ^3J = 5.4 Hz, 1 H, OH-1), 1.58-1.65 (m, 5 H, H-2, Me-5), 1.69 (q, ^4J = 1.2 Hz, 3 H, Me-5), 2.07 (*virt.* q, $^3J_1 \approx {}^3J_2$ = 7.4 Hz, 2 H, H-3), 3.65 (td, $^3J_1$ = 6.5 Hz, $^3J_2$ = 5.4 Hz, 2 H, H-1), 5.11-5.16 (m, 1 H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 17.8 (q, Me-5), 24.5 (t, C-3), 25.9 (q, Me-5), 32.9 (t, C-2), 62.9 (t, C-1), 124.0 (d, C-4), 132.4 (s, C-5).

The analytical data obtained matched those reported in the literature.[277]

6-Bromo-2-methylhex-2-ene (131)



129 **130** **131**

According to a modified literature procedure:[157]

Mesylation: Mesyl chloride (1.02 mL, 1.50 g, 13.1 mmol, 1.50 equiv) was added dropwise to a solution of alcohol **129** (1.00 g, 8.76 mmol, 1.00 equiv) and triethylamine (3.66 mL, 2.66 g, 26.3 mmol, 3.00 equiv) in dichloromethane (5 mL, 1.70 M) at 0 °C. The reaction mixture was

allowed to warm to room temperature and was subsequently stirred for two hours. [*N.b.*: Reaction monitoring by TLC was conducted by using a pentane-dichloromethane eluent, other typical mixtures could not lead to a distinction between the alcohol **129** and the mesylated product **130**.] Aqueous hydrochloric acid solution (1.00 M, 20 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL). The organic layers were combined, washed with saturated aqueous sodium hydrogen carbonate solution (30 mL) and dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. The orange crude product **130** was used in the next step without further purification.

Bromination: Dry lithium bromide (1.52 g, 17.5 mmol, 2.00 equiv) was added to a solution of the mesylated alcohol **130** in freshly distilled acetone (16 mL, 540 mM) and the resulting mixture was heated at reflux for 19 hours. The solvent was removed in vacuo and the crude product **131** was partitioned between a 1:1 mixture of water and pentane (100 mL). The aqueous layer was extracted with pentane (3 × 40 mL). The organic layers were combined and dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. The residue was purified by column chromatography (silica, P) to yield alkenyl bromide **131** (1.25 g, 7.06 mmol, 75%) as a colorless oil.

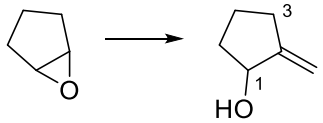
TLC: R_f = 0.41 (P) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.63 (d, ^4J = 1.3 Hz, 3 H, Me-2), 1.70 (q, ^4J = 1.3 Hz, 3 H, Me-2), 1.86-1.92 (m, 2 H, H-5), 2.14 (*virt.* q, $^3J_1 \approx {}^3J_2$ = 7.3 Hz, 2 H, H-4), 3.40 (t, ^3J = 6.8 Hz, 2 H, H-6), 5.04-5.11 (m, 1 H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 17.9 (q, Me-2), 25.9 (q, Me-2), 26.6 (t, C-4), 33.0 (t, C-5), 33.7 (t, C-6), 122.7 (d, C-3), 133.3 (s, C-2).

The analytical data obtained matched those reported in the literature.[278]

2-Methylenecyclopentan-1-ol (*rac*-133)



132 *rac*-**133**

$C_6H_{10}O$
MW = 98.15 g/mol

According to a literature procedure:[159] A solution of *n*-butyllithium (2.50 M in hexane, 61.6 mL, 154 mmol, 3.70 equiv) was added dropwise to a suspension of trimethylsulfonium iodide (34.0 g, 166 mmol, 4.00 equiv) in tetrahydrofuran (211 mL, 790 mM) at –20 °C. After

stirring for 30 minutes, a solution of cyclopentene oxide **132** (3.63 mL, 3.50 g, 41.6 mmol, 1.00 equiv) in tetrahydrofuran (41.6 mL, 1.00 M) was added dropwise and the resulting mixture was warmed to 0 °C. After stirring for one hour, the reaction mixture was warmed to room temperature and was subsequently stirred for two hours. Saturated aqueous ammonium chloride solution (100 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 100 mL). The organic layers were combined, dried with brine (100 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. Purification of the residue by column chromatography (silica, P/Et_2O = 9/1 → 4/1) afforded alcohol *rac*-**133** (1.37 g, 14.0 mmol, 34%) as a colorless oil.

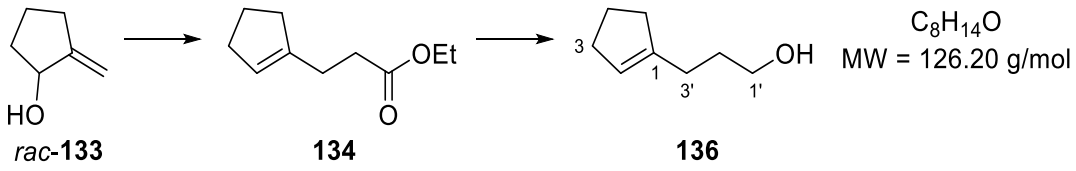
TLC: R_f = 0.38 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.39 (d, ^3J = 5.5 Hz, 1 H, OH-1), 1.57-1.67 (m, 2 H, *H*H-4, *H*H-5), 1.78-1.87 (m, 1 H, H*H*-4), 1.90-1.99 (m, 1 H, H*H*-5), 2.26-2.36 (m, 1 H, *H*H-3), 2.41-2.51 (m, 1 H, H*H*-3), 4.43 (tdd, ^3J = 7.8 Hz, $^4J_1$ = 3.8 Hz, $^4J_2$ = 1.7 Hz, 1 H, H-1), 5.02 (*virt.* qd, $^4J_1 \approx {}^4J_2 \approx {}^4J_3$ = 2.1 Hz, ^2J = 0.9 Hz, 1 H, C*H*H-2), 5.13 (*virt.* qd, $^4J_1 \approx {}^4J_2 \approx {}^4J_3$ = 1.6 Hz, ^2J = 0.9 Hz, 1 H, CH*H*-2).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 21.9 (t, C-4), 30.5 (t, C-3), 35.8 (t, C-5), 75.3 (d, C-1), 107.7 (t, CH_2-2), 155.5 (s, C-2).

The analytical data obtained matched those reported in the literature.[159]

3-(Cyclopent-1-en-1-yl)propan-1-ol (136)



rac-**133** **134** **136**

According to a modified literature procedure:[160]

Johnson-Claisen Rearrangement: In a round-bottom flask which was equipped with a *Dean-Stark* apparatus, a solution of alcohol *rac*-**133** (1.10 g, 11.2 mmol, 1.00 equiv) in triethyl orthoacetate (9.80 g, 11.1 mL, 60.4 mmol, 5.39 equiv) was acidified with propionic acid (216 mg, 245 µL, 2.91 mmol, 0.26 equiv). The reaction mixture was heated at reflux at 150 °C. After two hours no further condensation of ethanol was observed and the reaction mixture was allowed to cool to room temperature. The excess of triethyl orthoacetate was hydrolyzed by addition of aqueous potassium hydrogen sulfate solution (1.00 M, 10 mL) and stirring for two hours. The mixture was diluted with diethyl ether (20 mL) and the layers were separated. The

organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (2 × 10 mL) and brine (10 mL). After drying over sodium sulfate, filtration, and removal of the solvent in vacuo, the crude product **134** was converted in the next step without further purification. The crude product **134** consisted of a mixture of the ester **134** and the acylated starting material *rac*-**135** which were inseparable. In order to facilitate a separation, the crude product **134** was subjected to reduction conditions which enabled the isolation of the corresponding alcohol **136**.

Reduction with Lithiumaluminum Hydride: A solution of crude ester **134** (1.49 g, 8.86 mmol, 1.00 equiv) in diethyl ether (10.5 mL, 840 mM) was added to a suspension of lithiumaluminum hydride (336 mg, 8.86 mmol, 1.00 equiv) in diethyl ether (6.11 mL, 1.45 M) at 0 °C. The reaction mixture was warmed to room temperature and stirred for three hours. The excess of lithiumaluminum hydride was quenched by dropwise addition of methanol at 0 °C until no further gas evolution was observed. Aqueous hydrochloric acid solution (1.00 M, 50 mL) was added to the reaction mixture which was then stirred for 15 minutes. After separation of the layers, the aqueous layer was extracted with diethyl ether (3 × 50 mL). The organic layers were combined, dried with brine (100 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. The crude product **136** consisted of a mixture of alcohol **136** and starting material *rac*-**133** which were not separable using conventional methods. In order to facilitate a separation, a selective oxidation of allylic alcohol *rac*-**133** was performed. Manganese oxide (1.00 g, 11.5 mmol, 1.30 equiv) was added to a solution of the crude product mixture in dichloromethane (10 mL). The resulting suspension was stirred for five hours at room temperature. The reaction mixture was filtered through a short pad of Celite and the solvent was removed in vacuo. After purification of the residue by column chromatography (silica, CH_2Cl_2/Et_2O = 1/0 → 30/1), alcohol **136** (540 mg, 4.28 mmol, 38% over two steps) was obtained as a colorless oil.

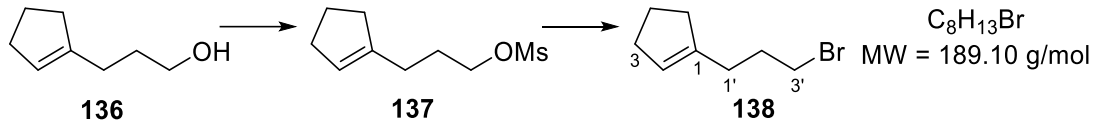
TLC: R_f = 0.42 (P/MTBE = 1/2) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.38 (s, 1 H, OH-1'), 1.69-1.76 (m, 2 H, H-2'), 1.82-1.89 (m, 2 H, H-4), 2.12-2.18 (m, 2 H, H-3'), 2.21-2.27 (m, 2 H, H-3), 2.27-2.32 (m, 2 H, H-5), 3.65 (t, ^3J = 6.5 Hz, 2 H, H-1'), 5.36 (*virt.* sept, $^3J \approx {}^4J_1 \approx {}^4J_2$ = 1.9 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 23.6 (t, C-4), 27.6 (t, C-3'), 30.8 (t, C-2'), 32.6 (t, C-5), 35.2 (t, C-3), 63.1 (t, C-1'), 123.9 (d, C-2), 144.4 (s, C-1).

The analytical data obtained matched those reported in the literature.[279]

1-(3-Bromopropyl)cyclopent-1-ene (138)



Analogously to a literature procedure:[157]

Mesylation: Mesyl chloride (410 µL, 607 mg, 5.30 mmol, 1.50 equiv) was added dropwise to a solution of alcohol **136** (446 mg, 3.53 mmol, 1.00 equiv) and triethylamine (1.48 mL, 1.07 g, 10.6 mmol, 3.00 equiv) in dichloromethane (2.08 mL, 1.70 M) at 0 °C. The reaction mixture was warmed to room temperature and was subsequently stirred for five hours. [*N.b.*: Reaction monitoring by TLC was conducted by using a pentane-dichloromethane eluent, other typical mixtures could not lead to a distinction between the alcohol **136** and the mesylated product **137**.] Aqueous hydrochloric acid solution (1.00 M, 20 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with dichloromethane (4 × 20 mL). The organic layers were combined, washed with saturated aqueous sodium hydrogen carbonate solution (50 mL) and dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. The orange crude product **137** was used in the next step without further purification.

Bromination: Dry lithium bromide (614 mg, 7.07 mmol, 2.00 equiv) was added to a solution of the mesylated alcohol **137** in freshly distilled acetone (13.1 mL, 540 mM) and the resulting mixture was heated at reflux for 17 hours. After cooling the reaction mixture to room temperature, the solvent was removed in vacuo. The residue was partitioned between a 1:1 mixture of water and pentane (100 mL). The aqueous layer was extracted with pentane (4 × 20 mL). The organic layers were combined and dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. After purification of the residue by column chromatography (silica, P), alkenyl bromide **138** (574 mg, 3.03 mmol, 86% over two steps) was obtained as a colorless oil.

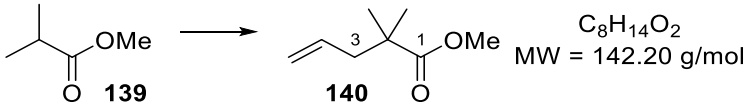
TLC: R_f = 0.56 (P) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.82-1.90 (m, 2 H, H-4), 1.97-2.04 (m, 2 H, H-2'), 2.19-2.26 (m, 4 H, H-5, H-1'), 2.27-2.33 (m, 2 H, H-3), 3.40 (t, ^3J = 6.8 Hz, 2 H, H-3'), 5.38 (*virt.* sept, $^3J \approx {}^4J_1 \approx {}^4J_2$ = 2.1 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 23.5 (t, C-4), 29.7 (t, C-1'), 30.9 (t, C-2'), 32.6 (t, C-3), 33.8 (t, C-3'), 35.1 (t, C-5), 124.6 (d, C-2), 142.9 (s, C-1).

The analytical data obtained matched those reported in the literature.[280]

Methyl 2,2-dimethylpent-4-enoate (140)



According to a modified literature procedure:[161] A solution of *n*-butyllithium (2.00 M in tetrahydrofuran, 21.5 mL, 43.1 mmol, 1.10 equiv) was added dropwise to a solution of diisopropylamine (6.08 mL, 4.36 g, 43.1 mmol, 1.10 equiv) in tetrahydrofuran (15 mL, 2.87 M) at –78 °C. The freshly prepared lithium diisopropylamide solution was warmed to 0 °C and was subsequently stirred for 30 minutes. After cooling to –78 °C, ester **139** (4.49 mL, 4.00 g, 39.2 mmol, 1.00 equiv) was added and the resulting mixture was stirred for one hour. A solution of allyl bromide (4.06 mL, 5.69 g, 47.0 mmol, 1.20 equiv) in tetrahydrofuran (7 mL, 6.71 M) was added dropwise to the enolate solution. After allowing the reaction suspension to warm to room temperature within 17 hours, the reaction mixture was diluted with pentane (30 mL). The suspension was filtered through a short pad of Celite and was washed with small portions of pentane. After removal of the solvent in vacuo and purification by column chromatography (silica, P/Et_2O = 50/1 → 20/1), ester **140** (3.20 g, 22.5 mmol, 58%) was obtained as a colorless oil.

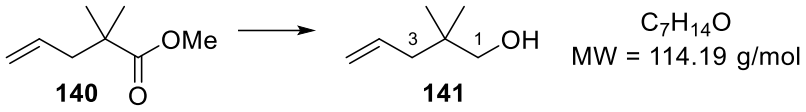
TLC: R_f = 0.48 (P/Et_2O = 9/1) [$KMnO_4$].

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.17 (s, 6 H, 2 × Me-2), 2.27 (*virt.* dt, ^3J = 7.4 Hz, $^4J_1 \approx {}^4J_2$ = 1.2 Hz, 2 H, H-3), 3.66 (s, 3 H, CO_2Me), 5.00-5.04 (m, 1 H, *H*H-5), 5.05-5.07 (m, 1 H, H*H*-5), 5.66-5.79 (m, 1 H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 25.0 (q, 2 C, 2 × Me-2), 42.5 (s, C-2), 44.9 (t, C-3), 51.8 (q, CO_2*Me*), 118.0 (t, C-5), 134.4 (d, C-4), 178.1 (s, *C*O_2Me).

The analytical data obtained matched those reported in the literature.[117]

2,2-Dimethylpent-4-en-1-ol (141)



According to a modified literature procedure:[117] A solution of ester **140** (3.10 g, 21.8 mmol, 1.00 equiv) in diethyl ether (20 mL, 1.09 M) was added to a suspension of lithiumaluminum hydride (1.08 g, 28.3 mmol, 1.30 equiv) in diethyl ether (18 mL, 1.57 M) at 0 °C. The reaction mixture was heated at reflux and was subsequently stirred for seven hours. After cooling the suspension to 0 °C, the excess of lithiumaluminum hydride was quenched by a dropwise addition of methanol until no further gas evolution was observed. Aqueous hydrochloric acid solution (1.00 M, 75 mL) was added to the reaction mixture which was then stirred for 15 minutes. After separation of the layers, the aqueous layer was extracted with diethyl ether (5 × 80 mL). The organic layers were combined, washed with saturated aqueous sodium hydrogen carbonate solution (200 mL), dried with brine (200 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. Without further purification, alcohol **141** (2.04 g, 17.9 mmol, 82%) was obtained as a colorless oil.

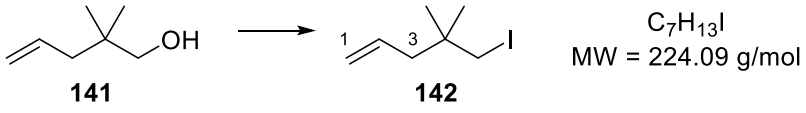
TLC: R_f = 0.14 (P/Et_2O = 4/1) [$KMnO_4$].

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.89 (s, 6 H, 2 × Me-2), 2.02 (*virt.* dt, ^3J = 7.5 Hz, $^4J_1 \approx {}^4J_2$ = 1.2 Hz, 2 H, H-3), 3.33 (s, 2 H, H-1), 5.02-5.08 (m, 2 H, H-5), 5.79-5.91 (m, 1 H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 24.0 (q, 2 C, 2 × Me-2), 35.7 (s, C-2), 43.5 (t, C-3), 71.9 (t, C-1), 117.3 (t, C-5), 135.5 (d, C-4).

The analytical data obtained matched those reported in the literature.[117]

5-Iodo-4,4-dimethylpent-1-ene (142)



According to a modified literature procedure:[162] Iodine (2.53 g, 9.98 mmol, 2.00 equiv) was added portionwise to a solution of alcohol **141** (570 mg, 4.99 mmol, 1.00 equiv) and triphenylphosphine (2.88 g, 10.9 mmol, 2.20 equiv) in pyridine (2.5 mL, 2.00 M) at 0 °C. The resulting suspension was heated to 170 °C and was subsequently stirred for 16 hours. After cooling to room temperature, the reaction mixture was transferred to a silica-packed column

and the product was eluated with pentane. After removal of the solvent in vacuo, alkenyl iodide **142** (872 mg, 3.89 mmol, 78%) was obtained as a colorless oil.

TLC: R_f = 0.56 (P) [$KMnO_4$].

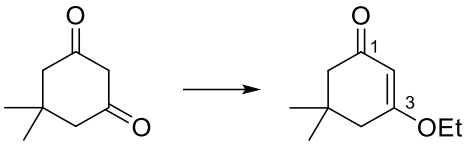
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.03 (s, 6 H, 2 × Me-4), 2.10 (*virt.* dt, ^3J = 7.5 Hz, $^4J_1 \approx {}^4J_2$ = 1.2 Hz, 2 H, H-3), 3.14 (s, 2 H, H-5), 5.08-5.14 (m, 2 H, H-1), 5.75 (ddt, $^3J_1$ = 16.7 Hz, $^3J_2$ = 10.4 Hz, $^3J_3$ = 7.5 Hz, 1 H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 24.0 (t, C-5), 26.9 (q, 2 C, 2 × Me-4), 33.8 (s, C-4), 45.3 (t, C-3), 118.3 (t, C-1), 134.5 (d, C-2).

The analytical data obtained matched those reported in the literature.[162]

6.3.5 Synthesis of Irradiation Precursors for Intramolecular [2+2] Photocycloaddition Reactions

3-Ethoxy-5,5-dimethylcyclohex-2-en-1-one (143)



143

$C_{10}H_{16}O_2$
MW = 168.24 g/mol

According to a modified literature procedure:[163] Ethanol (1.78 mL, 28.5 mmol, 2.00 equiv) and *p*-toluenesulfonic acid (136 mg, 713 μmol, 5.00 mol%) were added in sequence to a solution of 5,5-dimethyl-1,3-cyclohexanedione (2.00 g, 14.3 mmol, 1.00 equiv) in toluene (36 mL, 400 mM). The reaction mixture was stirred in a round-bottom flask which was equipped with a *Dean-Stark* apparatus. A portion of toluene which is equivalent to the *Dean-Stark* apparatus' dead volume was added to the reaction mixture and subsequently heated at reflux. After two hours, the collected toluene was removed. Ethanol (1.78 mL, 28.5 mmol, 2.00 equiv) and a dead volume of toluene were added. As soon as the *Dean-Stark* apparatus was filled, the remaining toluene was removed in vacuo affording an orange-brown residue. After purification of the residue by column chromatography (silica, P/Et_2O = 1/1), enol ether **143** (2.20 g, 13.1 mmol, 92%) was obtained as a pale yellow oil.

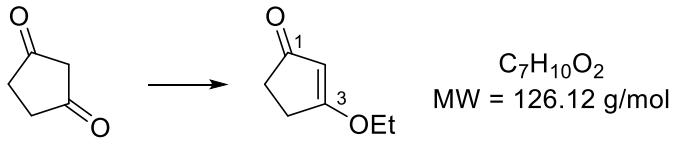
TLC: R_f = 0.39 (P/EtOAc = 3/2) [UV, $KMnO_4$].

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.06 (s, 6 H, 2 × Me-5), 1.35 (t, 3 H, ^3J = 7.0 Hz, CH_2CH_3), 2.20 (s, 2 H, H-6), 2.26 (s, 2 H, H-4), 3.89 (q, 2 H, ^3J = 7.0 Hz, CH_2CH_3), 5.33 (s, 1 H, H-2).

^{13}C NMR (75.5 MHz, $CDCl_3$, 300 K): δ [ppm] = 14.3 (q, CH_2CH_3), 28.2 (q, 2 C, 2 × Me-5), 32.6 (s, C-5), 43.1 (t, C-6), 50.9 (t, C-4), 64.4 (t, CH_2CH_3), 101.6 (d, C-2), 176.4 (s, C-3), 199.8 (s, C-1).

The analytical data obtained matched those reported in the literature.[281]

3-Ethoxycyclopent-2-en-1-one (144)



144

According to a modified literature procedure:[162] Ethanol (699 μL, 11.2 mmol, 2.20 equiv) and *p*-toluenesulfonic acid (48.5 mg, 255 μmol, 5.00 mol%) were added in sequence to a solution of 1,3-cyclopentanedione (500 mg, 5.10 mmol, 1.00 equiv) in toluene (15 mL, 340 mM). The reaction mixture was stirred in a round-bottom flask which was equipped with a *Dean-Stark* apparatus. A portion of toluene which is equivalent to the *Dean-Stark* apparatus' dead volume was added to the reaction mixture and subsequently heated at reflux. As soon as the *Dean-Stark* apparatus was filled, the remaining toluene was removed in vacuo affording an orange-brown residue. After purification by column chromatography (silica, P/EtOAc = 2/1), enol ether **144** (431 mg, 3.42 mmol, 67%) was obtained as a pale yellow oil.

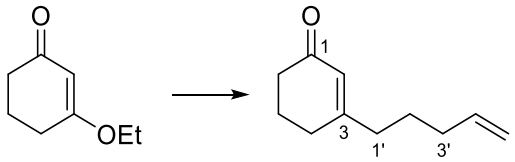
TLC: R_f = 0.29 (P/EtOAc = 1/1) [UV, $KMnO_4$].

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.41 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 2.41-2.46 (m, 2 H, H-5), 2.58-2.63 (m, 2 H, H-4), 4.04 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 5.28-5.30 (m, 1 H, H-2).

^{13}C NMR (75.5 MHz, $CDCl_3$, 300 K): δ [ppm] = 14.3 (q, CH_2CH_3), 28.7 (t, C-4), 34.1 (t, C-5), 67.9 (t, CH_2CH_3), 104.8 (d, C-2), 190.4 (s, C-3), 206.3 (s, C-1).

The analytical data obtained matched those reported in the literature.[162]

3-(Pent-4-en-1-yl)cyclohex-2-en-1-one (65)



118 **65**

$C_{11}H_{16}O$
MW = 164.25 g/mol

Following GP5, enol ether **118** (1.50 g, 10.7 mmol, 1.00 equiv) was converted with 5-bromopent-1-ene (1.65 mL, 2.07 g, 13.9 mmol, 1.30 equiv), iodine (27.2 mg, 107 µmol, 1.00 mol%) and magnesium turnings (338 mg, 13.9 mmol, 1.30 equiv) within 16 hours. After purification by column chromatography (silica, P/Et_2O = 4/1), enone **65** (1.41 g, 8.58 mmol, 80%) was obtained as a pale yellow oil.

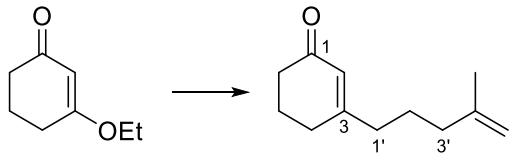
TLC: R_f = 0.19 (P/Et_2O = 4/1) [$KMnO_4$, UV].

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.60 (*virt.* quint, $^3J_1 \approx {}^3J_2$ = 7.5 Hz, 2 H, H-2'), 1.98 (*virt.* quint, $^3J_1 \approx {}^3J_2$ = 6.3 Hz, 2 H, H-5), 2.07 (*virt.* qt, $^3J_1 \approx {}^3J_2$ = 6.7 Hz, $^4J_1 \approx {}^4J_2$ = 1.4 Hz, 2 H, H-3'), 2.22 (td, ^3J = 7.7 Hz, ^4J = 1.0 Hz, 2 H, H-1'), 2.28 (td, ^3J = 6.2 Hz, ^4J = 1.4 Hz, 2 H, H-4), 2.33-2.38 (m, 2 H, H-6), 4.96-5.05 (m, 2 H, H-5'), 5.78 (ddt, $^3J_1$ = 16.9 Hz, $^3J_2$ = 10.1 Hz, $^3J_3$ = 6.6 Hz, 1 H, H-4'), 5.87 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.4 Hz, 1 H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.9 (t, C-5), 26.2 (t, C-2'), 29.8 (t, C-4), 33.3 (t, C-3'), 37.5 (t, C-1'), 37.5 (t, C-6), 115.4 (t, C-5'), 125.9 (d, C-2), 138.0 (d, C-4'), 166.3 (s, C-3), 200.0 (s, C-1).

The analytical data obtained matched those reported in the literature.[282]

3-(4-Methylpent-4-en-1-yl)cyclohex-2-en-1-one (145)



118 **145**

$C_{12}H_{18}O$
MW = 178.28 g/mol

Following GP5, enol ether **118** (592 mg, 4.23 mmol, 1.00 equiv) was converted with alkenyl bromide **126** (896 mg, 5.49 mmol, 1.30 equiv), iodine (10.7 mg, 42.3 µmol, 1.00 mol%) and magnesium turnings (134 mg, 5.49 mmol, 1.30 equiv) within two hours. After purification by

column chromatography (silica, P/Et_2O = 7/1), enone **145** (549 mg, 3.08 mmol, 73%) was obtained as a pale yellow oil.

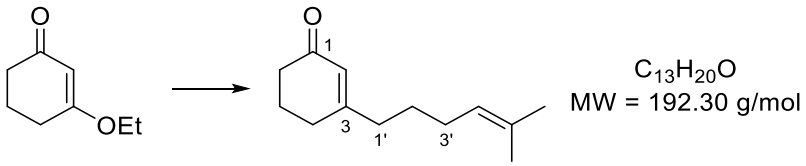
TLC: R_f = 0.39 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.60-1.69 (m, 2 H, H-2'), 1.71 (br s, 3 H, Me-4'), 1.96-2.05 (m, 4 H, H-5, H-3'), 2.18-2.23 (m, 2 H, H-1'), 2.26-2.31 (m, 2 H, H-4), 2.34-2.39 (m, 2 H, H-6), 4.68 (dq, ^2J = 2.2 Hz, ^4J = 1.0 Hz, 1 H, *H*H-5'), 4.73-4.75 (m, 1 H, H*H*-5'), 5.89 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.4 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.4 (q, Me-4'), 22.9 (t, C-5), 24.8 (t, C-2'), 29.9 (t, C-4), 37.3 (t, C-3'), 37.5 (t, C-6), 37.6 (t, C-1'), 110.7 (t, C-5'), 125.9 (d, C-2), 145.1 (s, C-4'), 166.5 (s, C-3), 200.1 (s, C-1).

The analytical data obtained matched those reported in the literature.[283]

3-(5-Methylhex-4-en-1-yl)cyclohex-2-en-1-one (146)



118 **146**

Following GP5, enol ether **118** (761 mg, 5.43 mmol, 1.00 equiv) was converted with alkenyl bromide **131** (1.25 g, 7.06 mmol, 1.30 equiv), iodine (13.8 mg, 54.3 µmol, 1.00 mol%) and magnesium turnings (172 mg, 7.06 mmol, 1.30 equiv) within 16 hours. After purification by column chromatography (silica, P/Et_2O = 5/1 → 4/1), enone **146** (835 mg, 4.34 mmol, 80%) was obtained as a pale yellow oil.

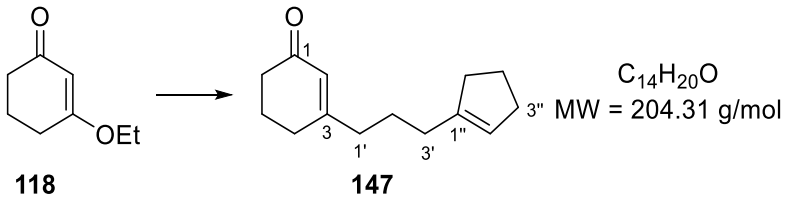
TLC: R_f = 0.37 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.53 (*virt.* quint, $^3J_1 \approx {}^3J_2$ = 7.5 Hz, 2 H, H-2'), 1.59 (d, ^4J = 1.5 Hz, 3 H, Me-5'), 1.69 (d, ^4J = 1.5 Hz, 3 H, Me-5'), 1.94-2.03 (m, 4 H, H-3', H-5), 2.17-2.23 (m, 2 H, H-1'), 2.25-2.30 (m, 2 H, H-4), 2.33-2.38 (m, 2 H, H-6), 5.09 (*virt.* tsept, ^3J = 7.2 Hz, $^4J_1 \approx {}^4J_2$ = 1.5 Hz, 1 H, H-4'), 5.87 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.3 Hz, 1 H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 17.9 (q, Me-5'), 22.9 (t, C-5), 25.9 (q, Me-5'), 27.2 (t, C-2'), 27.7 (t, C-3'), 29.8 (t, C-4), 37.5 (t, C-6), 37.8 (t, C-1'), 123.8 (d, C-4'), 125.9 (d, C-2), 132.5 (s, C-5'), 166.7 (s, C-3), 200.0 (s, C-1).

The analytical data obtained matched those reported in the literature.[172]

3-[3-(Cyclopent-1-en-1-yl)propyl]cyclohex-2-en-1-one (147)



118 **147**

Following GP5, enol ether **118** (372 mg, 2.65 mmol, 1.00 equiv) was converted with alkenyl bromide **138** (652 mg, 3.45 mmol, 1.30 equiv), iodine (6.73 mg, 26.5 μmol, 1.00 mol%) and magnesium turnings (83.8 mg, 3.45 mmol, 1.30 equiv) within two hours. After purification by column chromatography (silica, P/Et_2O = 5/1), enone **147** (325 mg, 1.59 mmol, 60%) was obtained as a pale yellow oil.

TLC: R_f = 0.35 (P/Et_2O = 1/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3042 (w, sp^2-CH), 2933 (m, sp^3-CH), 2890 (m, sp^3-CH), 2866 (m, sp^3-CH), 2842 (m, sp^3-CH), 1666 (vs, C=O), 1624 (m, sp^2-CC).

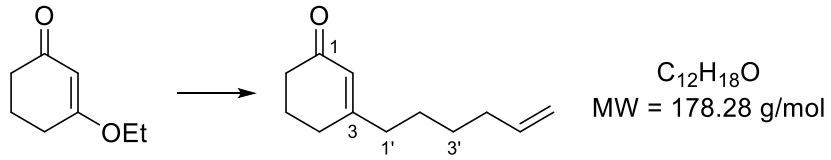
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.62-1.69 (m, 2 H, H-2'), 1.82-1.89 (m, 2 H, H-4''), 1.96-2.02 (m, 2 H, H-5), 2.06-2.11 (m, 2 H, H-3'), 2.18-2.24 (m, 4 H, H-1', H-5''), 2.27-2.33 (m, 4 H, H-4, H-3''), 2.34-2.38 (m, 2 H, H-6), 5.34 (*virt.* sept, $^3J \approx {}^4J$ = 1.9 Hz, 1 H, H-2''), 5.88 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.4 Hz, 1 H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.9 (t, C-5), 23.5 (t, C-4''), 25.1 (t, C-2'), 29.8 (t, C-4), 30.8 (t, C-3'), 32.6 (t, C-3''), 35.1 (t, C-5''), 37.5 (t, C-6), 37.9 (t, C-1'), 124.1 (d, C-2''), 125.9 (d, C-2), 143.9 (s, C-1''), 166.7 (s, C-3), 200.2 (s, C-1).

MS (EI, 70 eV): m/z (%) = 204 (30) $[M]^+$, 123 (100) $[M–C_6H_9]^+$, 110 (53) $[C_7H_{10}O]^+$, 95 (20) $[C_6H_7O]^+$, 79 (32), 67 (20).

HRMS (EI, 70 eV): calcd for $C_{14}H_{20}O$ $[M]^+$: 204.1509; found: 204.1506;
calcd for $C_{13}{}^{13}CH_{20}O$ $[M]^+$: 205.1542; found: 205.1543.

3-(Hex-5-en-1-yl)cyclohex-2-en-1-one (148)



118 **148**

Following GP5, enol ether **118** (500 mg, 3.57 mmol, 1.00 equiv) was converted with 6-bromohex-1-ene (620 µL, 756 mg, 4.64 mmol, 1.30 equiv), iodine (9.05 mg, 35.7 µmol, 1.00 mol%) and magnesium turnings (113 mg, 4.64 mmol, 1.30 equiv) within two hours. After purification by column chromatography (silica, P/Et_2O = 3/1), enone **148** (531 mg, 2.98 mmol, 84%) was obtained as a pale yellow oil.

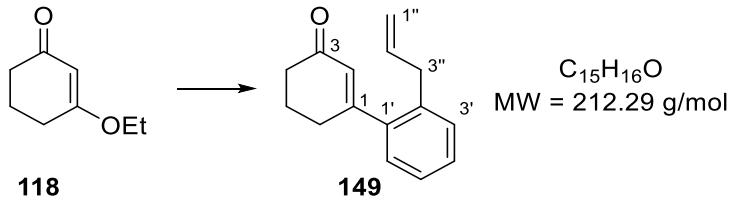
TLC: R_f = 0.39 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.37-1.44 (m, 2 H, H-3'), 1.48-1.55 (m, 2 H, H-2'), 1.95-2.01 (m, 2 H, H-5), 2.04-2.10 (m, 2 H, H-4'), 2.19-2.23 (m, 2 H, H-1'), 2.26-2.30 (m, 2 H, H-4), 2.33-2.37 (m, 2 H, H-6), 4.95 (ddt, ^3J = 10.2 Hz, ^2J = 2.3 Hz, ^4J = 1.3 Hz, 1 H, H-*E*-6'), 5.00 (*virt.* dq, ^3J = 17.1 Hz, $^2J \approx {}^4J$ = 1.7 Hz, 1 H, H-*Z*-6'), 5.78 (ddt, $^3J_1$ = 17.1 Hz, $^3J_2$ = 10.2 Hz, $^3J_3$ = 6.7 Hz, 1 H, H-5'), 5.87 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.4 Hz, 1 H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.9 (t, C-5), 26.5 (t, C-2'), 28.6 (t, C-3'), 29.8 (t, C-4), 33.6 (t, C-4'), 37.5 (t, C-6), 38.0 (t, C-1'), 114.9 (t, C-6'), 125.8 (d, C-2), 138.5 (d, C-5'), 166.6 (s, C-3), 200.0 (s, C-1).

The analytical data obtained matched those reported in the literature.[284]

2'-Allyl-5,6-dihydro-[1,1'-biphenyl]-3(4*H*)-one (149)



118 **149**

Following GP5, enol ether **118** (547 mg, 3.90 mmol, 1.00 equiv) was converted with 1-allyl-2-bromobenzene (1.00 g, 5.07 mmol, 1.30 equiv), iodine (9.91 mg, 39.0 µmol, 1.00 mol%) and magnesium turnings (123 mg, 5.07 mmol, 1.30 equiv) within 16 hours. After purification by column chromatography (silica, P/Et_2O = 7/1 → 6/1), enone **149** (545 mg, 2.57 mmol, 68%) was obtained as a pale yellow oil.

TLC: R_f = 0.27 (P/Et_2O = 2/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3060 (w, sp^2-CH), 3018 (w, sp^2-CH), 2946 (w, sp^3-CH), 2867 (w, sp^3-CH), 1666 (vs, C=O), 1637 (m, sp^2-CC), 1617 (m, sp^2-CC), 753 (vs, sp^2-CH).

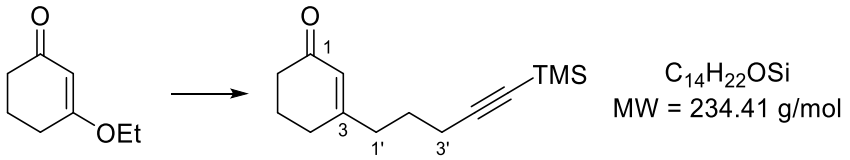
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 2.15 (*virt.* quint, $^3J_1 \approx {}^3J_2$ = 6.3 Hz, 2 H, H-5), 2.47-2.51 (m, 2 H, H-4), 2.58 (td, ^3J = 6.0 Hz, ^4J = 1.6 Hz, 2 H, H-6), 3.37 (*virt.* dt, ^3J = 6.4 Hz, $^4J_1 \approx {}^4J_2$ = 1.6 Hz, 2 H, H-3''), 4.98 (*virt.* dq, ^3J = 16.8 Hz, $^2J \approx {}^4J$ = 1.7 Hz, 1 H, H-*Z*-1''), 5.07 (*virt.* dq, ^3J = 10.1 Hz, $^2J \approx {}^4J$ = 1.5 Hz, 1 H, H-*E*-1''), 5.91 (ddt, $^3J_1$ = 16.8 Hz, $^3J_2$ = 10.1 Hz, $^3J_3$ = 6.4 Hz, 1 H, H-2''), 6.00 (t, ^4J = 1.6 Hz, 1 H, H-2), 7.11 (dd, ^3J = 7.8 Hz, ^4J = 1.9 Hz, 1 H, H-6'), 7.21-7.27 (m, 2 H, H-3', H-4'), 7.30 (ddd, $^3J_1$ = 7.8 Hz, $^3J_2$ = 7.0 Hz, ^4J = 1.5 Hz, 1 H, H-5').

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 23.3 (t, C-5), 31.9 (t, C-6), 37.4 (t, C-4), 37.6 (t, C-3''), 116.5 (t, C-1''), 126.5 (d, C-3'), 127.2 (d, C-6'), 128.5 (d, C-5'), 129.0 (d, C-2), 130.3 (d, C-4'), 136.0 (s, C-1'), 137.3 (d, C-2''), 140.9 (s, C-2'), 163.3 (s, C-1), 199.5 (s, C-3).

MS (EI, 70 eV): m/z (%) = 212 (18) $[M]^+$, 184 (86) $[M–C_2H_4]^+$, 155 (39), 141 (100), 128 (43), 115 (36).

HRMS (EI, 70 eV): calcd for $C_{15}H_{16}O$ $[M]^+$: 212.1196; found: 212.1183;
calcd for $C_{14}{}^{13}CH_{16}O$ $[M]^+$: 213.1229; found: 213.1220.

3-[5-(Trimethylsilyl)pent-4-yn-1-yl]cyclohex-2-en-1-one (150)



118 **150**

Following GP5, enol ether **118** (1.00 g, 7.13 mmol, 1.00 equiv) was converted with (5-bromopent-1-yn-1-yl)trimethylsilane (2.03 g, 9.27 mmol, 1.30 equiv), iodine (18.1 mg, 71.3 µmol, 1.00 mol%) and magnesium turnings (225 mg, 9.27 mmol, 1.30 equiv) within 16 hours. After purification by column chromatography (silica, P/Et_2O = 5/1), enone **150** (1.09 g, 4.67 mmol, 67%) was obtained as a pale yellow oil.

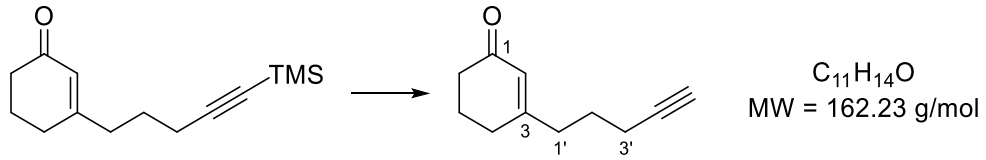
TLC: R_f = 0.35 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.15 (s, 9 H, $SiMe_3$), 1.69-1.76 (m, 2 H, H-2'), 1.96-2.03 (m, 2 H, H-5), 2.25 (t, ^3J = 7.0 Hz, 2 H, H-3'), 2.27-2.34 (m, 4 H, H-4, H-1'), 2.34-2.38 (m, 2 H, H-6), 5.88 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.4 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 0.3 (q, 3 C, $SiMe_3$), 19.6 (t, C-3'), 22.8 (t, C-5), 26.0 (t, C-2'), 29.8 (t, C-4), 37.0 (t, C-1'), 37.5 (t, C-6), 85.7 (s, C-5'), 106.3 (s, C-4'), 126.2 (d, C-2), 165.5 (s, C-3), 200.0 (s, C-1).

The analytical data obtained matched those reported in the literature.[162]

3-(Pent-4-yn-1-yl)cyclohex-2-en-1-one (155)



150 **155**

A solution of tetrabutylammonium fluoride (1.00 M in tetrahydrofuran, 1.71 mL, 1.71 mmol, 2.00 equiv) was added to a solution of enone **150** (200 mg, 853 µmol, 1.00 equiv) in tetrahydrofuran (1.00 M, 853 µL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was subsequently stirred for 22 hours. After pouring the mixture into water (10 mL), the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. After purification of the residue by column chromatography (silica, P/Et_2O = 4/1), enone **155** (109 mg, 674 µmol, 79%) was obtained as a pale yellow oil.

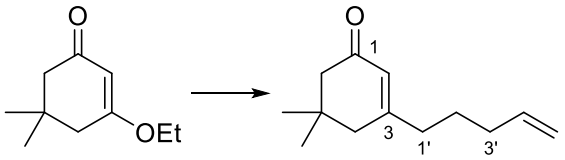
TLC: R_f = 0.29 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.70-1.78 (m, 2 H, H-2'), 1.96-2.03 (m, 3 H, H-5, H-5'), 2.23 (td, ^3J = 6.9 Hz, ^4J = 2.6 Hz, 2 H, H-3'), 2.28-2.32 (m, 2 H, H-4), 2.32-2.39 (m, 4 H, H-6, H-1'), 5.89 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.4 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 18.2 (t, C-3'), 22.8 (t, C-5), 25.7 (t, C-2'), 29.8 (t, C-4), 36.9 (t, C-1'), 37.5 (t, C-6), 69.3 (d, C-5'), 83.5 (s, C-4'), 126.1 (d, C-2), 165.4 (s, C-3), 200.0 (s, C-1).

The analytical data obtained matched those reported in the literature.[162]

5,5-Dimethyl-3-(pent-4-en-1-yl)cyclohex-2-en-1-one (151)



143 **151**

$C_{13}H_{20}O$
MW = 192.30 g/mol

Following GP5, enol ether **143** (447 mg, 2.66 mmol, 1.00 equiv) was converted with 5-bromopent-1-ene (409 µL, 515 mg, 3.45 mmol, 1.30 equiv), iodine (6.74 mg, 26.6 µmol, 1.00 mol%) and magnesium turnings (84.0 mg, 3.45 mmol, 1.30 equiv) within 16 hours. After purification by column chromatography (silica, P/Et_2O = 4/1), enone **151** (235 mg, 1.22 mmol, 46%) was obtained as a pale yellow oil.

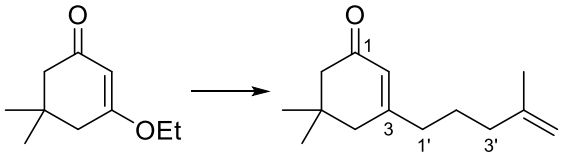
TLC: R_f = 0.25 (P/Et_2O = 4/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.03 (s, 6 H, 2 × Me-5), 1.59 (*virt.* quint, $^3J_1 \approx {}^3J_2$ = 7.5 Hz, 2 H, H-2'), 2.08 (*virt.* qt, $^3J_1 \approx {}^3J_2$ = 7.2 Hz, $^4J_1 \approx {}^4J_2$ = 1.3 Hz, 2 H, H-3'), 2.16 (s, 2 H, H-4), 2.17-2.21 (m, 2 H, H-1'), 2.21 (s, 2 H, H-6), 4.97-5.05 (m, 2 H, H-5'), 5.78 (ddt, $^3J_1$ = 17.0 Hz, $^3J_2$ = 10.2 Hz, $^3J_3$ = 6.7 Hz, 1 H, H-4'), 5.88 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.4 Hz, 1 H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 26.2 (t, C-2'), 28.4 (q, 2 C, 2 × Me-5), 33.3 (t, C-3'), 33.7 (s, C-5), 37.5 (t, C-1'), 44.1 (t, C-4), 51.2 (t, C-6), 115.4 (t, C-5'), 124.9 (d, C-2), 138.0 (d, C-4'), 163.9 (s, C-3), 200.2 (s, C-1).

The analytical data obtained matched those reported in the literature.[285]

5,5-Dimethyl-3-(4-methylpent-4-en-1-yl)cyclohex-2-en-1-one (152)



143 **152**

$C_{14}H_{22}O$
MW = 206.33 g/mol

Following GP5, enol ether **143** (450 mg, 2.92 mmol, 1.00 equiv) was converted with alkenyl bromide **126** (619 mg, 3.79 mmol, 1.30 equiv), iodine (7.41 mg, 29.2 µmol, 1.00 mol%) and magnesium turnings (92.2 mg, 3.79 mmol, 1.30 equiv) within one hour. After purification by column chromatography (silica, P/Et_2O = 4/1), enone **152** (237 mg, 1.15 mmol, 39%) was obtained as a pale yellow oil.

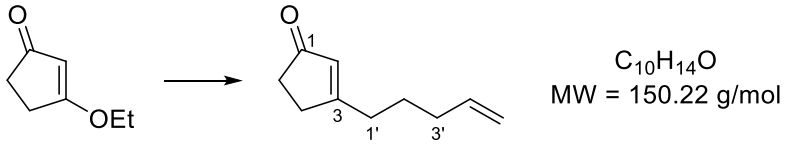
TLC: R_f = 0.54 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.03 (s, 6 H, 2 × Me-5), 1.60-1.68 (m, 2 H, H-2'), 1.71 (br s, 3 H, Me-4'), 2.01-2.05 (m, 2 H, H-3'), 2.15-2.20 (m, 4 H, H-4, H-1'), 2.21 (s, 2 H, H-6), 4.68 (dq, ^2J = 2.2 Hz, ^4J = 1.1 Hz, 1 H, *H*H-5'), 4.72-4.75 (m, 1 H, H*H*-5'), 5.88 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.4 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.4 (q, Me-4'), 24.8 (t, C-2'), 28.4 (q, 2 C, 2 × Me-5), 33.8 (s, C-5), 37.3 (t, C-3'), 37.6 (t, C-1'), 44.1 (t, C-4), 51.2 (t, C-6), 110.7 (t, C-5'), 124.9 (d, C-2), 145.1 (s, C-4'), 164.1 (s, C-3), 200.3 (s, C-1).

The analytical data obtained matched those reported in the literature.[283]

3-(Pent-4-en-1-yl)cyclopent-2-en-1-one (153)



144 **153**

Following GP5, enol ether **144** (249 mg, 1.97 mmol, 1.00 equiv) was converted with 5-bromopent-1-ene (303 µL, 382 mg, 2.56 mmol, 1.30 equiv), iodine (5.01 mg, 19.7 µmol, 1.00 mol%) and magnesium turnings (62.3 mg, 2.56 mmol, 1.30 equiv) within 16 hours. After purification by column chromatography (silica, P/Et_2O = 3/1), enone **153** (154 mg, 1.03 mmol, 52%) was obtained as a pale yellow oil.

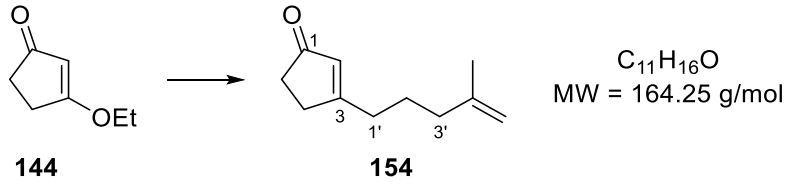
TLC: R_f = 0.61 (P/EtOAc = 1/1) [$KMnO_4$, UV].

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.69 (*virt.* quint, $^3J_1 \approx {}^3J_2$ = 7.4 Hz, 2 H, H-2'), 2.08-2.16 (m, 2 H, H-3'), 2.39-2.45 (m, 4 H, H-4, H-1'), 2.56-2.60 (m, 2 H, H-5), 4.96-5.09 (m, 2 H, H-5'), 5.80 (ddt, $^3J_1$ = 17.0 Hz, $^3J_2$ = 10.2 Hz, $^3J_3$ = 6.7 Hz, 1 H, H-4'), 5.96 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.5 Hz, 1 H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 26.4 (t, C-2'), 31.7 (t, C-5), 33.0 (t, C-1'), 33.4 (t, C-3'), 35.5 (t, C-4), 115.6 (t, C-5'), 129.7 (d, C-2), 137.8 (d, C-4'), 182.8 (s, C-3), 210.2 (s, C-1).

The analytical data obtained matched those reported in the literature.[286]

3-(4-Methylpent-4-en-1-yl)cyclopent-2-en-1-one (154)



144 **154**

Following GP5, enol ether **144** (300 mg, 2.38 mmol, 1.00 equiv) was converted with alkenyl bromide **126** (504 mg, 3.09 mmol, 1.30 equiv), iodine (6.04 mg, 23.8 µmol, 1.00 mol%) and magnesium turnings (75.1 mg, 3.09 mmol, 1.30 equiv) within one hour. After purification by column chromatography (silica, P/Et_2O = 3/1), enone **154** (166 mg, 1.01 mmol, 42%) was obtained as a pale yellow oil.

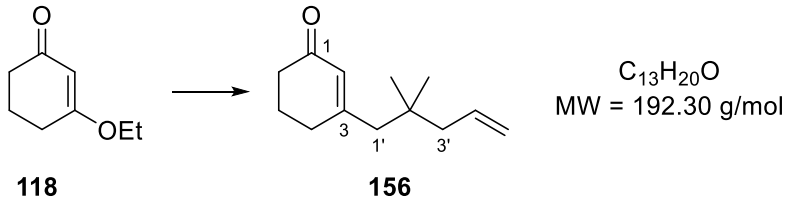
TLC: R_f = 0.26 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.69-1.77 (m, 5 H, H-2', Me-4'), 2.04-2.10 (m, 2 H, H-3'), 2.37-2.43 (m, 4 H, H-5, H-1'), 2.56-2.61 (m, 2 H, H-4), 4.69 (dq, ^2J = 2.2 Hz, ^4J = 1.1 Hz, 1 H, *H*H-5'), 4.74-4.76 (m, 1 H, H*H*-5'), 5.96 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.5 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.4 (q, Me-4'), 25.0 (t, C-2'), 31.7 (t, C-4), 33.1 (t, C-1'), 35.4 (t, C-5), 37.4 (t, C-3'), 110.8 (t, C-5'), 129.7 (d, C-2), 144.9 (s, C-4'), 183.0 (s, C-3), 210.3 (s, C-1).

The analytical data obtained matched those reported in the literature.[287]

3-(2,2-Dimethylpent-4-en-1-yl)cyclohex-2-en-1-one (156)



118 **156**

In analogy to a modified literature procedure:[164]

Organolithium Reagent: A solution of *tert*-butyllithium (1.90 M in pentane, 3.72 mL, 7.08 mmol, 2.00 equiv) was added dropwise to a solution of alkenyl iodide **142** (872 mg, 3.89 mmol, 1.10 equiv) in diethyl ether (7.8 mL, 500 mM) at –78 °C. The resulting organolithium reagent solution was stirred for two hours.

In analogy to a modified literature procedure:[133]

Addition of the Vinylogous Ester: A solution of enol ether **118** (496 mg, 3.54 mmol, 1.00 equiv) in diethyl ether (1.77 mL, 2.00 M) was added dropwise to the freshly prepared organolithium solution at –78 °C. After the reaction mixture was stirred for two hours, aqueous hydrochloric acid solution (1.00 M, 10 mL) was added and the resulting mixture was stirred for 15 minutes. The solution was allowed to warm to room temperature and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried with brine (10 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. After purification by column chromatography (silica, P/Et_2O = 4/1), a mixture of the title compound **156** and a byproduct was obtained. GC analysis and NMR analysis showed that the byproduct is alcohol **141**. The mixture was submitted to mesylating conditions (MsCl, Et_3N, CH_2Cl_2) and then purified by column chromatography (silica, CH_2Cl_2, then P/Et_2O = 4/1). After purification, enone **156** (201 mg, 1.05 mmol, 30%) was obtained as a pale yellow oil.

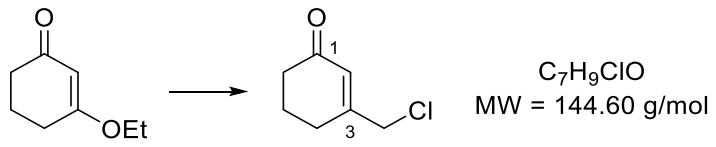
TLC: R_f = 0.42 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.92 (s, 6 H, 2 × Me-2'), 1.94-1.99 (m, 2 H, H-5), 2.01 (*virt.* dt, ^3J = 7.4 Hz, $^4J_1 \approx {}^4J_2$ = 1.3 Hz, 2 H, H-3'), 2.12 (s, 2 H, H-1'), 2.32-2.37 (m, 4 H, H-4, H-6), 5.03 (ddt, ^3J = 16.9 Hz, ^2J = 2.2 Hz, ^4J = 1.4 Hz, 1 H, *H*H-*E*-5'), 5.07 (ddt, ^3J = 10.2 Hz, ^2J = 2.2 Hz, ^4J = 1.0 Hz, 1 H, H*H*-*Z*-5'), 5.81 (ddt, $^3J_1$ = 16.9 Hz, $^3J_2$ = 10.2 Hz, $^3J_3$ = 7.4 Hz, 1 H, H-4'), 5.84-5.86 (m, 1 H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 23.2 (t, C-5), 27.4 (q, 2 × Me-2'), 32.7 (t, C-4), 35.2 (s, C-2'), 37.4 (t, C-6), 47.6 (t, C-3'), 50.2 (t, C-1'), 117.9 (t, C-5'), 129.4 (d, C-2), 134.9 (d, C-4'), 164.8 (s, C-3), 199.8 (s, C-1).

The analytical data obtained matched those reported in the literature.[162]

3-(Chloromethyl)cyclohex-2-en-1-one (159)



118 **159**

In analogy to a modified literature procedure:[165] A solution of methyllithium lithium bromide complex (2.20 M in diethyl ether, 26.0 mL, 57.1 mmol, 4.00 equiv) was added dropwise by a syringe pump (0.5 mL/min) to a solution of enol ether **118** (2.00 g, 14.3 mmol, 1.00 equiv) and

chloroiodomethane (11.3 g, 4.68 mL, 64.2 mmol, 4.50 equiv) in a 1:1 mixture of tetrahydrofuran and diethyl ether (29 mL, 500 mM) at –78 °C. After two hours, the excess of organolithium reagent was quenched with semi-saturated aqueous ammonium chloride solution (60 mL). After layer separation, the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried with brine (30 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. After purification of the residue by column chromatography (silica, P/Et_2O = 3/1), enone **159** (1.74 g, 12.0 mmol, 84%) was obtained as a pale-yellow oil. [*N.b.*: This substrate is not bench-stable and should be stored under argon at –20 °C.]

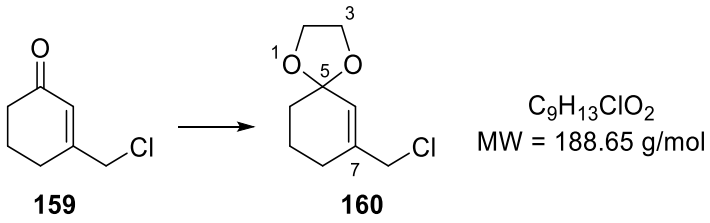
TLC: R_f = 0.28 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 2.06 (*virt.* quint, $^3J_1 \approx {}^3J_2$ = 6.3 Hz, 2 H, H-5), 2.39-2.45 (m, 4 H, H-4, H-6), 4.13 (*virt.* q, $^4J_1 \approx {}^4J_2$ = 0.9 Hz, 2 H, CH_2Cl), 6.10 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.4 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.6 (t, C-5), 27.4 (t, C-4), 37.5 (t, C-6), 47.1 (t, CH_2Cl), 127.5 (d, C-2), 158.3 (s, C-3), 199.5 (s, C-1).

The analytical data obtained matched those reported in the literature.[165]

7-(Chloromethyl)-1,4-dioxaspiro[4.5]dec-6-ene (160)



159 **160**

According to a modified literature procedure:[166] Freshly distilled trimethylsilyl trifluoromethanesulfonate (55.2 mg, 45.0 µL, 248 µmol, 10.0 mol%) was added dropwise to a solution of enone **159** (359 mg, 2.48 mmol, 1.00 equiv) and 1,2-bis(trimethylsiloxy)ethane (1.03 g, 1.22 mL, 4.97 mmol, 2.00 equiv) in dichloromethane (497 µL, 5.00 M) at –78 °C. After 68 hours, the reaction was quenched with dry triethylamine (1.00 mL) and the mixture was allowed to warm to room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography (silica, P/Et_2O = 10/1 → 1/1). The acetal **160** (329 mg, 1.74 mmol, 70%) was obtained as a colorless oil. Starting material **159** (36.7 mg, 254 µmol, 10%) was partially recovered. [*N.b.*: This substrate is not bench-stable and should be stored under argon at –20 °C.]

TLC: R_f = 0.46 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2951 (m, sp^3-CH), 2886 (m, sp^3-CH), 1450 (m, sp^3-CH), 1187 (s, sp^3-CO), 1098 (vs, sp^3-CO), 931 (vs, sp^2-CH), 675 (vs, sp^2-CH).

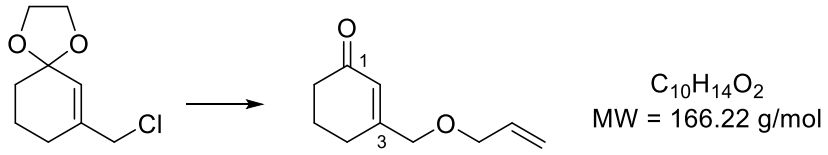
^{1}H NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 1.61-1.68 (m, 2 H, H-9), 1.69-1.74 (m, 2 H, H-10), 1.74-1.79 (m, 2 H, H-8), 3.46-3.56 (m, 6 H, CH_2Cl, H-2, H-3), 5.62 (br s, 1 H, H-6).

^{13}C NMR (126 MHz, C_6D_6, 300 K): δ [ppm] = 21.0 (t, C-9), 26.2 (t, C-8), 33.8 (t, C-10), 48.5 (t, CH_2Cl), 64.5 (t, 2 C, C-2, C-3), 106.1 (s, C-5), 127.2 (d, C-6), 139.2 (s, C-7).

MS (EI, 70 eV): m/z (%) = 188 (8) $[M]^+$, 160 (19), 153 (35) $[M–Cl]^+$, 144 (11), 116 (27), 99 (43), 86 (100) $[C_4H_6O_2]^+$, 67 (14), 55 (15), 42 (14).

HRMS (EI, 70 eV): calcd for $C_9H_{13}O_2{}^{35}Cl$ $[M]^+$: 188.0599; found: 188.0595.

3-[(Allyloxy)methyl]cyclohex-2-en-1-one (158)



160 **158**

Allyl alcohol (333 mg, 389 µL, 5.00 equiv) was added dropwise to a suspension of sodium hydride (60 wt% in paraffin oil, 229 mg, 5.72 mmol, 5.00 equiv) in tetrahydrofuran (2.29 mL, 2.50 M) at room temperature. After stirring for one hour, a solution of acetal **160** (216 mg, 1.14 mmol, 1.00 equiv) in tetrahydrofuran (458 µL, 2.50 M) was added and the resulting mixture was heated to 55 °C. After 22 hours, the mixture was treated with aqueous hydrochloric acid solution (20 mL, 1.00 M), diluted with diethyl ether (10 mL), and stirred for 30 minutes at room temperature. The layers were separated and the organic layer was washed with water (5 × 20 mL), dried with brine (20 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. The residue was purified by column chromatography (silica, P/Et_2O = 2/1 → 1/1) to provide enone **158** (87.4 mg, 526 µmol, 46%) as a pale yellow oil.

TLC: R_f = 0.26 (P/Et_2O = 1/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2928 (w, sp^3-CH), 2868 (w, sp^3-CH), 1667 (vs, C=O), 1138 (s, sp^3-CO), 1085 (vs, sp^3-CO), 890 (vs, sp^2-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.99-2.06 (m, 2 H, H-5), 2.25-2.30 (m, 2 H, H-4), 2.38-2.43 (m, 2 H, H-6), 4.01 (*virt.* dt, ^3J = 5.6 Hz, $^4J_1 \approx {}^4J_2$ = 1.5 Hz, 2 H,

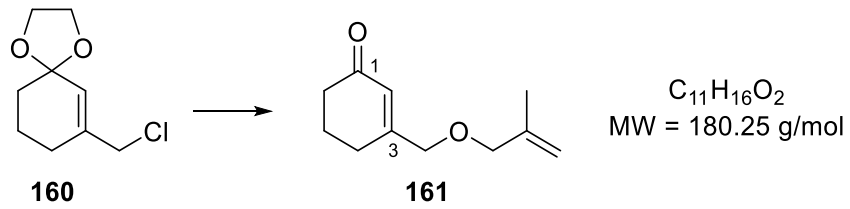
$CH_2OCH_2CHCH_2$), 4.07 (dt, $^4J_1$ = 1.7 Hz, $^4J_2$ = 0.9 Hz, 2 H, $CH_2OCH_2CHCH_2$), 5.22 (*virt.* dq, ^3J = 10.4 Hz, $^2J \approx {}^4J$ = 1.3 Hz, 1 H, CH_2OCH_2CHCHH-*E*), 5.30 (*virt.* dq, ^3J = 17.3 Hz, $^2J \approx {}^4J$ = 1.7 Hz, 1 H, CH_2OCH_2CHCHH-*Z*), 5.90 (ddt, $^3J_1$ = 17.3 Hz, $^3J_2$ = 10.4 Hz, $^3J_3$ = 5.6 Hz, 1 H, $CH_2OCH_2CHCH_2$), 6.11 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.6 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.6 (t, C-5), 26.5 (t, C-4), 38.0 (t, C-6), 71.9 (t, $CH_2OCH_2CHCH_2$), 72.0 (t, $CH_2OCH_2CHCH_2$), 117.7 (t, $CH_2OCH_2CHCH_2$), 124.9 (d, C-2), 134.2 (d, $CH_2OCH_2CHCH_2$), 161.5 (s, C-3), 199.7 (s, C-1).

MS (EI, 70 eV): m/z (%) = 166 (6) $[M]^+$, 137 (7), 125 (8) $[M–C_3H_5]^+$, 110 (55) $[M–C_3H_4O]^+$, 97 (16) $[C_6H_8O]^+$, 81 (33), 67 (17), 53 (15), 41 (100) $[C_3H_5]^+$.

HRMS (EI, 70 eV): calcd for $C_{10}H_{14}O_2$ $[M]^+$: 166.0988; found: 166.0983;
calcd for $C_9{}^{13}CH_{14}O_2$ $[M]^+$: 167.1022; found: 167.1036.

3-{[(2-Methylallyl)oxy]methyl}cyclohex-2-en-1-one (161)



160 **161**

2-Methyl-2-propen-1-ol (573 mg, 671 μL, 5.00 equiv) was added dropwise to a suspension of sodium hydride (60 wt% in paraffin oil, 318 mg, 7.95 mmol, 5.00 equiv) in tetrahydrofuran (3.18 mL, 2.50 M) at room temperature. After stirring for one hour, a solution of acetal **160** (300 mg, 1.59 mmol, 1.00 equiv) in tetrahydrofuran (636 μL, 2.50 M) was added to the suspension and the resulting mixture was heated to 65 °C. After 15 hours, benzyl bromide (2.72 g, 2.89 mL, 15.9 mmol, 10.0 equiv) was added and the resulting mixture was stirred for five hours in order to remove the excess of the allylic alcohol which coelutes with the title compound **161**. Subsequently, aqueous hydrochloric acid solution (10 mL, 1.00 M) was added and stirred for one hour. The reaction mixture was diluted with diethyl ether (20 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried with brine (30 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. Purification of the residue by column chromatography (silica, CH_2Cl_2/Et_2O = 1/0 → 50/1) afforded enone **161** (227 mg, 1.26 mmol, 79%) as a pale yellow oil.

TLC: R_f = 0.28 (P/Et_2O = 1/1) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2925 (w, sp^3-CH), 2868 (w, sp^3-CH), 1670 (vs, C=O), 1141 (s, sp^3-CO), 1089 (vs, sp^3-CO), 890 (vs, sp^2-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.74 (s, 3 H, $CH_2OCH_2CMeCH_2$), 1.98-2.05 (m, 2 H, H-5), 2.24-2.30 (m, 2 H, H-4), 2.38-2.43 (m, 2 H, H-6), 3.90 (br s, 2 H, $CH_2OCH_2CMeCH_2$), 4.03 (br s, 2 H, $CH_2OCH_2CMeCH_2$), 4.91 (br s, 1 H, $CH_2OCH_2CMeCHH$), 4.97 (br s, 1 H, $CH_2OCH_2CMeCHH$), 6.11 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.6 Hz, 1 H, H-2).

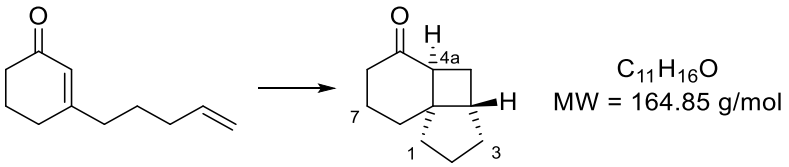
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 19.6 (q, $CH_2OCH_2CMeCH_2$), 22.6 (t, C-5), 26.5 (t, C-4), 37.9 (t, C-6), 71.8 (t, $CH_2OCH_2CMeCH_2$), 74.8 (t, $CH_2OCH_2CMeCH_2$), 112.8 (t, $CH_2OCH_2CMeCH_2$), 124.8 (d, C-2), 141.7 (s, $CH_2OCH_2CMeCH_2$), 161.6 (s, C-3), 199.8 (s, C-1).

MS (EI, 70 eV): m/z (%) = 180 (3) $[M]^+$, 151 (7), 137 (8), 125 (21) $[M–C_4H_7]^+$, 110 (42) $[C_7H_{10}O]^+$, 97 (17) $[C_6H_8O]^+$, 81 (29), 67 (16), 55 (100) $[C_4H_7]^+$, 41 (7).

HRMS (EI, 70 eV): calcd for $C_{11}H_{16}O_2$ $[M]^+$: 180.1145; found: 180.1145;
calcd for $C_{10}{}^{13}CH_{16}O_2$ $[M]^+$: 181.1178; found: 181.1195.

6.3.6 Intramolecular [2+2] Photocycloaddition Reactions

(3a*S*,4a*S*,8a*R*)-Octahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5(6*H*)-one (66)



65 **66**

Racemic [2+2] Photocycloaddition:

Following GP6, enone **65** (131 mg, 800 μmol, 1.00 equiv) was irradiated in dichloromethane (40 mL) for eight hours. After purification by column chromatography (silica, P/Et_2O = 4/1), ketone *rac*-**66** (119 mg, 725 μmol, 91%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP7, enone **65** (16.4 mg, 100 μmol, 1.00 equiv) was irradiated in dichloromethane (5 mL). After purification by column chromatography (silica, P/Et_2O = 4/1), ketone **66** (13.2 mg, 80.4 μmol, 80%, 83% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.42 (P/Et_2O = 6/4) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.34 (*virt.* td, $^2J \approx {}^3J_1$ = 12.6 Hz, $^3J_2$ = 6.8 Hz, 1 H, *H*H-1), 1.50-1.58 (m, 2 H, H-8), 1.58-1.64 (m, 3 H, H*H*-1, H-3), 1.77-1.93 (m, 3 H, H-2, *H*H-4), 1.93-2.04 (m, 2 H, H-7), 2.07 (ddd, ^2J = 13.1 Hz, $^3J_1$ = 9.7 Hz, $^3J_2$ = 7.0 Hz, 1 H, H*H*-4), 2.17 (dddd, ^2J = 18.0 Hz, $^3J_1$ = 11.4 Hz, $^3J_2$ = 6.9 Hz, ^4J = 1.1 Hz, 1 H, *H*H-6), 2.37-2.43 (m, 1 H, H-3a), 2.48 (*virt.* ddq, $^3J_1$ = 11.4 Hz, $^3J_2$ = 7.0 Hz, $^4J_1 \approx {}^4J_2$ = 1.2 Hz, 1 H, H-4a), 2.57 (*virt.* dddt, ^2J = 18.0 Hz, $^3J_1$ = 4.7 Hz, $^3J_2$ = 3.4 Hz, $^4J_1 \approx {}^4J_2$ = 1.2 Hz, 1 H, H*H*-6).

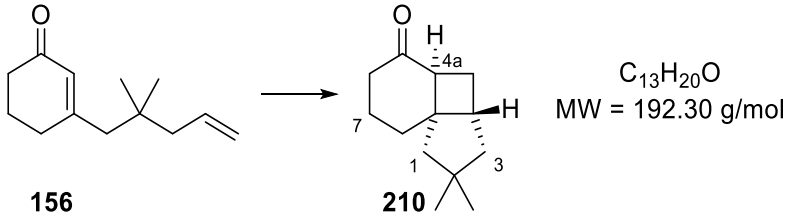
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 21.2 (t, C-7), 25.1 (t, C-2), 26.9 (t, C-4), 32.9 (t, C-8), 33.1 (t, C-3), 39.6 (d, C-3a), 39.6 (t, C-6), 40.4 (t, C-1), 47.3 (d, C-4a), 50.0 (s, C-8a), 215.7 (s, C-5).

Chiral GC: τ_R (major) = 157.2 min, τ_R (minor) = 161.8 min, [60 °C (1 min), 100 °C (30 °C/min), 100 °C (157 min), 135 °C (3 °C/min), 200 °C (20 °C/min), 200 °C (3 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +156 (c = 1.01, CH_2Cl_2) [83% *ee*].

The analytical data obtained matched those reported in the literature.[162]

(3a*R*,4a*S*,8a*S*)-2,2-Dimethyloctahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5(6*H*)-one (210)



Racemic [2+2] Photocycloaddition:

Following GP6, enone **156** (38.5 mg, 200 µmol, 1.00 equiv) was irradiated in dichloromethane (10 mL) for three hours. After purification by column chromatography (silica, P/Et_2O = 4/1), ketone *rac*-**210** (33.5 mg, 174 µmol, 87%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP7, enone **156** (38.5 mg, 200 µmol, 1.00 equiv) was irradiated in dichloromethane (10 mL). After purification by column chromatography (silica, P/Et_2O = 6/1), ketone **210** (33.0 mg, 172 µmol, 86%, 86% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.51 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927 (s, sp^3-CH), 2863 (m, sp^3-CH), 1696 (vs, C=O), 1462 (m, sp^3-CH), 907 (w).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.94 (s, 3 H, Me-2), 1.17 (s, 3 H, Me-2), 1.49 (dd, ^2J = 13.4 Hz, ^4J = 1.7 Hz, 1 H, *H*H-1), 1.51 (dd, ^2J = 13.1 Hz, ^3J = 6.2 Hz, 1 H, *H*H-3), 1.57 (ddd, ^2J = 14.0 Hz, $^3J_1$ = 11.1 Hz, $^3J_2$ = 3.3 Hz, 1 H, *H*H-8), 1.70 (d, ^2J = 13.4 Hz, 1 H, H*H*-1), 1.75 (dddd, ^2J = 14.0 Hz, $^3J_1$ = 6.4 Hz, $^3J_2$ = 3.0 Hz, ^4J = 1.1 Hz, 1 H, H*H*-8), 1.81-1.91 (m, 2 H, H*H*-3, *H*H-7), 1.94-2.07 (m, 2 H, *H*H-4, H*H*-7), 2.12-2.18 (m, 1 H, H*H*-4), 2.18-2.25 (m, 1 H, *H*H-6), 2.44-2.49 (m, 1 H, H-3a), 2.49-2.56 (m, 1 H, H*H*-6), 2.77-2.82 (m, 1 H, H-4a).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 20.7 (t, C-7), 27.9 (t, C-4), 29.6 (q, Me-2), 30.0 (q, Me-2), 35.0 (t, C-8), 38.9 (t, C-6), 41.8 (d, C-3a), 43.2 (s, C-2)*, 49.4 (t, C-3), 50.9 (d, C-4a), 51.3 (s, C-8a)*, 56.6 (t, C-1), 216.7 (s, C-5).

*Assignment of signals is interconvertible.

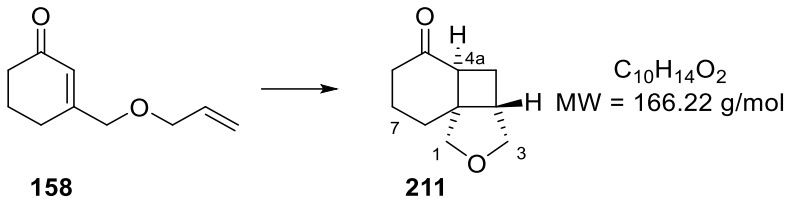
MS (EI, 70 eV): m/z (%) = 192 (33) $[M]^+$, 177 (23) $[M–CH_3]^+$, 164 (17) $[M–CO]^+$, 159 (11), 136 (15), 122 (30) $[C_8H_{10}O]^+$, 110 (100) $[M–C_6H_{10}]^+$, 107 (58), 93 (20), 83 (23) $[C_6H_{11}]^+$, 67 (24), 55 (51) $[C_4H_7]^+$, 41 (20).

HRMS (EI, 70 eV): calcd for $C_{13}H_{20}O$ $[M]^+$: 192.1509; found: 192.1504;
calcd for $C_{12}{}^{13}CH_{20}O$ $[M]^+$: 193.1542; found: 193.1541.

Chiral GC: τ_R (major) = 173.4 min, τ_R (minor) = 174.0 min, [60 °C (1 min), 100 °C (30 °C/min), 100 °C (157 min), 135 °C (3 °C/min), 200 °C (20 °C/min), 200 °C (3 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +97.7 (c = 1.45, CH_2Cl_2) [86% *ee*].

(3a*S*,4a*S*,8a*R*)-Hexahydro-1*H*-benzo[1,4]cyclobuta[1,2-*c*]furan-5(6*H*)-one (211)



Racemic [2+2] Photocycloaddition:

Following GP6, enone **158** (16.6 mg, 100 µmol, 1.00 equiv) was irradiated in dichloromethane (5 mL) for five hours. After purification by column chromatography (silica, P/EtOAc = 1/1), ketone *rac*-**211** (14.4 mg, 86.6 µmol, 87%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP7, enone **158** (33.2 mg, 200 µmol, 1.00 equiv) was irradiated in dichloromethane (10 mL). After purification by column chromatography (silica, P/EtOAc = 1/1), ketone **211** (22.6 mg, 136 µmol, 68%, 82% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.31 (P/EtOAc = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2938 (m, sp^3-CH), 2843 (m, sp^3-CH), 1697 (vs, C=O), 1107 (s, sp^3-CO), 914 (vs, sp^3-CO).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.52 (ddd, ^2J = 13.9 Hz, $^3J_1$ = 11.9 Hz, $^3J_2$ = 4.3 Hz, 1 H, *H*H-8), 1.70 (dddd, ^2J = 13.9 Hz, $^3J_1$ = 4.5 Hz, $^3J_2$ = 3.2 Hz, ^4J = 1.5 Hz, 1 H, H*H*-8), 1.94-2.13 (m, 4 H, H-4, H-7), 2.18 (dddd, ^2J = 17.4 Hz, $^3J_1$ = 12.3 Hz, $^3J_2$ = 6.0 Hz, ^4J = 1.1 Hz, 1 H, *H*H-6), 2.54-2.61 (m, 2 H, H-3a, H*H*-6), 2.71 (dd, $^3J_1$ = 10.7 Hz, $^3J_2$ = 7.2 Hz, 1 H, H-4a), 3.28 (d, ^2J = 9.3 Hz, 1 H, *H*H-1), 3.61 (dd, ^2J = 9.3 Hz, ^3J = 5.2 Hz, 1 H, *H*H-3), 3.86 (d, ^2J = 9.3 Hz, 1 H, H*H*-1), 3.86 (d, ^2J = 9.3 Hz, 1 H, H*H*-3).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 21.3 (t, C-7), 26.8 (t, C-4), 28.6 (t, C-8), 39.9 (t, C-6), 40.9 (d, C-3a), 46.6 (d, C-4a), 51.1 (s, C-8a), 74.4 (t, C-3), 78.9 (t, C-1), 214.1 (s, C-5).

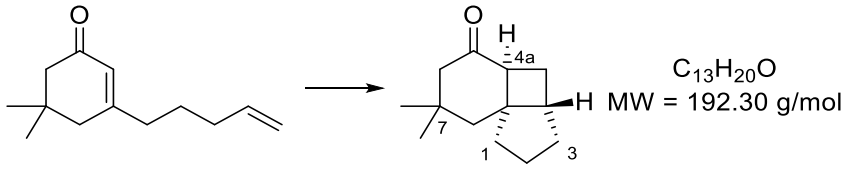
MS (EI, 70 eV): m/z (%) = 166 (58) $[M]^+$, 137 (27) $[M–CO]^+$, 121 (84) $[M–C_2H_5O]^+$, 110 (100) $[M–C_3H_4O]^+$, 96 (82) $[M–C_4H_6O]^+$, 82 (78) $[C_5H_6O]^+$, 79 (90), 67 (66), 55 (58) $[C_4H_7]^+$, 41 (61) $[C_3H_5]^+$.

HRMS (EI, 70 eV): calcd for $C_{10}H_{14}O_2$ $[M]^+$: 166.0988; found: 166.0985;
calcd for $C_9{}^{13}CH_{14}O_2$ $[M]^+$: 167.1022; found: 167.1022.

Chiral GC: τ_R (minor) = 37.5 min, τ_R (major) = 37.7 min, [60 °C (0 min), 245 °C (3 °C/min), 245 °C (3 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{26}$ = +138 (c = 1.41, CH_2Cl_2) [82% *ee*].

(3a*S*,4a*S*,8a*R*)-7,7-Dimethyloctahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5(6*H*)-one (212)



151 **212**

Racemic [2+2] Photocycloaddition:

Following GP6, enone **151** (38.5 mg, 200 µmol, 1.00 equiv) was irradiated in dichloromethane (10 mL) for five hours. After purification by column chromatography (silica, P/Et_2O = 6/1), ketone *rac*-**212** (30.4 mg, 158 µmol, 79%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP7, enone **151** (38.5 mg, 200 µmol, 1.00 equiv) was irradiated in dichloromethane (10 mL). After purification by column chromatography (silica, P/Et_2O = 6/1), ketone **212** (32.6 mg, 170 µmol, 85%, 89% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.63 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2941 (s, sp^3-CH), 2895 (m, sp^3-CH), 2868 (m, sp^3-CH), 1700 (vs, C=O), 1467 (m, sp^3-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.98 (s, 3 H, Me-7), 1.06 (s, 3 H, Me-7), 1.36 (*virt.* td, $^2J \approx {}^3J_1$ = 12.3 Hz, $^3J_2$ = 7.2 Hz, 1 H, *H*H-1), 1.52 (dd, ^2J = 12.6 Hz, ^3J = 6.0 Hz, 1 H, *H*H-3), 1.54-1.62 (m, 2 H, H*H*-3, *H*H-8), 1.69 (d, ^2J = 14.5 Hz, 1 H, H*H*-8), 1.72-1.78 (m, 1 H, H*H*-1), 1.78-1.89 (m, 3 H, H-2, *H*H-4), 2.15 (d, ^2J = 14.8 Hz, 1 H, *H*H-6), 2.19 (ddd, ^2J = 13.0 Hz, $^3J_1$ = 9.5 Hz, $^3J_2$ = 6.6 Hz, 1 H, H*H*-4), 2.25 (d, ^2J = 14.8 Hz, 1 H, H*H*-6), 2.36 (dd, $^3J_1$ = 11.6 Hz, $^3J_2$ = 6.6 Hz, 1 H, H-4a), 2.38-2.43 (m, 1 H, H-3a).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 24.8 (t, C-2), 27.3 (t, C-4), 28.5 (q, Me-7), 31.0 (q, Me-7), 33.0 (t, C-3), 34.6 (s, C-7), 42.7 (d, C-3a), 43.1 (t, C-1), 46.0 (d, C-4a), 47.7 (t, C-8), 49.6 (s, C-8a), 53.8 (t, C-6), 216.7 (s, C-5).

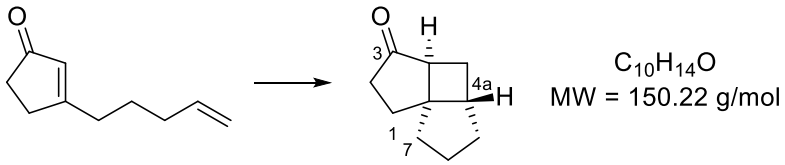
MS (EI, 70 eV): m/z (%) = 192 (40) $[M]^+$, 177 (18) $[M–CH_3]^+$, 149 (41) $[M–C_3H_7]^+$, 136 (81) $[M–C_4H_8]^+$, 125 (35) $[C_8H_{13}O]^+$, 108 (56) $[C_7H_8O]^+$, 93 (44), 82 (100) $[C_6H_{10}]^+$, 54 (30), 41 (18).

HRMS (EI, 70 eV): calcd for $C_{13}H_{20}O$ $[M]^+$: 192.1509; found: 192.1513.

Chiral GC: τ_R (minor) = 169.7 min, τ_R (major) = 170.3 min, [60 °C (1 min), 100 °C (30 °C/min), 100 °C (157 min), 135 °C (3 °C/min), 200 °C (20 °C/min), 200 °C (3 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +156 (c = 1.31, CH_2Cl_2) [89% *ee*].

(3a*S*,4a*S*,7a*R*)-Octahydro-3*H*-cyclobuta[1,2:1,4]di[5]annulen-3-one (213)



153 **213**

Racemic [2+2] Photocycloaddition:

Following GP6, enone **153** (30.0 mg, 200 µmol, 1.00 equiv) was irradiated in dichloromethane (10 mL) for 47 hours. After purification by column chromatography (silica, P/Et_2O = 5/1), ketone *rac*-**213** (16.6 mg, 111 µmol, 56%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP7, enone **153** (30.0 mg, 200 µmol, 1.00 equiv) was irradiated in dichloromethane (10 mL). After purification by column chromatography (silica, P/Et_2O = 5/1), ketone **213** (16.2 mg, 108 µmol, 54%, 80% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.26 (P/Et_2O = 5/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.42 (ddd, ^2J = 13.0 Hz, $^3J_1$ = 10.7 Hz, $^3J_2$ = 9.1 Hz, 1 H, *H*H-7), 1.54-1.59 (m, 1 H, *H*H-5), 1.59-1.67 (m, 1 H, H*H*-5), 1.68-1.74 (m, 1 H, H*H*-7), 1.76-1.83 (m, 1 H, *H*H-4), 1.83-1.91 (m, 4 H, *H*H-6, H*H*-4, H-1), 1.92 (*virt.* dq, ^2J = 4.8 Hz, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 2.2 Hz, 1 H, H*H*-6), 2.22 (ddd, $^3J_1$ = 10.7 Hz, $^3J_2$ = 4.4 Hz, ^4J = 2.0 Hz, 1 H, H-3a), 2.35 (*virt.* ddt, ^2J = 17.9 Hz, $^3J_1$ = 7.8 Hz, $^3J_2 \approx {}^4J$ = 2.0 Hz, 1 H, *H*H-2), 2.49-2.56 (m, 1 H, H-4a), 2.78 (*virt.* dddt, ^2J = 17.9 Hz, $^3J_1$ = 12.5 Hz, $^3J_2$ = 9.6 Hz, $^4J_1 \approx {}^4J_2$ = 0.8 Hz, 1 H, H*H*-2).

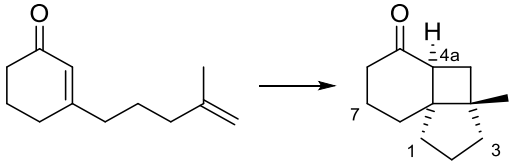
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 25.8 (t, C-4), 26.0 (t, C-6), 32.1 (t, C-1), 33.4 (t, C-5), 37.4 (t, C-7), 38.2 (t, C-2), 40.6 (d, C-4a), 47.1 (d, C-3a), 53.0 (s, C-7a), 222.8 (s, C-3).

Chiral GC: τ_R (minor) = 82.4 min, τ_R (major) = 90.8 min, [60 °C (1 min), 100 °C (30 °C/min), 100 °C (157 min), 135 °C (3 °C/min), 200 °C (20 °C/min), 200 °C (3 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +292 (c = 1.10, CH_2Cl_2) [80% *ee*].

The analytical data obtained matched those reported in the literature.[287]

(3a*S*,4a*S*,8a*S*)-3a-Methyloctahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5(6*H*)-one (214)



145 214

$C_{12}H_{18}O$
MW = 178.28 g/mol

Racemic [2+2] Photocycloaddition:

Following GP6, enone **145** (35.7 mg, 200 μmol, 1.00 equiv) was irradiated in dichloromethane (10 mL) for five hours. After purification by column chromatography (silica, P/Et_2O = 5/1), ketone *rac*-**214** (24.2 mg, 136 μmol, 68%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP7, enone **145** (35.7 mg, 200 μmol, 1.00 equiv) was irradiated in dichloromethane (10 mL). After purification by column chromatography (silica, P/Et_2O = 5/1), ketone **214** (29.5 mg, 165 μmol, 83%, 86% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.58 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.06 (s, 3 H, Me-3a), 1.29-1.36 (m, 1 H, *H*H-3), 1.36-1.42 (m, 1 H, *H*H-1), 1.45 (ddd, ^2J = 13.7 Hz, $^3J_1$ = 9.1 Hz, $^3J_2$ = 4.2 Hz, 1 H, *H*H-8), 1.57-1.63 (m, 1 H, H*H*-3), 1.71-1.83 (m, 4 H, H*H*-1, H-2, H*H*-8), 1.86 (ddd, ^2J = 12.7 Hz, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1 H, *H*H-4), 1.88-1.98 (m, 2 H, H-7), 2.01 (dd, ^2J = 12.7 Hz, ^3J = 11.0 Hz, 1 H, H*H*-4), 2.21-2.28 (m, 1 H, *H*H-6), 2.37-2.44 (m, 2 H, H-4a, H*H*-6).

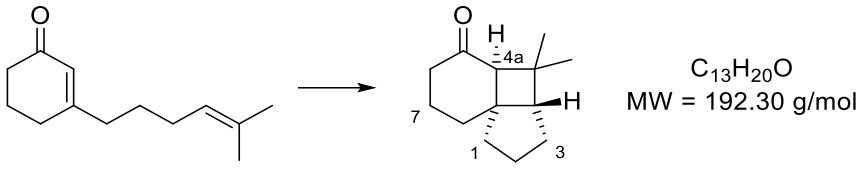
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.0 (t, C-7), 22.9 (q, Me-3a), 23.9 (t, C-2), 29.5 (t, C-8), 35.1 (t, C-4), 40.0 (t, C-6), 41.7 (t, C-1), 42.0 (t, C-3), 44.6 (s, C-3a), 45.3 (d, C-4a), 51.3 (s, C-8a), 216.5 (s, C-5).

Chiral GC: τ_R (minor) = 131.9 min, τ_R (major) = 136.7 min, [60 °C (1 min), 100 °C (30 °C/min), 100 °C (157 min), 135 °C (3 °C/min), 200 °C (20 °C/min), 200 °C (3 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +155 (c = 1.14, CH_2Cl_2) [86% *ee*].

The analytical data obtained matched those reported in the literature.[283]

(3a*S*,4a*S*,8a*R*)-4,4-Dimethyloctahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5(6*H*)-one (166)



146 **166**

Racemic [2+2] Photocycloaddition:

Following GP6, enone **146** (38.5 mg, 200 µmol, 1.00 equiv) was irradiated in dichloromethane (10 mL) for 5.5 hours. After purification by column chromatography (silica, P/Et_2O = 6/1), a product mixture was obtained, which contains inseparable impurities. To facilitate purification, the mixture was submitted to ozonolysis which was conducted at –78 °C in dichloromethane (3 mL). Completion of the reaction was indicated by blue coloration during ozon introduction. The blue color was removed by an argon gasflow and dimethyl sulfide (1 mL) was added. Subsequently, the mixture was warmed to room temperature and the solvent was removed in vacuo. The residue was purified by column chromatography (silica, P/Et_2O = 6/1). After the work-up process, ketone **166** (19.7 mg, 102 µmol, 51%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP7, enone **146** (38.5 mg, 200 µmol, 1.00 equiv) was irradiated in dichloromethane (10 mL). After purification by column chromatography (silica, P/Et_2O = 6/1), a product mixture was obtained, which contains inseparable impurities. To facilitate purification, the mixture was submitted to ozonolysis which was conducted at –78 °C in dichloromethane (3 mL). Completion of the reaction was indicated by blue coloration during ozon introduction. The blue color was removed by an argon gasflow and dimethyl sulfide (1 mL) was added. Subsequently, the mixture was warmed to room temperature and the solvent was removed in vacuo. The residue was purified by column chromatography (silica, P/Et_2O = 6/1). After the work-up process, ketone **166** (6.20 mg, 32.2 µmol, 16%, 55% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.66 (P/EtOAc = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.03 (s, 3 H, Me-4), 1.05 (s, 3 H, Me-4), 1.21-1.30 (m, 1 H, *H*H-1), 1.50-1.62 (m, 1 H, *H*H-3), 1.68-1.78 (m, 5 H, H*H*-1, *H*H-2, H*H*-3, *H*H-7, *H*H-8), 1.80-1.91 (m, 2 H, H*H*-2, H*H*-8), 1.91-1.98 (m, 1 H, H*H*-7), 1.98-2.00 (m, 1 H, H-3a), 2.17 (s, 1 H, H-4a), 2.18-2.33 (m, 2 H, H-6).

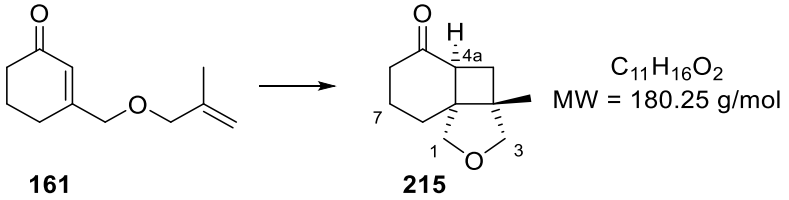
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 21.4 (t, C-7), 25.1 (q, Me-4), 26.9 (t, C-2), 27.6 (q, Me-4), 28.2 (t, C-3), 34.5 (t, C-8), 36.9 (s, C-4), 40.4 (t, C-1), 41.1 (t, C-6), 45.1 (s, C-8a), 52.0 (d, C-3a), 57.4 (d, C-4a), 214.3 (s, C-5).

Chiral GC: τ_R (minor) = 157.6 min, τ_R (major) = 161.9 min, [60 °C (1 min), 100 °C (30 °C/min), 100 °C (157 min), 135 °C (3 °C/min), 200 °C (20 °C/min), 200 °C (3 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +140 (c = 1.10, CH_2Cl_2) [55% *ee*].

The analytical data obtained matched those reported in the literature.[172]

(3a*S*,4a*S*,8a*R*)-3a-Methylhexahydro-1*H*-benzo[1,4]cyclobuta[1,2-*c*]furan-5(6*H*)-one (215)



Racemic [2+2] Photocycloaddition:

Following GP6, enone **161** (18.0 mg, 100 μmol, 1.00 equiv) was irradiated in dichloromethane (5 mL) for eight hours. After purification by column chromatography (silica, P/EtOAc = 2/1), ketone *rac*-**215** (14.4 mg, 79.9 μmol, 80%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP7, enone **161** (36.1 mg, 200 μmol, 1.00 equiv) was irradiated in dichloromethane (10 mL). After purification by column chromatography (silica, P/EtOAc = 2/1), ketone **215** (25.8 mg, 143 μmol, 72%, 84% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.37 (P/EtOAc = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2935 (m, sp^3-CH), 2838 (m, sp^3-CH), 1699 (vs, C=O), 1054 (s, sp^3-CO), 932 (s, sp^3-CO).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.08 (s, 3 H, Me-3a), 1.45 (ddd, ^2J = 14.4 Hz, $^3J_1$ = 8.6 Hz, $^3J_2$ = 5.9 Hz, 1 H, *H*H-8), 1.77 (*virt.* dt, ^2J = 14.4 Hz, $^3J_1 \approx {}^3J_2$ = 5.0 Hz, 1 H, H*H*-8), 1.87-2.02 (m, 3 H, *H*H-4, H-7), 2.20-2.31 (m, 2 H, H*H*-4, *H*H-6), 2.46 (*virt.* dt, ^2J = 16.6 Hz, $^3J_1 \approx {}^3J_2$ = 5.2 Hz, 1 H, H*H*-6), 2.68 (dd, $^3J_1$ = 11.0 Hz, $^3J_2$ = 7.0 Hz, 1 H, H-4a), 3.26 (d, ^2J = 9.1 Hz, 1 H, *H*H-3), 3.30 (d, ^2J = 9.2 Hz, 1 H, *H*H-1), 3.83 (d, ^2J = 9.1 Hz, 1 H, H*H*-3), 3.95 (d, ^2J = 9.2 Hz, 1 H, H*H*-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 18.1 (q, Me-3a), 21.9 (t, C-7), 24.9 (t, C-8), 34.8 (t, C-4), 40.2 (t, C-6), 45.0 (d, C-4a), 45.5 (s, C-3a), 51.7 (s, C-8a), 80.0 (t, C-1), 81.1 (t, C-3), 214.6 (s, C-5).

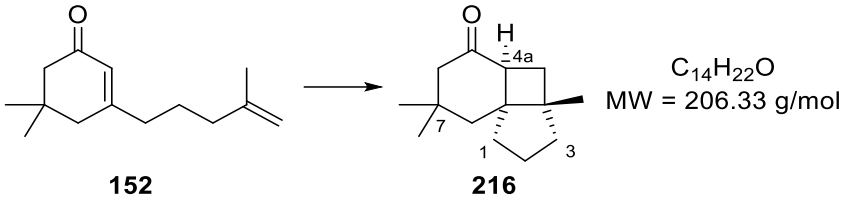
MS (EI, 70 eV): m/z (%) = 180 (15) $[M]^+$, 135 (55) $[C_9H_{11}O]^+$, 122 (31), 109 (100) $[C_7H_9O]^+$, 95 (46), 79 (61), 67 (51), 55 (97) $[C_4H_7]^+$, 41 (45) $[C_3H_5]^+$.

HRMS (EI, 70 eV): calcd for $C_{11}H_{16}O_2$ $[M]^+$: 180.1145; found: 180.1143;
calcd for $C_{10}{}^{13}CH_{16}O_2$ $[M]^+$: 181.1178; found: 181.1183.

Chiral GC: τ_R (minor) = 42.7 min, τ_R (major) = 43.3 min, [60 °C (0 min), 130 °C (30 °C/min), 130 °C (38 min), 160 °C (5 °C/min), 240 °C (15 °C/min), 240 °C (2 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{26}$ = +142 (c = 1.47, CH_2Cl_2) [84% *ee*].

(3a*S*,4a*S*,8a*S*)-3a,7,7-Trimethyloctahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5(6*H*)-one (216)



152 **216**

Racemic [2+2] Photocycloaddition:

Following GP6, enone **152** (41.3 mg, 200 μmol, 1.00 equiv) was irradiated in dichloromethane (10 mL) for five hours. After purification by column chromatography (silica, P/Et_2O = 6/1), ketone *rac*-**216** (36.4 mg, 176 μmol, 88%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP7, enone **152** (41.3 mg, 200 μmol, 1.00 equiv) was irradiated in dichloromethane (10 mL). After purification by column chromatography (silica, P/Et_2O = 6/1), ketone **216** (34.7 mg, 168 μmol, 84%, 96% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.62 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.90 (s, 3 H, Me-7), 1.01 (s, 3 H, Me-3a), 1.04 (s, 3 H, Me-7), 1.23-1.34 (m, 2 H, *H*H-3, *H*H-8), 1.39 (*virt.* td, $^2J \approx {}^3J_1$ = 12.2 Hz, $^3J_2$ = 7.0 Hz, 1 H, *H*H-1), 1.62 (*virt.* ddt, ^2J = 12.7 Hz, ^3J = 6.2 Hz, $^4J_1 \approx {}^4J_2$ = 1.5 Hz, 1 H, H*H*-3), 1.69-1.84 (m, 3 H, H-2, *H*H-4), 1.91 (d, ^2J = 14.2 Hz, 1 H, H*H*-8), 1.93-1.99 (m, 1 H, H*H*-1), 2.02 (dd, ^2J = 12.5 Hz, ^3J = 11.2 Hz, 1 H, H*H*-4), 2.12 (ddd, ^2J = 16.1 Hz, $^4J_1$ = 2.5 Hz, $^4J_2$ = 1.3 Hz, 1 H, *H*H-6), 2.21 (dd, ^2J = 16.1 Hz, ^4J = 0.8 Hz, 1 H, H*H*-6), 2.36 (ddd, $^3J_1$ = 11.2 Hz, $^3J_2$ = 7.7 Hz, ^4J = 1.3 Hz, 1 H, H-4a).

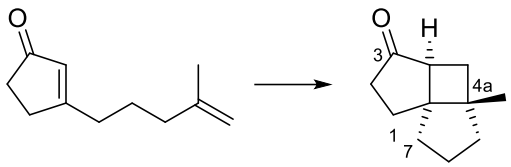
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 24.3 (q, Me-3a), 24.3 (t, C-2), 28.0 (q, Me-7), 31.8 (q, Me-7), 33.9 (s, C-7), 34.8 (t, C-4), 40.8 (t, C-3), 42.8 (t, C-8), 43.7 (d, C-4a), 44.0 (t, C-1), 45.4 (s, C-3a), 50.0 (s, C-8a), 52.7 (t, C-6), 216.2 (s, C-5).

Chiral GC: τ_R (major) = 94.3 min, τ_R (minor) = 95.0 min, [60 °C (0.5 min), 70 °C (10 °C/min), 114 °C (0.4 °C/min), 200 °C (10 °C/min), 200 °C (3 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +228 (c = 1.27, CH_2Cl_2) [96% *ee*].

The analytical data obtained matched those reported in the literature.[283]

(3a*S*,4a*S*,7a*S*)-4a-Methyloctahydro-3*H*-cyclobuta[1,2:1,4]di[5]annulen-3-one (217)



154 **217**

$C_{11}H_{16}O$
MW = 164.25 g/mol

Racemic [2+2] Photocycloaddition:

Following GP6, enone **154** (32.9 mg, 200 μmol, 1.00 equiv) was irradiated in dichloromethane (10 mL) for eight hours at λ = 350 nm. After purification by column chromatography (silica, P/Et_2O = 5/1), ketone *rac*-**217** (20.6 mg, 125 μmol, 63%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP7, enone **154** (32.9 mg, 200 μmol, 1.00 equiv) was irradiated in dichloromethane (10 mL). After purification by column chromatography (silica, P/Et_2O = 5/1), ketone **217** (20.2 mg, 123 μmol, 61%, 76% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.60 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.14 (s, 3 H, Me-4a), 1.30-1.38 (m, 1 H, *H*H-5), 1.44-1.52 (m, 1 H, *H*H-7), 1.59-1.70 (m, 3 H, *H*H-4, H*H*-5, H*H*-7), 1.70-1.84 (m, 3 H, *H*H-1, H-6), 2.01-2.09 (m, 2 H, H*H*-1, H*H*-4), 2.20 (ddd, $^3J_1$ = 11.0 Hz, $^3J_2$ = 4.7 Hz, ^4J = 2.0 Hz, 1 H, H-3a), 2.34 (*virt.* ddt, ^2J = 18.8 Hz, $^3J_1$ = 9.8 Hz, $^3J_2 \approx {}^4J$ = 2.0 Hz, 1 H, *H*H-2), 2.62-2.71 (m, 1 H, H*H*-2).

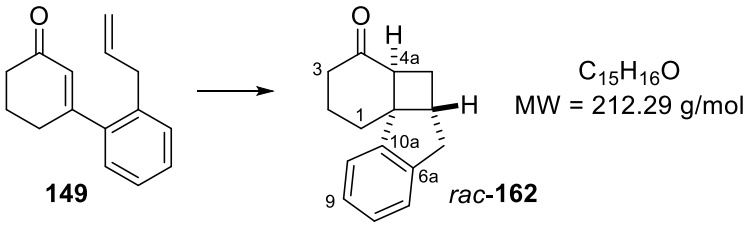
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 23.2 (q, Me-4a), 25.1 (t, C-6), 27.1 (t, C-1), 34.5 (t, C-4), 38.5 (t, C-7), 38.8 (t, C-2), 42.3 (t, C-5), 43.8 (s, C-4a), 45.6 (d, C-3a), 53.6 (s, C-7a), 223.4 (s, C-3).

Chiral GC: τ_R (minor) = 14.8 min, τ_R (major) = 14.9 min, [60 °C (0 min), 120 °C (30 °C/min), 120 °C (10 min), 240 °C (30 °C/min), 240 °C (2 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +222 (c = 1.08, CH_2Cl_2) [76% *ee*].

The analytical data obtained matched those reported in the literature.[287]

(4a*S*,5a*R*,10b*S*)-2,3,4a,5,5a,6-Hexahydrobenzo[1,4]cyclobuta[1,2-*a*]inden-4(1*H*)-one (*rac*-162)



Racemic [2+2] Photocycloaddition:

Following GP6, enone **149** (42.5 mg, 200 μmol, 1.00 equiv) was irradiated in dichloromethane (10 mL) for two hours. After purification by column chromatography (silica, P/Et_2O = 5/1), ketone *rac*-**162** (35.1 mg, 165 μmol, 83%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP7, enone **149** (42.5mg, 200 μmol, 1.00 equiv) was irradiated in dichloromethane (10 mL). The reaction yielded a product mixture of inseparable isomers.

TLC: R_f = 0.60 (P/Et_2O = 2/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2955 (m, sp^3-CH), 2897 (m, sp^3-CH), 2835 (w, sp^3-CH), 1701 (vs, C=O), 753 (vs, sp^2-CH), 723 (vs, sp^2-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.32 (dd, ^2J = 9.4 Hz, ^3J = 6.8 Hz, 1 H, *H*H-5), 1.92-1.97 (m, 1 H, *H*H-1), 1.98-2.06 (m, 1 H, *H*H-2), 2.06-2.15 (m, 1 H, H*H*-1), 2.18-2.29 (m, 3 H, H*H*-2, *H*H-3, H-5a), 2.35 (dd, ^2J = 9.4 Hz, ^3J = 5.9 Hz, 1 H, H*H*-5), 2.47-2.53 (m, 1 H, H*H*-3), 3.13-3.21 (m, 3 H, H-4a, H-6), 7.15-7.24 (m, 4 H, H-Ar).

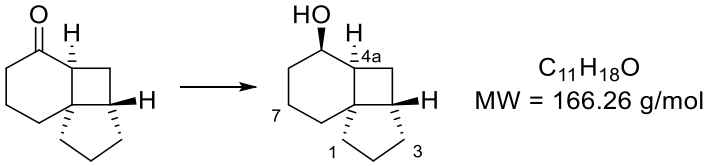
^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.4 (t, C-2), 27.2 (t, C-1), 33.7 (t, C-5), 34.0 (d, C-4a), 35.6 (t, C-6), 41.3 (t, C-3), 47.9 (s, C-10b), 55.1 (d, C-5a), 121.5 (d, C-Ar), 125.4 (d, C-Ar), 126.5 (d, C-Ar), 128.8 (d, C-Ar), 133.9 (s, C-6a), 148.5 (s, C-10a), 213.4 (s, C-4).

MS (EI, 70 eV): m/z (%) = 212 (53) $[M]^+$, 184 (100) $[M–C_2H_4]^+$, 155 (35), 141 (75), 128 (32), 115 (26).

HRMS (EI, 70 eV): calcd for $C_{15}H_{16}O$ $[M]^+$: 212.1196; found: 212.1184;
calcd for $C_{14}{}^{13}CH_{16}O$ $[M]^+$: 213.1229; found: 213.1222.

6.3.7 *Mosher*-Analysis of Absolute Configuration

(3a*S*,4a*S*,5*R*,8a*R*)-Decahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5-ol (218)



66 **218**

In analogy to a modified literature procedure:[288] A solution of L-selectride (1.00 M in tetrahydrofuran, 1.01 mL, 1.01 mmol, 3.00 equiv) was added dropwise to a solution of ketone **66** (55.4 mg, 337 μmol, 1.00 equiv) in tetrahydrofuran (6.75 mL, 50.0 mM) at –78 °C. The mixture was stirred for three hours and was subsquently allowed to warm to room temperature over the course of 14 hours. Water (3.00 mL), methanol (3.00 mL), aqueous sodium hydroxide solution (5 wt%, 3.00 mL), and hydrogen peroxide solution (50 wt%, 1.0 mL) were added in sequence and the resulting mixture was stirred for one hour, during which a colorless precipitate is formed. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried with brine (50 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. The residue was purified by column chromatography (silica, P/Et_2O = 2/1) to provide alcohol **218** (52.0 mg, 313 μmol, 93%, d.r. = 94/6) as a colorless oil.

Separation of the Diastereomers:

A mixture of diastereomers **218** and *epi*-**218** (52.0 mg) was separated by column chromatography (silica, P/Et_2O = 5/1) with a conventional column (36 mm diameter, 300 mm length). The collected fractions were analyzed by gas chromatography and were combined to three fractions [(content of *epi*-**218**)]: [F1 (≥99.5%)], [F2 (1<99.5%)], [F3 (≤1%)]. The fraction F2 was purified under the same conditions several times until less than 2 mg of the diastereomeric mixture were available.

TLC: R_f = 0.32 (P/Et_2O = 1/1) [CAM, $KMnO_4$].

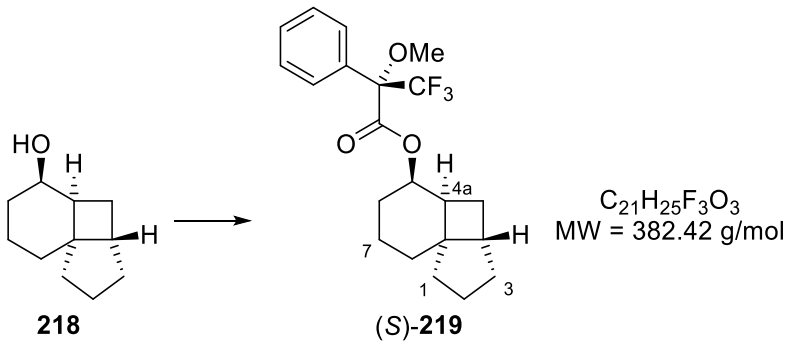
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.17 (*virt.* td, $^2J \approx {}^3J_1$ = 12.3 Hz, $^3J_2$ = 6.7 Hz, 1 H, *H*H-1), 1.23-1.37 (m, 2 H, *H*H-4, *H*H-8), 1.49-1.70 (m, 7 H, H*H*-1, H-3, *H*H-6, *H*H-7, H*H*-8, OH-5), 1.74-2.00 (m, 4 H, H-2, H*H*-6, H*H*-7), 2.10 (ddd, ^2J = 12.4 Hz, $^3J_1$ = 9.1 Hz, $^3J_2$ = 7.4 Hz, 1 H, H*H*-4), 2.20 (*virt.* dt, $^3J_1$ = 9.1 Hz, $^3J_2 \approx {}^3J_3$ = 6.4 Hz, 1 H, H-4a), 2.28 (*virt.* td, $^3J_1 \approx {}^3J_2$ = 8.5 Hz, $^3J_3$ = 4.0 Hz, 1 H, H-3a), 3.94 (*virt.* dt, $^3J_1$ = 11.0 Hz, $^3J_2 \approx {}^3J_3$ = 5.7 Hz, 1 H, H-5).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 19.8 (t, C-7), 21.2 (t, C-4), 25.6 (t, C-2), 27.0 (t, C-6), 29.9 (t, C-8), 33.0 (t, C-3), 39.5 (d, C-3a), 40.5 (d, C-4a), 40.6 (t, C-1), 49.4 (s, C-8a), 68.6 (d, C-5).

Specific Rotation: $[\alpha]_D^{27}$ = +92.2 (c = 1.26, CH_2Cl_2) [83% *ee*].

The analytical data obtained matched those reported in the literature.[289]

(3a*S*,4a*S*,5*R*,8a*R*)-Decahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate [(*S*)-219]



218 (*S*)-**219**

In analogy to a modified literature procedure:[193] (*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propanoyl chloride (30.4 mg, 22.5 µL, 120 µmol, 2.00 equiv) was added to a solution of alcohol **218** (10.0 mg, 60.2 µmol, 1.00 equiv), pyridine (14.5 µL, 180 µmol, 3.00 equiv) and DMAP

(1.47 mg, 12.0 μmol, 20.0 mol%) in dichloromethane (1.2 mL, 50.0 mM) at room temperature. The resulting mixture was stirred for 20 hours. The reaction mixture was transferred to a silica-packed column. After purification by column chromatography (silica, CH_2Cl_2/Et_2O = 1/0 → 95/5), ester (*S*)-**219** (14.6 mg, 38.2 μmol, 63%) was obtained as a colorless oil and starting material **218** (2.60 mg, 15.6 μmol, 26%) was recovered.

TLC: R_f = 0.82 (CH_2Cl_2) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2934 (m, sp^3-CH), 2851 (w, sp^3-CH), 1742 (vs, C=O), 1268 (s, sp^3-CF), 1165 (vs, sp^3-CO), 1017 (vs, sp^3-CF), 718 (vs, sp^2-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.14-1.28 (m, 2 H, *H*H-1, *H*H-4), 1.38-1.45 (m, 1 H, *H*H-8), 1.48 (dd, ^2J = 12.9 Hz, ^3J = 6.7 Hz, 1 H, *H*H-3), 1.52-1.71 (m, 4 H, H*H*-1, H*H*-3, *H*H-7, H*H*-8), 1.78 (*virt.* dt, ^2J = 13.0 Hz, $^3J_1 \approx {}^3J_2$ = 6.8 Hz, 1 H, *H*H-2), 1.82-1.97 (m, 4 H, H*H*-2, H-6, H*H*-7), 2.02 (ddd, ^2J = 12.9 Hz, $^3J_1$ = 9.2 Hz, $^3J_2$ = 7.1 Hz, 1 H, H*H*-4), 2.23-2.30 (m, 1 H, H-3a), 2.35 (*virt.* dt, $^3J_1$ = 9.2 Hz, $^3J_2 \approx {}^3J_3$ = 6.7 Hz, 1 H, H-4a), 3.53 (s, 3 H, OMe-2'), 5.27 (*virt.* dt, $^3J_1$ = 9.2 Hz, $^3J_2 \approx {}^3J_3$ = 6.3 Hz, 1 H, H-5), 7.36-7.42 (m, 3 H, 2 × H-*m*-Ph, H-*p*-Ph), 7.48-7.54 (m, 2 H, 2 × H-*o*-Ph).

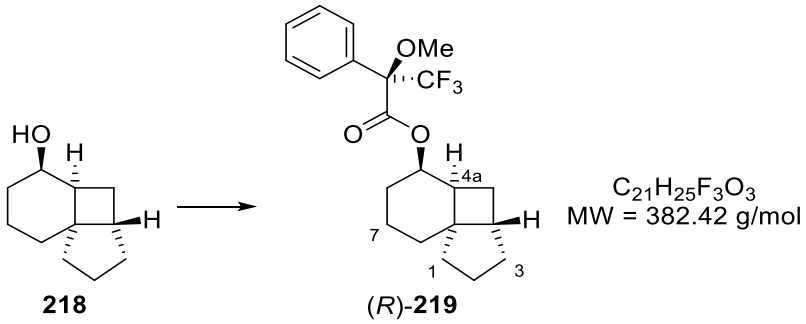
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 19.3 (t, C-7), 22.0 (t, C-4), 23.7 (t, C-6), 25.6 (t, C-2), 30.0 (t, C-8), 32.8 (t, C-3), 37.3 (d, C-4a), 40.0 (d, C-3a), 40.5 (t, C-1), 49.2 (s, C-8a), 55.5 (q, OMe-2'), 75.0 (d, C-5), 84.6 (qs, $^2J_{CF}$ = 27.6 Hz, C-2'), 123.5 (qs, $^1J_{CF}$ = 288 Hz, CF_3-2'), 127.5 (d, 2 C, 2 × C-*o*-Ph), 128.4 (d, 2 C, 2 × C-*m*-Ph), 129.6 (d, C-*p*-Ph), 132.6 (s, C-*i*-Ph), 166.1 (s, C-1').

^{19}F NMR (376 MHz, $CDCl_3$, 298 K): δ [ppm] = –72.2 (s, 3 F, CF_3-2').

MS (EI, 70 eV): m/z (%) = 382 (0.2) $[M]^+$, 189 (35) $[C_9H_8F_3O]^+$, 149 (100) $[C_{11}H_{17}]^+$, 107 (40) $[C_8H_{11}]^+$, 81 (41) $[C_6H_9]^+$, 67 (41).

HRMS (EI, 70 eV): calcd for $C_{21}H_{25}O_3F_3$ $[M]^+$: 382.1750; found: 382.1748.

(3a*S*,4a*S*,5*R*,8a*R*)-Decahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate [(*R*)-219]



218 (*R*)-**219**

In analogy to a modified literature procedure:[193] (*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl chloride (30.4 mg, 22.5 µL, 120 µmol, 2.00 equiv) was added to a solution of alcohol **218** (10.0 mg, 60.2 µmol, 1.00 equiv), pyridine (14.5 µL, 180 µmol, 3.00 equiv) and DMAP (1.47 mg, 12.0 µmol, 20.0 mol%) in dichloromethane (1.2 mL, 50.0 mM) at room temperature. The resulting mixture was stirred for 20 hours. The reaction mixture was transferred to a silica-packed column. After purification by column chromatography (silica, CH_2Cl_2/Et_2O = 1/0 → 95/5), ester (*R*)-**219** (14.6 mg, 38.2 µmol, 63%) was obtained as a colorless oil and starting material **218** (2.80 mg, 16.8 µmol, 28%) was recovered.

TLC: R_f = 0.82 (CH_2Cl_2) [$KMnO_4$, UV].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2932 (m, sp^3-CH), 2851 (w, sp^3-CH), 1741 (vs, C=O), 1267 (s, sp^3-CF), 1165 (vs, sp^3-CO), 1017 (vs, sp^3-CF), 717 (vs, sp^2-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.19 (*virt.* td, $^2J \approx {}^3J_1$ = 12.4 Hz, $^3J_2$ = 6.7 Hz, 1 H, *H*H-1), 1.30-1.42 (m, 2 H, *H*H-4, *H*H-8), 1.51 (dd, ^2J = 12.9 Hz, ^3J = 6.7 Hz, 1 H, *H*H-3), 1.56-1.70 (m, 4 H, H*H*-1, H*H*-3, *H*H-7, H*H*-8), 1.75-1.98 (m, 5 H, H-2, H-6, H*H*-7), 2.14 (ddd, ^2J = 12.8 Hz, $^3J_1$ = 9.3 Hz, $^3J_2$ = 7.1 Hz, 1 H, H*H*-4), 2.27-2.35 (m, 1 H, H-3a), 2.38 (*virt.* dt, $^3J_1$ = 9.3 Hz, $^3J_2 \approx {}^3J_3$ = 6.6 Hz, 1 H, H-4a), 3.52 (s, 3 H, OMe-2'), 5.28 (*virt.* dt, $^3J_1$ = 9.9 Hz, $^3J_2 \approx {}^3J_3$ = 6.1 Hz, 1 H, H-5), 7.35-7.42 (m, 3 H, 2 × H-*m*-Ph, H-*p*-Ph), 7.47-7.54 (m, 2 H, 2 × H-*o*-Ph).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 19.2 (t, C-7), 22.2 (t, C-4), 23.3 (t, C-6), 25.5 (t, C-2), 29.9 (t, C-8), 32.9 (t, C-3), 37.5 (d, C-4a), 39.8 (d, C-3a), 40.5 (t, C-1), 49.3 (s, C-8a), 55.5 (q, OMe-2'), 75.0 (d, C-5), 84.7 (qs, $^2J_{CF}$ = 27.5 Hz, C-2'), 123.5 (qs, $^1J_{CF}$ = 289 Hz, CF_3-2'), 127.5 (d, 2 C, 2 × C-*o*-Ph), 128.4 (d, 2 C, 2 × C-*m*-Ph), 129.6 (d, C-*p*-Ph), 132.6 (s, C-*i*-Ph), 166.1 (s, C-1').

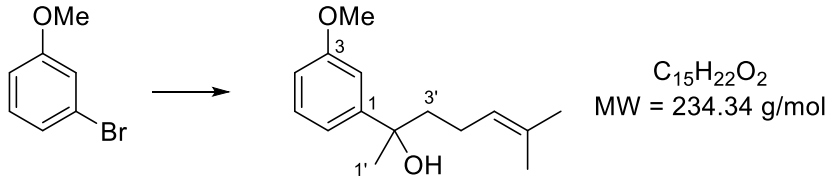
^{19}F NMR (376 MHz, $CDCl_3$, 298 K): δ [ppm] = –72.1 (s, 3 F, CF_3-2').

MS (EI, 70 eV): m/z (%) = 382 (0.1) $[M]^+$, 189 (34) $[C_9H_8F_3O]^+$, 149 (100) $[C_{11}H_{17}]^+$, 107 (38) $[C_8H_{11}]^+$, 81 (40) $[C_6H_9]^+$, 67 (40).

HRMS (EI, 70 eV): calcd for $C_{21}H_{25}O_3F_3$ $[M]^+$: 382.1750; found: 382.1752;
calcd for $C_{20}{}^{13}CH_{25}O_3F_3$ $[M]^+$: 383.1784; found: 383.1784.

6.3.8 Total Synthesis of *rac*-Italicene and *rac*-Isoitalicene

***rac*-2-(3-Methoxyphenyl)-6-methylhept-5-en-2-ol (*rac*-223)**



222 *rac*-**223**

In analogy to a modified literature procedure:[172] A solution of *n*-butyllithium (2.50 M in hexane, 32.1 mL, 80.2 mmol, 1.00 equiv) was added dropwise by a syringe pump (1 mL/min) to a solution of aryl bromide **222** (15.0 g, 80.2 mmol, 1.00 equiv) in tetrahydrofuran (200 mL, 400 mM) at –78 °C. Over the course of the addition, the resulting mixture turns from yellow to brown forming a colorless precipitate. After 45 minutes, 6-methylhept-5-en-2-one (10.8 g, 12.7 mL, 85.8 mmol, 1.07 equiv) was added dropwise by a syringe pump (1 mL/min) to the suspension, in the meantime the resulting mixture turns into a clear brown solution. The solution was allowed to warm to room temperature and was subsequently poured into water (400 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 200 mL). The combined organic layers were dried with brine (400 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. The residue was purified by column chromatography (silica, CH_2Cl_2) to provide alcohol *rac*-**223** (14.6 g, 62.3 mmol, 78%) as a pale yellow oil.

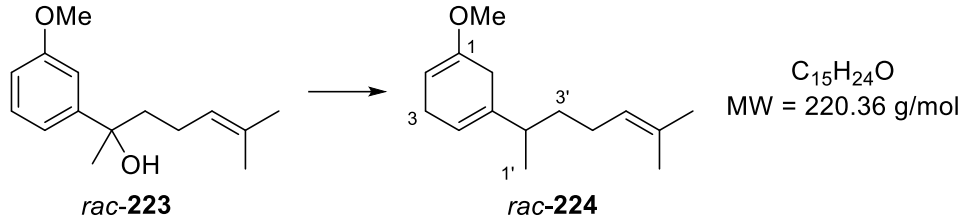
TLC: R_f = 0.31 (CH_2Cl_2) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.49 (d, ^4J = 1.3 Hz, 3 H, Me-6'), 1.53 (s, 3 H, Me-2'), 1.65 (d, ^4J = 1.3 Hz, 3 H, Me-6'), 1.77-2.03 (m, 5 H, H-3', H-4', OH-2'), 3.82 (s, 3 H, OMe-3), 5.09 (tqq, ^3J = 7.1 Hz, $^4J_1$ = 1.3 Hz, $^4J_2$ = 1.3 Hz, 1 H, H-5'), 6.78 (ddd, ^3J = 8.0 Hz, $^4J_1$ = 2.6 Hz, $^4J_2$ = 0.9 Hz, 1 H, H-4), 6.98 (ddd, ^3J = 8.0 Hz, $^4J_1$ = 1.7 Hz, $^4J_2$ = 0.9 Hz, 1 H, H-6), 7.02 (dd, $^4J_1$ = 2.6 Hz, $^4J_2$ = 1.7 Hz, 1 H, H-2), 7.26 (*virt.* t, $^3J_1 \approx {}^3J_2$ = 9.5 Hz, 1 H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 17.8 (q, Me-6'), 23.1 (t, C-3'), 25.8 (q, Me-6'), 30.7 (q, Me-2'), 43.8 (t, C-4'), 55.4 (q, OMe-3), 75.2 (s, C-2'), 111.1 (d, C-2), 111.7 (d, C-4), 117.4 (d, C-6), 124.3 (d, C-5'), 129.3 (d, C-5), 132.4 (s, C-6'), 149.9 (s, C-1), 159.7 (s, C-3).

The analytical data obtained matched those reported in the literature.[172]

***rac*-1-Methoxy-5-(6-methylhept-5-en-2-yl)cyclohexa-1,4-diene (*rac*-224)**



rac-**223** *rac*-**224**

In analogy to a modified literature procedure:[172] Ammonia (140 mL, 150 mM) was condensed into a solution of alcohol *rac*-**223** (5.00 g, 21.3 mmol, 1.00 equiv) in dry ethanol (36 mL, 600 mM) at –78 °C. The resulting mixture was warmed at reflux at –25 °C. Sodium (4.91 g, 213 mmol, 10.0 equiv) was added in small pieces over the course of one hour. After complete addition, the reaction mixture was dark blue for at least 30 minutes which indicated complete conversion of the starting material *rac*-**223**. The cooling bath was removed and residual ammonia was evaporated with the help of a heat-gun (100 °C). The resulting suspension was treated with water (300 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 300 mL). The combined organic layers were dried with brine (500 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. Purification of the residue by column chromatography was performed with deactivated silica (slurry with CH_2Cl_2/NH_3(25%) = 100/0.2) with pentane as eluent. Alkene *rac*-**224** (2.98 g, 13.5 mmol, 63%) was obtained as a colorless oil.

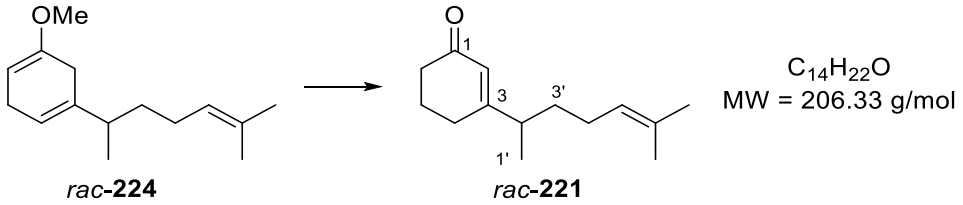
TLC: R_f = 0.75 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 0.97 (d, ^3J = 6.9 Hz, 3 H, Me-2'), 1.24-1.33 (m, 1 H, *H*H-3'), 1.41-1.50 (m, 1 H, H*H*-3'), 1.53 (s, 3 H, Me-6'), 1.66 (s, 3 H, Me-6'), 1.97 (*virt.* q, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 7.6 Hz, 2 H, H-4'), 2.12 (*virt.* sext, $^3J_1 \approx {}^3J_2$ = 7.0 Hz, 1 H, H-2'), 2.75-2.85 (m, 4 H, H-3, H-6), 3.30 (s, 3 H, OMe-1), 4.47-4.51 (m, 1 H, H-2), 5.13-5.20 (m, 1 H, H-5'), 5.43-5.48 (m, 1 H, H-4).

^{13}C NMR (101 MHz, C_6D_6, 300 K): δ [ppm] = 17.8 (q, Me-6'), 19.7 (q, Me-2'), 25.9 (q, Me-6'), 26.5 (t, C-4'), 27.2 (t, C-3), 28.9 (t, C-6), 35.2 (t, C-3'), 40.5 (d, C-2'), 53.6 (q, OMe-1), 90.5 (d, C-2), 118.6 (d, C-4), 125.3 (d, C-5'), 131.0 (s, C-6'), 138.7 (s, C-5), 153.8 (s, C-1).

The analytical data obtained matched those reported in the literature.[172]

***rac*-3-(6-Methylhept-5-en-2-yl)cyclohex-2-en-1-one (*rac*-221)**



rac-**224** *rac*-**221**

An aqueous hydrochloric acid solution (3.00 M, 847 µL, 2.54 mmol, 20.0 mol%) was added to an emulsion of enol ether *rac*-**224** (2.98 g, 13.5 mmol, 1.00 equiv) in methanol (42 mL, 300 mM) at room temperature. Upon addition of the acid, the emulsion turns into a solution which was stirred for two hours. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution (100 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 100 mL). The organic layers were combined, dried with brine (100 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. After purification of the residue by column chromatography (silica, P/Et_2O = 5/1), enone *rac*-**221** (2.29 g, 11.1 mmol, 87%) was obtained as a pale yellow oil.

TLC: R_f = 0.53 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.08 (d, ^3J = 6.9 Hz, 3 H, Me-2'), 1.36-1.44 (m, 1 H, *H*H-3'), 1.52 (dddd, ^2J = 14.1 Hz, $^3J_1$ = 8.5 Hz, $^3J_2$ = 7.7 Hz, $^3J_3$ = 6.5 Hz, 1 H, H*H*-3'), 1.57 (d, ^4J = 1.3 Hz, 3 H, Me-6'), 1.68 (d, ^4J = 1.3 Hz, 3 H, Me-6'), 1.88-1.95 (m, 2 H, H-4'), 1.95-2.01 (m, 2 H, H-5), 2.25-2.29 (m, 2 H, H-4), 2.29-2.33 (m, 1 H, H-2'), 2.35-2.39 (m, 2 H, H-6), 5.06 (tqq, ^3J = 7.1 Hz, $^4J_1$ = 1.3 Hz, $^4J_2$ = 1.3 Hz, 1 H, H-5'), 5.87 (td, $^4J_1$ = 1.5 Hz, $^4J_2$ = 0.7 Hz, 1 H, H-2).

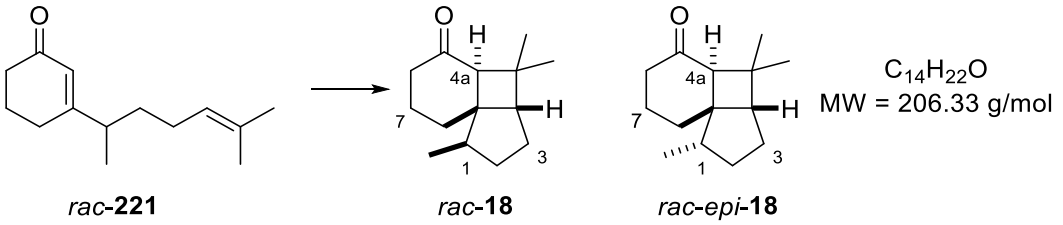
^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 17.9 (q, Me-6'), 19.0 (q, Me-2'), 23.1 (t, C-5), 25.8 (q, Me-6'), 26.0 (t, C-4'), 27.1 (t, C-4), 34.9 (t, C-3'), 37.9 (t, C-6), 41.4 (d, C-2'), 123.9 (d, C-5'), 125.3 (d, C-2), 132.2 (s, C-6'), 171.0 (s, C-3), 200.3 (s, C-1).

The analytical data obtained matched those reported in the literature.[172]

(1*R*,3a*S*,4a*S*,8a*S*)-1,4,4-Trimethyloctahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5(6*H*)-one (*rac*-18)

and

(1*S*,3a*S*,4a*S*,8a*S*)-1,4,4-Trimethyloctahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5(6*H*)-one (*rac-epi*-18)



rac-**221** *rac*-**18** *rac-epi*-**18**

Racemic [2+2] Photocycloaddition:

Following GP6, enone *rac*-**221** (273 mg, 1.32 mmol, 1.00 equiv) was irradiated in dichloromethane (66 mL) for 14 hours. Different from GP6, the reaction mixture was treated with triethylamine (1 mL) instead of basic alumina and the solvent was removed in vacuo. The residue was purified by column chromatography (silica, P/Et_2O = 5/1). Starting material *rac*-**221** as well as the product mixture, which was submitted to ozonolysis, were isolated. The ozonolysis was conducted at –78 °C in dichloromethane (3 mL). Completion of the reaction was indicated by blue coloration during ozon introduction. The blue color was removed by an argon gasflow and dimethyl sulfide (1 mL) was added. Subsequently, the mixture was warmed to room temperature, the solvent was removed in vacuo and the residue was purified by column chromatography (silica, P/Et_2O = 5/1). After the work-up process, ketones *rac*-**18** and *rac-epi*-**18** (211 mg, 1.02 mmol, 77%, d.r. = 67/33, *rac*-**18**/*rac-epi*-**18**) were obtained as a colorless oil and starting material *rac*-**221** (17.7 mg, 85.8 µmol, 6%) was recovered.

Enantioselective [2+2] Photocycloaddition:

Following GP7, enone *rac*-**221** (41.3 mg, 200 µmol, 1.00 equiv) was irradiated in dichloromethane (10 mL) using catalyst **50** for one hour. After purification by column chromatography (silica, P/Et_2O = 6/1), ketones **18** and *epi*-**18** [5.30 mg, 25.7 µmol, 13%, d.r. = 84/16, **18** (43% *ee*)/*epi*-**18** (21% *ee*)] were obtained as a colorless oil and starting material *ent*-**221** (29.1 mg, 141 µmol, 71%, 10% *ee*) was recovered.

Separation of the Diastereomers *rac*-**18** and *rac-epi*-**18**:

A mixture of diastereomers *rac*-**18** and *rac-epi*-**18** (500 mg) was separated by column chromatography (silica, P/Et_2O = 30/1) with a conventional column (36 mm diameter, 300 mm length). The collected fractions were analyzed by gas chromatography and were combined to six fractions [(content of *rac-epi*-**18**)]: [F1 (≥99.5%)], [F2 (90<99.5%)], [F3 (10<90%)]; [(content of *rac*-**18**)]: [F4 (90<99%)], [F5 (99<99.5)], [F6 (≥99.5%)]. The fractions F3, F4 and F5 were purified under the same conditions iteratively (subsequently from F3 to F5) until F3 contained less than 15 mg of the product mixture. Finally, F2, F3, F4, F5 were purified subsequently.

TLC: R_f = 0.66 (P/Et_2O = 1/1) [CAM, $KMnO_4$].

rac-**18**:

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.84 (d, ^3J = 7.2 Hz, 3 H, Me-1), 1.03 (s, 3 H, Me-4β), 1.07 (s, 3 H, Me-4α), 1.48-1.55 (m, 1 H, *H*H-2), 1.59-1.76 (m, 4 H, H-3, *H*H-7, *H*H-8), 1.84-2.07 (m, 5 H, H-1, H*H*-2, H-3a, H*H*-7, H*H*-8), 2.15-2.25 (m, 2 H, H-4a, *H*H-6), 2.28-2.36 (m, 1 H, H*H*-6).

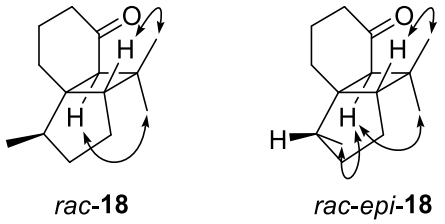
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 16.7 (q, Me-1), 20.5 (t, C-7), 25.1 (t, C-3), 25.7 (q, Me-4β), 27.6 (q, Me-4α), 29.0 (t, C-8), 34.7 (t, C-2), 37.0 (s, C-4), 40.9 (t, C-6), 41.0 (d, C-1), 47.8 (s, C-8a), 51.6 (d, C-3a), 58.4 (d, C-4a), 214.7 (s, C-5).

rac-epi-**18**:

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.89 (d, ^{3}J = 6.7 Hz, 3 H, Me-1), 1.03 (s, 3 H, Me-4β), 1.06 (s, 3 H, Me-4α), 1.42 (virt. qd, $^2J \approx {}^3J_1 \approx {}^3J_2$ = 12.3 Hz, $^3J_3$ = 6.6 Hz, 1 H, HH-2), 1.48-1.73 (m, 4 H, H-1, H-3, HH-8), 1.73-1.91 (m, 3 H, HH-2, HH-7, HH-8), 1.94-2.04 (m, 1 H, HH-7), 2.06 (d, ^{3}J = 8.0 Hz, 1 H, H-3a), 2.11-2.21 (m, 1 H, HH-6), 2.25-2.35 (m, 2 H, H-4a, HH-6).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 12.8 (q, Me-1), 21.5 (t, C-7), 24.9 (q, Me-4β), 26.6 (t, C-3), 27.3 (q, Me-4α), 33.0 (t, C-8), 35.4 (t, C-2), 36.3 (s, C-4), 41.1 (t, C-6), 44.7 (d, C-1), 46.5 (s, C-8a), 52.2 (d, C-4a), 53.1 (d, C-3a), 214.1 (s, C-5).

Important NOE contacts:



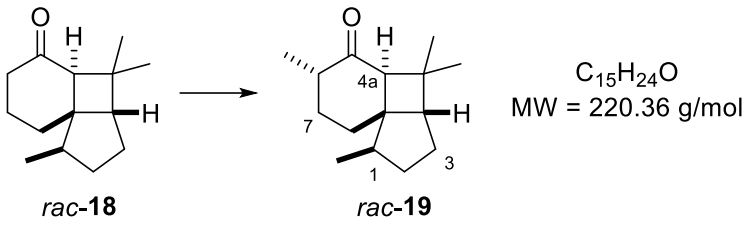
rac-**18** *rac-epi*-**18**

Chiral GC: (*epi*-**18**): τ_R (major) = 24.3 min, τ_R (minor) = 24.6 min; (**18**): τ_R (minor) = 25.3 min, τ_R (major) = 25.9 min, [60 °C (0.5 min), 200 °C (4 °C/min), 200 °C (5 min)], Lipodex E.

(*ent*-**221**): τ_R (major) = 43.5 min, τ_R (minor) = 45.0 min, [60 °C (0.5 min), 130 °C (15 °C/min), 130 °C (50 min), 200 °C (15 °C/min), 200 °C (5 min)], Lipodex E.

The analytical data obtained matched those reported in the literature.[172]

(1*R*,3a*S*,4a*S*,6*S*,8a*S*)-1,4,4,6-Tetramethyloctahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5(6*H*)-one (*rac*-19)



rac-**18** *rac*-**19**

A solution of *n*-butyllithium (2.50 M in hexane, 3.54 mL, 8.85 mmol, 6.00 equiv) was added to a solution of diisopropylamine (955 mg, 1.33 mL, 9.44 mmol, 6.40 equiv) in tetrahydrofuran (15 mL, 630 mM) at –78 °C. The resulting mixture was stirred for one hour at –78 °C. A solution of ketone *rac*-**18** (304 mg, 1.47 mmol, 1.00 equiv) in tetrahydrofuran (15 mL, 100 mM) was added dropwise to the freshly prepared lithium diisopropylamide solution at –78 °C. After six hours, DMPU (2.27 g, 2.14 mL, 17.7 mmol, 12.0 equiv) and iodomethane (1.67 g, 735 µL, 11.8 mmol, 8.00 equiv) were added in sequence, during which a colorless precipitate was formed. The suspension was allowed to slowly warm to room temperature over the course of 15 hours. The brown reaction mixture was transferred to a silica-packed column, the reaction vessel was rinsed with dichloromethane and the reaction mixture was filtered with a solvent mixture (P/Et_2O = 5/1). The product containing fractions were combined and after removal of the solvent in vacuo, the residue was purified by column chromatography (silica,

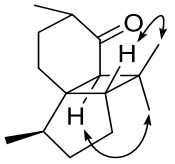
P/Et_2O = 10/1). Ketone *rac*-**19** (305 mg, 1.38 mmol, 94%, d.r. = 90/10) was obtained as a colorless oil.

TLC: R_f = 0.77 (P/Et_2O = 1/1) [CAM, $KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.82 (d, ^3J = 7.2 Hz, 3 H, Me-1), 1.01 (s, 3 H, Me-4β), 1.09 (s, 3 H, Me-4α), 1.09 (d, ^3J = 7.1 Hz, 3 H, Me-6), 1.33 (*virt.* tdd, $^2J \approx {}^3J_1$ = 13.5 Hz, $^3J_2$ = 11.9 Hz, $^3J_3$ = 2.3 Hz, 1 H, *H*H-7), 1.49-1.56 (m, 1 H, *H*H-2), 1.56-1.64 (m, 1 H, *H*H-3), 1.70 (*virt.* tt, $^2J \approx {}^3J_1$ = 13.0 Hz, $^3J_2 \approx {}^3J_3$ = 7.6 Hz, 1 H, H*H*-3), 1.76-1.83 (m, 1 H, *H*H-8), 1.84-1.92 (m, 2 H, H-1, H*H*-7), 1.94 (d, ^3J = 8.2 Hz, 1 H, H-3a), 2.01 (*virt.* tt, $^2J \approx {}^3J_1$ = 13.1 Hz, $^3J_2 \approx {}^3J_3$ = 6.9 Hz, 1 H, H*H*-2), 2.07-2.15 (m, 2 H, H-6, H*H*-8), 2.19 (s, 1 H, H-4a).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 16.5 (q, Me-6), 16.9 (q, Me-1), 24.9 (t, C-3), 25.5 (q, Me-4β), 27.9 (q, Me-4α), 29.0 (t, C-8), 29.3 (t, C-7), 34.6 (t, C-2), 37.2 (s, C-4), 39.9 (d, C-1), 45.8 (d, C-6), 48.7 (s, C-8a), 51.9 (d, C-3a), 57.9 (d, C-4a), 216.5 (s, C-5).

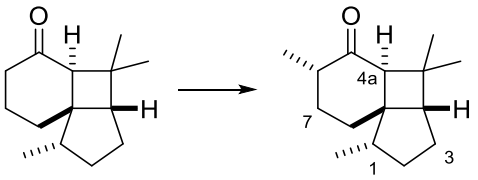
Important NOE contacts:



rac-**19**

The analytical data obtained matched those reported in the literature.[172]

(1*S*,3a*S*,4a*S*,6*S*,8a*S*)-1,4,4,6-Tetramethyloctahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5(6*H*)-one (*rac*-*epi*-19)



rac-*epi*-**18** *rac*-*epi*-**19**

$C_{15}H_{24}O$
MW = 220.36 g/mol

A solution of *n*-butyllithium (2.50 M in hexane, 1.51 mL, 3.76 mmol, 6.00 equiv) was added to a solution of diisopropylamine (406 mg, 566 µL, 4.01 mmol, 6.40 equiv) in tetrahydrofuran (6.27 mL, 640 mM) at –78 °C. The resulting mixture was stirred for one hour at –78 °C. A solution of ketone *rac*-*epi*-**18** (129 mg, 627 µmol, 1.00 equiv) in tetrahydrofuran (6.27 mL, 100 mM) was added dropwise to the freshly prepared lithium diisopropylamide solution at

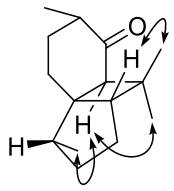
–78 °C. After six hours, DMPU (965 mg, 910 µL, 7.53 mmol, 12.0 equiv) and iodomethane (712 mg, 312 µL, 5.02 mmol, 8.00 equiv) were added in sequence, during which a colorless precipitate was formed. The suspension was allowed to slowly warm to room temperature over the course of 15 hours. The brown reaction mixture was transferred to a silica-packed column, the reaction vessel was rinsed with dichloromethane and the reaction mixture was filtered with a solvent mixture (P/Et_2O = 5/1). The product containing fractions were combined and after removal of the solvent in vacuo, the residue was purified by column chromatography (silica, P/Et_2O = 10/1). Ketone *rac-epi*-**19** (119 mg, 540 µmol, 86%) was obtained as a colorless oil.

TLC: R_f = 0.77 (P/Et_2O = 1/1) [CAM, $KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.90 (d, ^3J = 6.7 Hz, 3 H, Me-1), 1.00 (s, 3 H, Me-4β), 1.07 (d, ^3J = 7.0 Hz, 3 H, Me-6), 1.09 (s, 3 H, Me-4α), 1.41 (*virt.* qd, $^2J \approx {}^3J_1 \approx {}^3J_2$ = 12.3 Hz, $^3J_3$ = 7.0 Hz, 1 H, *H*H-2), 1.49-1.67 (m, 4 H, H-1, H-3, *H*H-7), 1.75 (*virt.* dt, ^2J = 12.4 Hz, $^3J_1 \approx {}^3J_2$ = 6.2 Hz, 1 H, H*H*-2), 1.89 (ddd, ^2J = 13.7 Hz, $^3J_1$ = 5.6 Hz, $^3J_2$ = 3.5 Hz, 1 H, *H*H-8), 1.94-2.07 (m, 3 H, H-3a, H*H*-7, H*H*-8), 2.16-2.26 (m, 1 H, H-6), 2.31 (s, 1 H, H-4a).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 13.2 (q, Me-1), 15.8 (q, Me-6), 24.9 (q, Me-4β), 26.3 (t, C-3), 27.8 (q, Me-4α), 30.4 (t, C-7), 33.7 (t, C-8), 35.7 (t, C-2), 36.7 (s, C-4), 45.1 (d, C-6), 45.9 (d, C-1), 47.0 (s, C-8a), 51.8 (d, C-4a), 54.2 (d, C-3a), 215.6 (s, C-5).

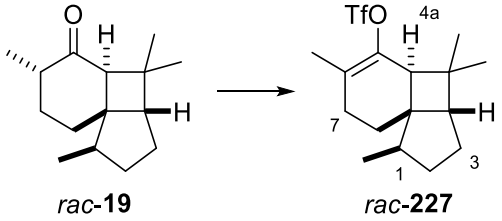
Important NOE contacts:



rac-epi-**19**

The analytical data obtained matched those reported in the literature.[172]

(1*R*,3a*S*,4a*S*,8a*S*)-1,4,4,6-Tetramethyl-1,2,3,3a,4,4a,7,8-octahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5-yl trifluoromethanesulfonate (*rac*-227)



rac-**19** *rac*-**227**

$C_{16}H_{23}F_3O_3S$
MW = 352.41 g/mol

A solution of *n*-butyllithium (2.50 M in hexane, 363 µL, 908 µmol, 4.00 equiv) was added to a solution of diisopropylamine (96.4 mg, 135 µL, 953 µmol, 4.20 equiv) in tetrahydrofuran (2.27 mL, 420 mM) at –78 °C. The resulting mixture was stirred for 30 minutes. A solution of ketone *rac*-**19** (50.0 mg, 227 µmol, 1.00 equiv) in tetrahydrofuran (2.27 mL, 100 mM) was added dropwise to the freshly prepared lithium diisopropylamide solution at –78 °C. After seven and a half hours, a solution of *Comins* reagent (401 mg, 1.02 mmol, 4.50 equiv) in tetrahydrofuran (1.02 mL, 1.00 M) was added dropwise to the enolate solution, during which the solution turned deep brown. After five minutes, the reaction mixture was allowed to warm to room temperature in the course of 30 minutes. The brown reaction mixture was transferred to a column packed with deactivated, neutral alumina*, the reaction vessel was rinsed with dichloromethane and the reaction mixture was filtered with a solvent mixture (P/CH_2Cl_2 = 15/1). The product containing fractions were combined and after removal of the solvent in vacuo, the residue was purified by column chromatography (deactivated neutral alumina, P/CH_2Cl_2 = 15/1) three consecutive times in order to remove residual *Comins* reagent. Triflate *rac*-**227** (59.8 mg, 170 µmol, 75%) was obtained as a colorless oil.

*Deactivation is described in the general information.

TLC: R_f = 0.47 (P) [CAM, $KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2953 (m, sp^3-CH), 2870 (m, sp^3-CH), 1410 (s, SO), 1201 (vs, sp^3-CF), 1141 (vs, sp^3-CF), 898 (vs, SO).

^{1}H NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 0.58 (d, ^3J = 7.2 Hz, 3 H, Me-1), 1.00 (s, 3 H, Me-4β), 1.04 (s, 3 H, Me-4α), 1.24-1.39 (m, 2 H, *H*H-2, *H*H-8), 1.41-1.51 (m, 3 H, H-3, H*H*-8), 1.51-1.74 (m, 7 H, H-1, H-3a, Me-6, H-7), 1.85 (*virt.* dtd, ^2J = 13.3 Hz, $^3J_1 \approx {}^3J_2$ = 9.5 Hz, $^3J_3$ = 6.7 Hz, 1 H, H*H*-2), 2.39 (br s, 1 H, H-4a).

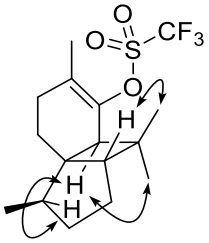
^{13}C NMR (126 MHz, C_6D_6, 300 K): δ [ppm] = 15.9 (q, Me-1), 17.3 (q, Me-6), 24.8 (t, C-3), 24.9 (q, Me-4β), 26.8 (q, Me-4α), 26.8 (t, C-8), 29.5 (t, C-7), 34.9 (t, C-2), 35.6 (s, C-4), 40.6

(d, C-1), 48.7 (s, C-8a), 49.4 (d, C-4a), 51.1 (d, C-3a), 119.1 (qs, $^{1}J_{CF}$ = 320 Hz, CF_3), 128.5 (s, C-6)*, 145.2 (s, C-5).

*The ^{13}C signal of C-6 overlaps with the solvent signal of C_6D_6. However, the signal can be located with the help of a HMBC crosspeak with the proton signal of Me-6 to assign the ^{13}C signal of C-6.

^{19}F NMR (376 MHz, C_6D_6, 298 K): δ [ppm] = –75.4 (s, 3 F, CF_3).

Important NOE contacts:

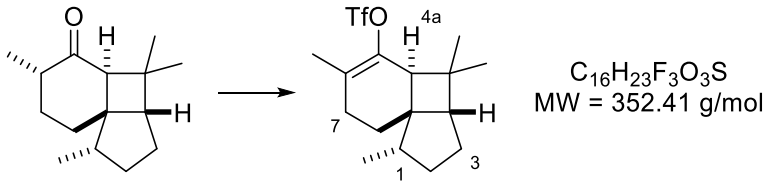


rac-**227**

MS (EI, 70 eV): m/z (%) = 352 (51) $[M]^+$, 308 (14), 281 (74), 266 (100), 252 (14), 220 (17), 205 (68), 187 (64), 159 (56), 145 (73), 109 (39), 82 (55), 55 (42) $[C_4H_7]^+$.

HRMS (EI, 70 eV): calcd for $C_{16}H_{23}O_3F_3{}^{32}S$ $[M]^+$: 352.1315; found: 352.1310;
calcd for $C_{15}{}^{13}CH_{23}O_3F_3{}^{32}S$ $[M]^+$: 353.1348; found: 353.1344.

(1*S*,3a*S*,4a*S*,8a*S*)-1,4,4,6-Tetramethyl-1,2,3,3a,4,4a,7,8-octahydrocyclopenta[1,4]cyclobuta[1,2]benzen-5-yl trifluoromethanesulfonate (*rac-epi*-227)



rac-epi-**19** *rac-epi*-**227**

A solution of *n*-butyllithium (2.50 M in hexane, 363 µL, 908 µmol, 4.00 equiv) was added to a solution of diisopropylamine (96.4 mg, 135 µL, 953 µmol, 4.20 equiv) in tetrahydrofuran (2.27 mL, 420 mM) at –78 °C. The resulting mixture was stirred for 40 minutes. A solution of ketone *rac-epi*-**19** (50.0 mg, 227 µmol, 1.00 equiv) in tetrahydrofuran (2.27 mL, 100 mM) was added dropwise to the freshly prepared lithium diisopropylamide solution at –78 °C. After eight and a half hours, a solution of *Comins* reagent (401 mg, 1.02 mmol, 4.50 equiv) in tetrahydrofuran (1.02 mL, 1.00 M) was added dropwise to the enolate solution, during which the solution turned deep brown. After five minutes, the reaction mixture was allowed to warm

to room temperature in the course of 30 minutes. The brown reaction mixture was transferred to a column packed with deactivated, neutral alumina*, the reaction vessel was rinsed with dichloromethane and the reaction mixture was filtered with a solvent mixture ($P/CH_2Cl_2 = 15/1$). The product containing fractions were combined and after removal of the solvent in vacuo, the residue was purified by column chromatography (deactivated neutral alumina, $P/CH_2Cl_2 = 15/1$) three consecutive times in order to remove residual *Comins* reagent. Triflate *rac-epi*-**227** (63.8 mg, 181 μmol, 80%) was obtained as a colorless oil.

*Deactivation is described in the general information.

TLC: $R_f = 0.47$ (P) [CAM, $KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2953 (m, sp^3-CH), 2870 (m, sp^3-CH), 1410 (s, SO), 1201 (vs, sp^3-CF), 1141 (vs, sp^3-CF), 898 (vs, SO).

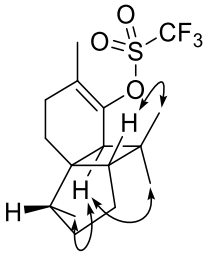
^{1}H NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 0.85 (d, ^3J = 5.6 Hz, 3 H, Me-1), 0.95 (s, 3 H, Me-4α), 0.97 (s, 3 H, Me-4β), 1.26-1.36 (m, 4 H, *H*H-1, *H*H-2, *H*H-3, *H*H-8), 1.40-1.52 (m, 2 H, H*H*-3, H*H*-8), 1.55-1.61 (m, 2 H, H*H*-2, H-3a), 1.62 (s, 3 H, Me-6), 1.72 (*virt.* dt, ^2J = 16.7 Hz, $^3J_1 \approx {}^3J_2$ = 6.1 Hz, 1 H, *H*H-7), 1.90 (*virt.* dt, ^2J = 16.7 Hz, $^3J_1 \approx {}^3J_2$ = 6.7 Hz, 1 H, H*H*-7), 2.49 (br s, 1 H, H-4a).

^{13}C NMR (126 MHz, C_6D_6, 300 K): δ [ppm] = 13.0 (q, Me-1), 17.2 (q, Me-6), 23.9 (q, Me-4β), 26.5 (t, C-3), 26.7 (q, Me-4α), 30.5 (t, C-7), 31.0 (t, C-8), 35.7 (t, C-2), 35.8 (s, C-4), 43.2 (d, C-4a), 44.6 (d, C-1), 48.1 (s, C-8a), 52.8 (d, C-3a), 119.1 (qs, $^1J_{CF}$ = 320 Hz, CF_3), 128.6 (s, C-6)*, 145.5 (s, C-5).

*The ^{13}C signal of C-6 overlaps with the solvent signal of C_6D_6. However, the signal can be located with the help of a HMBC crosspeak with the proton signal of Me-6 to assign the ^{13}C signal of C-6.

^{19}F NMR (376 MHz, C_6D_6, 298 K): δ [ppm] = –75.4 (s, 3 F, CF_3).

Important NOE contacts:

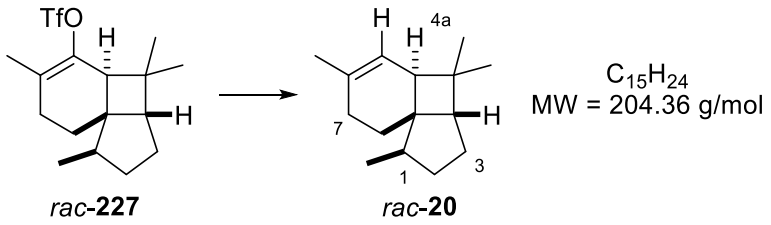


rac-epi-**227**

MS (EI, 70 eV): m/z (%) = 352 (51) $[M]^+$, 308 (14), 281 (74), 266 (100), 252 (14), 220 (17), 205 (68), 187 (64), 159 (56), 145 (73), 109 (39), 82 (55), 55 (42) $[C_4H_7]^+$.

HRMS (EI, 70 eV): calcd for $C_{16}H_{23}O_3F_3{}^{32}S$ $[M]^+$: 352.1315; found: 352.1310;
calcd for $C_{15}{}^{13}CH_{23}O_3F_3{}^{32}S$ $[M]^+$: 353.1348; found: 353.1344.

(1*R*,3a*S*,4a*S*,8a*S*)-1,4,4,6-Tetramethyl-1,2,3,3a,4,4a,7,8-octahydrocyclopenta[1,4]cyclobuta[1,2]benzene // *rac*-Italicene (*rac*-20)



rac-**227** *rac*-**20**

Palladium(II) acetate (3.91 mg, 17.0 µmol, 10.0 mol%) was added to a solution of triflate *rac*-**227** (59.8 mg, 170 µmol, 1.00 equiv), triphenylphosphine (13.4 mg, 50.9 µmol, 30.0 mol%) and lithium formate monohydrate (59.4 mg, 848 µmol, 5.00 equiv) in dimethylformamide (3.39 mL, 50.0 mM). The resulting mixture was heated to 60 °C. The reaction mixture turned black in seven minutes. After stirring for 20 minutes, the reaction mixture was allowed to cool to room temperature. The suspension was transferred to a column packed with deactivated, neutral alumina*, the reaction vessel was rinsed with dichloromethane and the reaction mixture was filtered with pentane. The product containing fractions were combined and after removal of the solvent in vacuo, the residue was purified by column chromatography (deactivated neutral alumina, pentane) three consecutive times to remove residual triphenylphosphine. In order to remove pentane completely without loosing too much of the volatile product *rac*-**20**, the vessel was evacuated at room temperature to 100 mbar and loaded with air in sequence five times. The title compound *rac*-**20** (31.5 mg, 154 µmol, 91%) was obtained as a colorless oil.

*Deactivation is described in the general information.

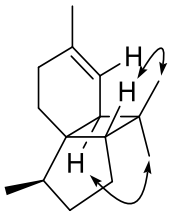
TLC: R_f = 0.71 (P) [CAM, $KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.78 (d, ^3J = 7.2 Hz, 3 H, Me-1), 0.91 (s, 3 H, Me-4β), 0.96 (s, 3 H, Me-4α), 1.46 (dd, ^2J = 12.4 Hz, ^3J = 6.9 Hz, 1 H, *H*H-2α), 1.53-1.59 (m, 1 H, *H*H-3β), 1.60-1.69 (m, 2 H, H*H*-3α, *H*H-8), 1.69-1.76 (m, 5 H, H-1, H-3a, Me-6), 1.76-1.81 (m, 2 H, H-7), 1.84 (*virt.* dt, ^2J = 12.8 Hz, $^3J_1 \approx {}^3J_2$ = 3.5 Hz, 1 H, H*H*-8), 1.88 (br s,

1 H, H-4a), 2.02 (*virt.* tt, $^{2}J \approx {}^{3}J_{1}$ = 12.3 Hz, $^{3}J_{2} \approx {}^{3}J_{3}$ = 7.0 Hz, 1 H, H*H*-2β), 5.30-5.34 (m, 1 H, H-5).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 16.6 (q, Me-1), 24.5 (q, Me-6), 24.9 (t, C-3), 24.9 (q, Me-4β), 27.2 (q, Me-4α), 27.8 (t, C-7), 28.1 (t, C-8), 34.8 (s, C-4), 35.0 (t, C-2), 39.7 (d, C-1), 45.4 (s, C-8a), 48.0 (d, C-4a), 51.5 (d, C-3a), 121.1 (d, C-5), 136.2 (s, C-6).

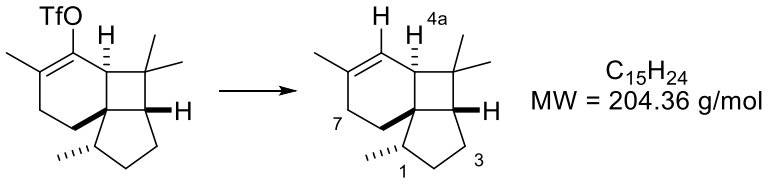
Important NOE contacts:



rac-**20**

The analytical data obtained matched those reported in the literature.[135]

(1*S*,3a*S*,4a*S*,8a*S*)-1,4,4,6-Tetramethyl-1,2,3,3a,4,4a,7,8-octahydrocyclopenta[1,4]cyclobuta[1,2]benzene // *rac*-Isoitalicene (*rac-epi*-20)



rac-epi-**227** *rac-epi*-**20**

Palladium(II) acetate (4.06 mg, 18.1 μmol, 10.0 mol%) was added to a solution of triflate *rac-epi*-**227** (63.8 mg, 181 μmol, 1.00 equiv), triphenylphosphine (14.3 mg, 54.3 μmol, 30.0 mol%) and lithium formate monohydrate (63.3 mg, 905 μmol, 5.00 equiv) in dimethylformamide (3.62 mL, 50.0 mM). The resulting mixture was heated to 60 °C. The reaction mixture turned black in ten minutes. After stirring for 20 minutes, the reaction mixture was allowed to cool to room temperature. The suspension was transferred to a column packed with deactivated, neutral alumina*, the reaction vessel was rinsed with dichloromethane and the reaction mixture was filtered with pentane. The product containing fractions were combined and after removal of the solvent in vacuo, the residue was purified by column chromatography (deactivated neutral alumina, pentane) three consecutive times to remove residual triphenylphosphine. In order to remove pentane completely without loosing too much of the volatile product *rac*-**20**, the vessel was evacuated at room temperature to 100 mbar and loaded

with air in sequence five times. The title compound *rac*-**20** (35.8 mg, 175 μmol, 97%) was obtained as a colorless oil.

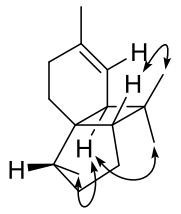
*Deactivation is described in the general information.

TLC: R_f = 0.71 (P) [CAM, $KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.82 (d, ^3J = 6.3 Hz, 3 H, Me-1), 0.90 (s, 3 H, Me-4β), 0.91 (s, 3 H, Me-4α), 1.39-1.67 (m, 5 H, H-1, *H*H-2, H-3, *H*H-8), 1.68-1.77 (m, 5 H, H*H*-2, H-3a, Me-6), 1.82 (ddd, ^2J = 14.9 Hz, $^3J_1$ = 9.5 Hz, $^3J_2$ = 5.5 Hz, 1 H, H*H*-8), 1.90 (*virt.* dt, ^2J = 16.5 Hz, $^3J_1 \approx {}^3J_2$ = 5.8 Hz, 1 H, *H*H-7), 1.94-2.02 (m, 2 H, H-4a, H*H*-7), 5.36-5.40 (m, 1 H, H-5).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 13.5 (q, Me-1), 24.1 (q, Me-4β), 24.5 (q, Me-6), 26.5 (t, C-3), 27.2 (q, Me-4α), 28.6 (t, C-7), 33.1 (t, C-8), 35.2 (s, C-4), 36.3 (t, C-2), 41.0 (d, C-4a), 43.9 (s, C-8a), 45.0 (d, C-1), 53.6 (d, C-3a), 121.8 (d, C-5), 135.7 (s, C-6).

Important NOE contacts:

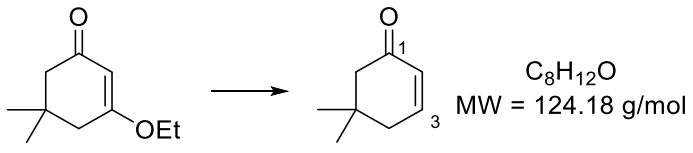


rac-epi-**20**

The analytical data obtained matched those reported in the literature.[135]

6.3.9 Synthesis of Irradiation Precursors for Intermolecular [2+2] Photocycloaddition Reactions

5,5-Dimethylcyclohex-2-en-1-one (242)



143 **242**

According to a modified literature procedure:[163] A solution of enol ether **143** (540 mg, 3.50 mmol, 1.00 equiv) in tetrahydrofuran (2.33 mL, 1.50 M) was added dropwise to a suspension of lithiumaluminum hydride (53.2 mg, 1.40 mmol, 40.0 mol%) in tetrahydrofuran (1.40 mL, 1.00 M) at 0 °C. The reaction mixture was allowed to warm to room temperature.

After two hours, the reaction mixture was cooled to 0 °C and excess lithiumaluminum hydride was quenched by dropwise addition of methanol until no gas evolution was observed. Aqueous hydrochloric acid solution (1.00 M, 10 mL) was added and the reaction mixture was stirred for 30 minutes. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The organic layers were combined, dried with brine (50 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. The residue was purified by column chromatography (silica, P/Et_2O = 8/1) to provide enone **242** (292 mg, 2.35 mmol, 70%) as a colorless oil.

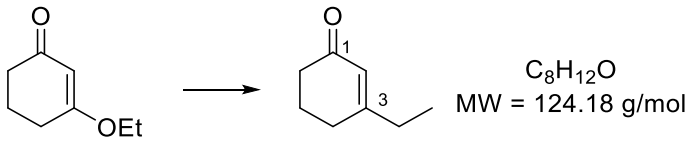
TLC: R_f = 0.50 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.05 (s, 6 H, 2 × Me-5), 2.24 (dd, ^3J = 4.1 Hz, ^4J = 2.1 Hz, 2 H, H-4), 2.27 (s, 2 H, H-6), 6.03 (dt, ^3J = 10.1 Hz, ^4J = 2.1 Hz, 1 H, H-2), 6.86 (dt, $^3J_1$ = 10.1 Hz, $^3J_2$ = 4.1 Hz, 1 H, H-3).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 28.5 (q, 2 C, 2 × Me-5), 34.0 (s, C-5), 40.0 (t, C-4), 51.9 (t, C-6), 129.1 (d, C-2), 148.6 (d, C-3), 200.2 (s, C-1).

The analytical data obtained matched those reported in the literature.[290]

3-Ethylcyclohex-2-en-1-one (243)



118 **243**

Following GP8 excluding the *Grignard* reagent formation, enol ether **118** (200 mg, 1.43 mmol, 1.00 equiv) was converted with ethylmagnesium bromide (1.50 M in tetrahydrofuran, 1.24 mL, 1.85 mmol, 1.30 equiv) within one hour. After purification by column chromatography (silica, P/Et_2O = 2/1), enone **243** (147 mg, 1.18 mmol, 83%) was obtained as a pale yellow oil.

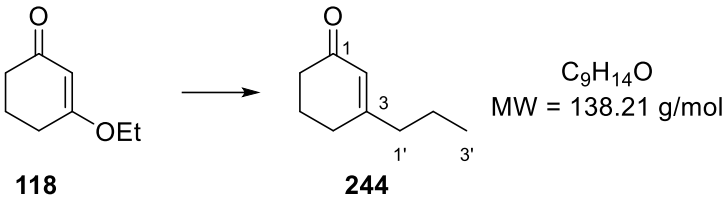
TLC: R_f = 0.33 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.09 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 1.95-2.02 (m, 2 H, H-5), 2.21-2.26 (m, 2 H, CH_2CH_3), 2.27-2.31 (m, 2 H, H-4), 2.34-2.38 (m, 2 H, H-6), 5.87 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.5 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 11.4 (q, CH_2CH_3), 22.9 (t, C-5), 29.9 (t, C-4), 31.0 (t, CH_2CH_3), 37.5 (t, C-6), 124.7 (d, C-2), 168.1 (s, C-3), 200.2 (s, C-1).

The analytical data obtained matched those reported in the literature.[291]

3-Propylcyclohex-2-en-1-one (244)



118 **244**

Following GP8, enol ether **118** (200 mg, 1.43 mmol, 1.00 equiv) was converted with 1-bromopropane (169 µL, 228 mg, 1.85 mmol, 1.30 equiv), iodine (3.62 mg, 14.3 µmol, 1.00 mol%) and magnesium turnings (45.1 mg, 1.85 mmol, 1.30 equiv) within three hours. After purification by column chromatography (silica, P/Et_2O = 4/1), enone **244** (139 mg, 1.01 mmol, 71%) was obtained as a pale yellow oil.

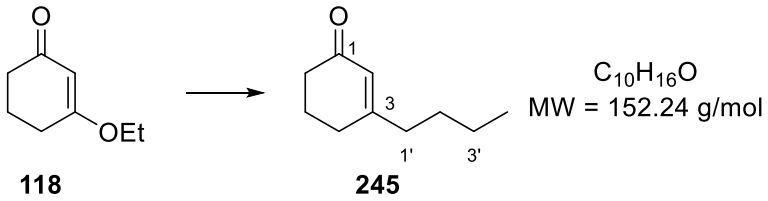
TLC: R_f = 0.37 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.93 (t, ^3J = 7.4 Hz, 3 H, H-3'), 1.54 (*virt.* sext, $^3J_1 \approx {}^3J_2$ = 7.3 Hz, 2 H, H-2'), 1.98 (*virt.* quint, $^3J_1 \approx {}^3J_2$ = 6.3 Hz, 2 H, H-5), 2.17-2.21 (m, 2 H, H-1'), 2.26-2.30 (m, 2 H, H-4), 2.34-2.38 (m, 2 H, H-6), 5.87 (br s, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 13.9 (q, C-3'), 20.3 (t, C-2'), 22.9 (t, C-5), 29.8 (t, C-4), 37.5 (t, C-6), 40.2 (t, C-1'), 125.9 (d, C-2), 166.7 (s, C-3), 200.2 (s, C-1).

The analytical data obtained matched those reported in the literature.[292]

3-Butylcyclohex-2-en-1-one (245)



118 **245**

Following GP8 excluding the *Grignard* reagent formation, enol ether **118** (200 mg, 1.43 mmol, 1.00 equiv) was converted with a solution of *n*-butyllithium (2.50 M in tetrahydrofuran, 742 µL, 1.85 mmol, 1.30 equiv) within three hours. After purification by column chromatography (silica, P/Et_2O = 2/1), enone **245** (166 mg, 1.09 mmol, 76%) was obtained as a pale yellow oil.

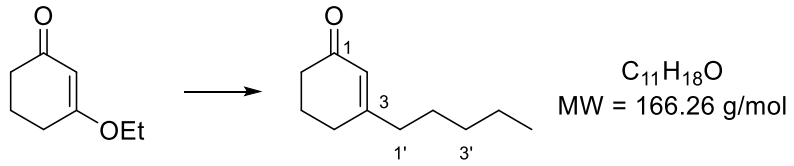
TLC: R_f = 0.41 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.92 (t, ^3J = 7.3 Hz, 3 H, H-4'), 1.29-1.38 (m, 2 H, H-3'), 1.45-1.52 (m, 2 H, H-2'), 1.95-2.02 (m, 2 H, H-5), 2.18-2.23 (m, 2 H, H-1'), 2.26-2.30 (m, 2 H, H-4), 2.33-2.37 (m, 2 H, H-6), 5.87 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.3 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 14.0 (q, C-4'), 22.5 (t, C-3'), 22.9 (t, C-5), 29.2 (t, C-2'), 29.8 (t, C-4), 37.5 (t, C-6), 37.9 (t, C-1'), 125.8 (d, C-2), 167.0 (s, C-3), 200.2 (s, C-1).

The analytical data obtained matched those reported in the literature.[293]

3-Pentylcyclohex-2-en-1-one (246)



118 **246**

Following GP8, enol ether **118** (200 mg, 1.43 mmol, 1.00 equiv) was converted with 1-bromopentane (230 µL, 280 mg, 1.85 mmol, 1.30 equiv), iodine (3.62 mg, 14.3 µmol, 1.00 mol%) and magnesium turnings (45.1 mg, 1.85 mmol, 1.30 equiv) within three hours. After purification by column chromatography (silica, P/Et_2O = 2/1), enone **246** (162 mg, 974 µmol, 68%) was obtained as a pale yellow oil.

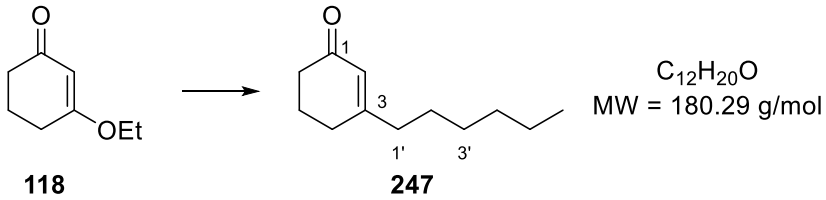
TLC: R_f = 0.38 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.89 (t, ^3J = 7.0 Hz, 3 H, H-5'), 1.25-1.37 (m, 4 H, H-3', H-4'), 1.46-1.54 (m, 2 H, H-2'), 1.92-2.02 (m, 2 H, H-5), 2.18-2.23 (m, 2 H, H-1'), 2.25-2.30 (m, 2 H, H-4), 2.33-2.38 (m, 2 H, H-6), 5.87 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.3 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 14.1 (q, C-5'), 22.6 (t, C-4'), 22.9 (t, C-5), 26.7 (t, C-2'), 29.8 (t, C-4), 31.6 (t, C-3'), 37.5 (t, C-6), 38.2 (t, C-1'), 125.8 (d, C-2), 167.9 (s, C-3), 200.2 (s, C-1).

The analytical data obtained matched those reported in the literature.[292]

3-Hexylcyclohex-2-en-1-one (247)



118 **247**

Following GP8, enol ether **118** (200 mg, 1.43 mmol, 1.00 equiv) was converted with 1-bromohexane (260 µL, 306 mg, 1.85 mmol, 1.30 equiv), iodine (3.62 mg, 14.3 µmol, 1.00 mol%) and magnesium turnings (45.1 mg, 1.85 mmol, 1.30 equiv) within three hours. After purification by column chromatography (silica, P/Et_2O = 2/1), enone **247** (198 mg, 1.10 mmol, 77%) was obtained as a pale yellow oil.

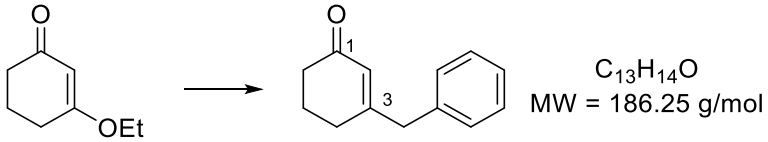
TLC: R_f = 0.38 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.86-0.91 (m, 3 H, H-6'), 1.24-1.35 (m, 6 H, H-3', H-4', H-5'), 1.45-1.53 (m, 2 H, H-2'), 1.95-2.02 (m, 2 H, H-5), 2.18-2.23 (m, 2 H, H-1'), 2.26-2.30 (m, 2 H, H-4), 2.33-2.38 (m, 2 H, H-6), 5.87 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.3 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 14.2 (q, C-6'), 22.7 (t, C-5'), 22.9 (t, C-5), 27.0 (t, C-2'), 29.1 (t, C-3'), 29.8 (t, C-4), 31.7 (t, C-4'), 37.5 (t, C-6), 38.2 (t, C-1'), 125.8 (d, C-2), 167.0 (s, C-3), 200.2 (s, C-1).

The analytical data obtained matched those reported in the literature.[294]

3-Benzylcyclohex-2-en-1-one (248)



118 **248**

Following GP8 excluding the *Grignard* reagent formation, enol ether **118** (200 mg, 1.43 mmol, 1.00 equiv) was converted with benzylmagnesium chloride (2.00 M in tetrahydrofuran, 927 µL, 1.85 mmol, 1.30 equiv) within three hours. After purification by column chromatography (silica, P/Et_2O = 4/1), enone **248** (106 mg, 570 µmol, 40%) was obtained as a pale yellow oil.

TLC: R_f = 0.30 (P/Et_2O = 1/1) [$KMnO_4$, UV].

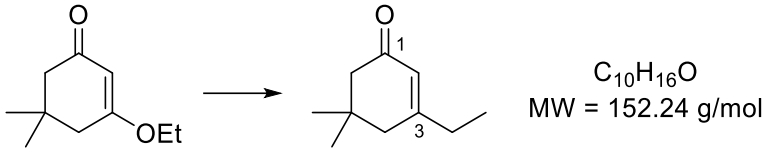
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.93-1.99 (m, 2 H, H-5), 2.24-2.28 (m, 2 H, H-4), 2.34-2.38 (m, 2 H, H-6), 3.51 (s, 2 H, CH_2Ph), 5.87 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.4 Hz, 1 H,

H-2), 7.14-7.18 (m, 2 H, 2 × H-*o*-Ph), 7.23-7.28 (m, 1 H, H-*p*-Ph), 7.29-7.34 (m, 2 H, 2 × H-*m*-Ph).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.8 (t, C-5), 29.4 (t, C-4), 37.5 (t, C-6), 44.7 (t, *C*H_2Ph), 127.0 (d, C-2), 127.0 (d, C-*p*-Ph), 128.8 (d, 2 C, 2 × C-*m*-Ph), 129.2 (d, 2 C, 2 × C-*o*-Ph), 137.1 (s, C-*i*-Ph), 164.9 (s, C-3), 200.1 (s, C-1).

The analytical data obtained matched those reported in the literature.[295]

3-Ethoxy-5,5-dimethylcyclohex-2-en-1-one (249)



143 **249**

Following GP8 excluding the *Grignard* reagent formation, enol ether **143** (200 mg, 1.19 mmol, 1.00 equiv) was converted with ethylmagnesium bromide (3.00 M in tetrahydrofuran, 515 µL, 1.55 mmol, 1.30 equiv) within three hours. After purification by column chromatography (silica, P/Et_2O = 2/1), ketone **249** (111 mg, 726 µmol, 61%) was obtained as a pale yellow oil.

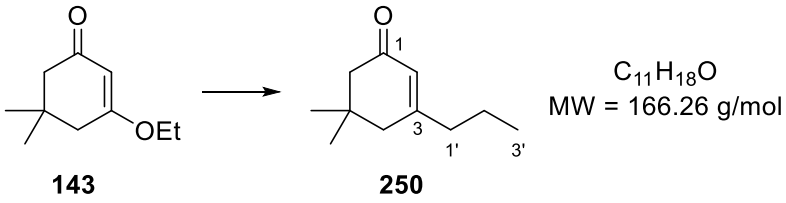
TLC: R_f = 0.48 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.03 (s, 6 H, 2 × Me-5), 1.09 (t, ^{3}J = 7.4 Hz, 3 H, CH_2CH_3-3), 2.16-2.23 (m, 6 H, H-4, H-6, CH_2CH_3-3), 5.88 (*virt.* quint, $^{4}J_1 \approx {}^{4}J_2$ = 1.5 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 11.4 (q, CH_2CH_3-3), 28.4 (q, 2 C, 2 × Me-5), 31.1 (t, *C*H_2CH_3-3), 33.7 (s, C-5), 44.1 (t, C-4), 51.2 (t, C-6), 123.6 (d, C-2), 165.7 (s, C-3), 200.4 (s, C-1).

The analytical data obtained matched those reported in the literature.[296]

5,5-Dimethyl-3-propylcyclohex-2-en-1-one (250)



143 **250**

Following GP8, enol ether **143** (250 mg, 1.49 mmol, 1.00 equiv) was converted with 1-bromopropane (176 µL, 238 mg, 1.93 mmol, 1.30 equiv), iodine (3.77 mg, 14.9 µmol, 1.00 mol%) and magnesium turnings (47.0 mg, 1.93 mmol, 1.30 equiv) within 24 hours. After purification by column chromatography (silica, P/Et_2O = 5/1), enone **250** (128 mg, 770 µmol, 52%) was obtained as a pale yellow oil.

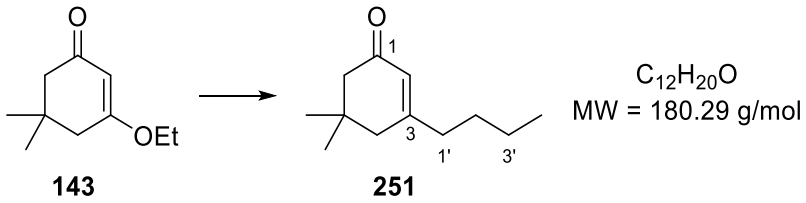
TLC: R_f = 0.51 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.94 (t, ^3J = 7.4 Hz, 3 H, H-3'), 1.03 (s, 6 H, 2 × Me-5), 1.49-1.59 (m, 2 H, H-2'), 2.14-2.18 (m, 4 H, H-4, H-1'), 2.21 (s, 2 H, H-6), 5.87 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.3 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 13.9 (q, C-3'), 20.2 (t, C-2'), 28.4 (q, 2 C, 2 × Me-5), 33.7 (s, C-5), 40.2 (t, C-1'), 44.0 (t, C-4), 51.2 (t, C-6), 124.8 (d, C-2), 164.2 (s, C-3), 200.4 (s, C-1).

The analytical data obtained matched those reported in the literature.[296]

3-Butyl-5,5-dimethylcyclohex-2-en-1-one (251)



143 **251**

Following GP8 excluding the *Grignard* reagent formation, enol ether **143** (200 mg, 1.19 mmol, 1.00 equiv) was converted with a solution of *n*-butyllithium (2.50 M in tetrahydrofuran, 618 µL, 1.55 mmol, 1.30 equiv) within 26 hours. After purification by column chromatography (silica, P/Et_2O = 2/1), enone **251** (162 mg, 896 µmol, 75%) was obtained as a pale yellow oil.

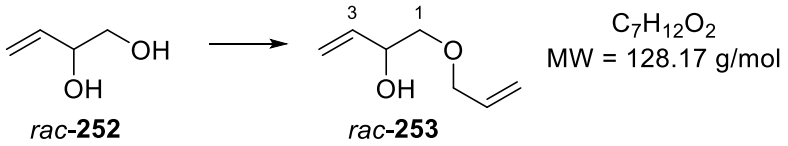
TLC: R_f = 0.55 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.92 (t, ^3J = 7.3 Hz, 3 H, H-4'), 1.03 (s, 6 H, 2 × Me-5), 1.29-1.38 (m, 2 H, H-3'), 1.44-1.51 (m, 2 H, H-2'), 2.15-2.22 (m, 6 H, H-4, H-6, H-1'), 5.87 (*virt.* quint, $^4J_1 \approx {}^4J_2$ = 1.3 Hz, 1 H, H-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 14.0 (q, C-4'), 22.5 (t, C-3'), 28.4 (q, 2 C, 2 × Me-5), 29.1 (t, C-2'), 33.8 (s, C-5), 37.9 (t, C-1'), 44.1 (t, C-4), 51.2 (t, C-6), 124.7 (d, C-2), 164.5 (s, C-3), 200.4 (s, C-1).

The analytical data obtained matched those reported in the literature.[297]

1-(Allyloxy)but-3-en-2-ol (*rac*-253)



rac-**252** *rac*-**253**

According to a literature procedure:[226] A suspension of diol *rac*-**252** (2.86 mL, 3.00 g, 34.1 mmol, 1.00 equiv) and dibutyltin oxide (8.48 g, 34.1 mmol, 1.00 equiv) in dry methanol (262 mL, 130 mM) was stirred for eight hours at reflux at 90 °C. After cooling to room temperature, the solvent was removed in vacuo. Residual methanol was removed by azeotropic distillation (dichloromethane). The residue was dissolved in dichloromethane (262 mL, 130 mM) and allyl bromide (3.18 mL, 4.45 g, 36.8 mmol, 1.08 equiv) was added. The resulting solution was heated at reflux at 70 °C and was stirred for three days. The solvent was removed in vacuo and the residue was dryloaded with an appropriate amount of silica. The dryloaded residue was filtered through a short column (P/Et_2O = 1/0 → 7/3). The product containing fractions were combined and concentrated. After purification of the residue by column chromatography (silica, P/Et_2O = 9/1), alcohol *rac*-**253** (1.01 g, 7.88 mmol, 23%) was obtained as a colorless oil.

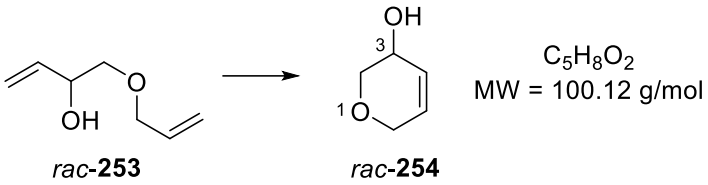
TLC: R_f = 0.41 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 2.39-2.45 (m, 1 H, OH-2), 3.34 (dd, ^2J = 9.6 Hz, ^3J = 8.0 Hz, 1 H, *H*H-1), 3.51 (dd, ^2J = 9.6 Hz, ^3J = 3.4 Hz, 1 H, H*H*-1), 4.04 (dt, ^3J = 5.7 Hz, ^4J = 1.4 Hz, 2 H, OC*H*$_2$CHCH$_2$), 4.30-4.36 (m, 1 H, H-2), 5.18-5.23 (m, 2 H, *H*H-*E*-4, OCH_2CHCHH-*E*), 5.29 (*virt.* dq, ^3J = 17.2 Hz, $^2J \approx {}^4J$ = 1.6 Hz, 1 H, OCH_2CHCHH-*Z*), 5.37 (*virt.* dt, ^3J = 17.3 Hz, $^2J \approx {}^4J$ = 1.5 Hz, 1 H, H*H*-*Z*-4), 5.80-5.96 (m, 2 H, H-3, OCH_2CHCH_2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 71.7 (d, C-2), 72.4 (t, O*C*H_2CHCH_2), 74.0 (t, C-1), 116.7 (t, C-4), 117.6 (t, OCH_2CH*C*H_2), 134.5 (d, OCH_2*C*HCH_2), 136.6 (d, C-3).

The analytical data obtained matched those reported in the literature.[226]

3,6-Dihydro-2*H*-pyran-3-ol (*rac*-254)



rac-**253** *rac*-**254**

According to a literature procedure:[226] A solution of alcohol *rac*-**253** (500 mg, 3.90 mmol, 1.00 equiv) in dichloromethane (6.0 mL) was added to a solution of the *Grubbs-Hoveyda* II catalyst (24.4 mg, 39.0 μmol, 1.00 mol%) in dichloromethane (150 mL) at room temperature. The resulting green mixture was stirred in an open reaction vessel in order to continuously remove produced ethylene. After two hours, ethyl vinyl ether (2.0 mL) was added in order to decompose the catalyst. The reaction solution turns brown. After removal of the solvent in vacuo, the residue was purified by column chromatography (silica, P/Et_2O = 1/1) to afford alcohol *rac*-**254** (312 mg, 3.12 mmol, 80%) as a colorless oil.

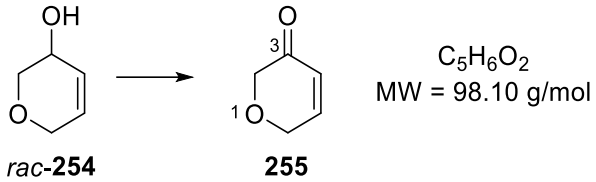
TLC: R_f = 0.13 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.94 (d, ^3J = 9.3 Hz, 1 H, OH-3), 3.74 (dd, ^2J = 11.8 Hz, ^3J = 3.0 Hz, 1 H, *H*H-2), 3.85 (ddd, ^2J = 11.8 Hz, ^3J = 2.9 Hz, ^4J = 1.0 Hz, 1 H, H*H*-2), 3.95-4.01 (m, 1 H, H-3), 4.06 (*virt.* dq, ^2J = 16.9 Hz, $^3J \approx {}^4J_1 \approx {}^4J_2$ = 2.1 Hz, 1 H, *H*H-6), 4.16 (*virt.* ddt, ^2J = 16.9 Hz, ^3J = 3.1 Hz, $^4J_1 \approx {}^4J_2$ = 1.3 Hz, 1 H, H*H*-6), 5.90-5.94 (m, 1 H, H-5), 5.96-6.01 (m, 1 H, H-4).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 62.8 (d, C-3), 65.5 (t, C-6), 70.9 (t, C-2), 126.8 (d, C-4), 130.1 (d, C-5).

The analytical data obtained matched those reported in the literature.[226]

2*H*-Pyran-3(6*H*)-one (255)



rac-**254** **255**

According to a literature procedure:[226] In a round-bottom flask, molecular sieve powder (4 Å, 1.00 g) was activated and a solution of tetrapropylammonium perruthenate (54.8 mg, 156 μmol, 5.00 mol%) and *N*-methylmorpholine *N*-oxide (1.20 g, 10.2 mmol, 3.28 equiv) in dichloromethane (20 mL) was added at room temperature. Alcohol *rac*-**254** (312 mg, 3.12 mmol, 1.00 equiv) was added to the resulting suspension which was stirred for five hours. The reaction mixture was treated with silica (2 g) and the solvent was removed in vacuo. After purification of the residue by column chromatography (silica, P/Et_2O = 1/1), enone **255** (179 mg, 1.83 mmol, 59%) was obtained as a pale yellow oil. [*N.b.*: This substrate is not bench-stable and should be stored under argon at –20 °C.]

TLC: R_f = 0.25 (P/Et_2O = 1/1) [$KMnO_4$, UV].

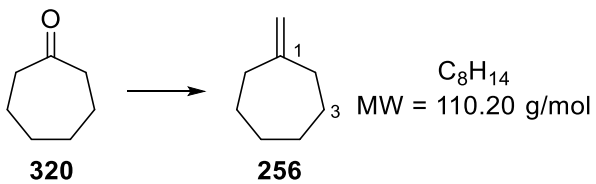
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 4.17 (s, 2 H, H-2), 4.37 (*virt.* t, $^3J \approx {}^4J$ = 2.5 Hz, 2 H, H-6), 6.18 (dt, ^3J = 10.6 Hz, ^4J = 2.1 Hz, 1 H, H-4), 7.10 (dt, ^3J = 10.6 Hz, ^4J = 3.1 Hz, 1 H, H-5).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 64.7 (t, C-6), 72.4 (t, C-2), 127.0 (d, C-4), 148.4 (d, C-5), 194.6 (s, C-3).

The analytical data obtained matched those reported in the literature.[226]

6.3.10 Synthesis of Alkenes

Methylenecycloheptane (256)



320 **256**

Following GP9, cycloheptanone (**320**) (13.0 mL, 12.3 g, 110 mmol, 1.10 equiv) was converted with methyltriphenylphosphonium bromide (35.7 g, 100 mmol, 1.00 equiv) and sodium hydride (60 wt% in paraffin oil, 4.00 g, 100 mmol, 1.00 equiv) in dimethylsulfoxide (150 mL).

Following fractioned distillation, alkene **256** (7.69 g, 69.8 mmol, 70%) was obtained as a colorless oil.

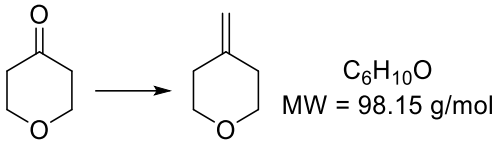
Bp: 50 °C (50 mbar).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.49-1.82 (m, 8 H, H-3, H-4, H-5, H-6), 2.25-2.30 (m, 4 H, H-2, H-7), 4.68 (quint, ^4J = 1.0 Hz, 2 H, H_2C-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 28.6 (t, 2 C, C-3, C-6), 29.7 (t, 2 C, C-4, C-5), 36.3 (t, 2 C, C-2, C-7), 110.4 (t, H_2C-1), 152.5 (s, C-1).

The analytical data obtained matched those reported in the literature.[298]

4-Methylenetetrahydro-2*H*-pyran (257)



257

Following GP9, tetrahydro-4*H*-pyran-4-one (4.95 g, 49.4 mmol, 1.10 equiv) was converted with methyltriphenylphosphonium bromide (16.1 g, 45.0 mmol, 1.00 equiv) and sodium hydride (60 wt% in paraffin oil, 1.80 g, 45.0 mmol, 1.00 equiv) in dimethylsulfoxide (68 mL). Following fractioned distillation, alkene **257** (1.19 g, 12.1 mmol, 27%) was obtained as a colorless oil.

Bp: 60 °C (30 mbar).

TLC: R_f = 0.37 (P/Et_2O = 9/1) [$KMnO_4$].

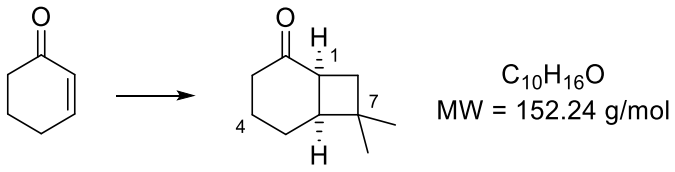
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 2.14-2.17 (m, 4 H, 2 × OCH_2CH_2), 3.58-3.60 (m, 4 H, 2 × OCH_2CH_2), 4.62 (quint, ^4J = 1.0 Hz, 2 H, CCH_2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 35.7 (t, 2 C, 2 × OCH_2CH_2), 69.5 (t, 2 C, 2 × OCH_2CH_2), 108.4 (t, CCH_2), 144.7 (s, CCH_2).

The analytical data obtained matched those reported in the literature.[299]

6.3.11 Intermolecular [2+2] Photocycloaddition Reactions

(1*S*,6*S*)-7,7-Dimethylbicyclo[4.2.0]octan-2-one (229)



238 **229**

Racemic [2+2] Photocycloaddition:

Following GP10, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and isobutene (approx. 1 mL) were irradiated in dichloromethane (9 mL) for 24 hours. After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 4/1, long), ketone *rac*-**229** (16.2 mg, 106 µmol, 53%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and isobutene (approx. 1 mL) were irradiated in dichloromethane (9 mL). After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 4/1, long), ketone **229** (18.4 mg, 121 µmol, 60%, 91% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.51 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.97 (s, 3 H, Me-7), 1.15 (s, 3 H, Me-7), 1.56-1.68 (m, 1 H, *H*H-5), 1.69-1.80 (m, 2 H, *H*H-4, H*H*-5), 1.94-2.04 (m, 3 H, H*H*-4, H-8), 2.32-2.36 (m, 2 H, H-3), 2.38-2.45 (m, 1 H, H-6), 2.95 (*virt.* q, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 8.9 Hz, 1 H, H-1).

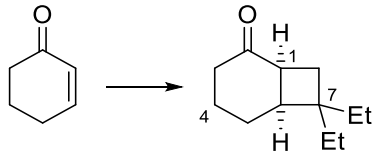
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.8 (t, C-4), 23.2 (t, C-5), 24.1 (q, Me-7), 30.0 (q, Me-7), 36.3 (s, C-7), 37.5 (t, C-8), 39.7 (d, C-1), 39.7 (t, C-3), 45.1 (d, C-6), 216.0 (s, C-2).

Chiral GC: τ_R (major) = 35.2 min, τ_R (minor) = 35.4 min, [60 °C (0.5 min), 85 °C (15 °C/min), 85 °C (30 min), 200 °C (15 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +163 (c = 1.39, CH_2Cl_2) [91% *ee*].

The analytical data obtained matched those reported in the literature.[300]

(1*S*,6*S*)-7,7-Diethylbicyclo[4.2.0]octan-2-one (240)



238 **240**

$C_{12}H_{20}O$
MW = 180.29 g/mol

Racemic [2+2] Photocycloaddition:

Following GP10, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and 2-ethylbut-1-ene (**239**) (733 µL, 505 mg, 6.00 mmol, 30.0 equiv) were irradiated in dichloromethane (9.27 mL) for 22 hours. After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 5/1, long), ketone *rac*-**240** (18.5 mg, 103 µmol, 51%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **238** (9.61 mg, 100 µmol, 1.00 equiv) and 2-ethylbut-1-ene (**239**) (611 µL, 421 mg, 5.00 mmol, 50.0 equiv) were irradiated in dichloromethane (4.39 mL). After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 5/1, long), ketone **240** (13.1 mg, 72.6 µmol, 73%, 90% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.61 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2961 (s, sp^3-CH), 2936 (s, sp^3-CH), 2875 (m, sp^3-CH), 1702 (vs, C=O), 1457 (s, sp^3-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.70 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 0.77 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 1.31 (dq, ^2J = 14.5 Hz, ^3J = 7.4 Hz, 1 H, $CHHCH_3$), 1.37-1.57 (m, 3 H, $CHHCH_3$, CH_2CH_3), 1.57-1.65 (m, 1 H, *H*H-5), 1.69-1.80 (m, 2 H, *H*H-4, H*H*-5), 1.89-2.02 (m, 3 H, H*H*-4, H-8), 2.27-2.38 (m, 2 H, H-3), 2.48 (*virt.* tdd, $^3J_1 \approx {}^3J_2$ = 9.1 Hz, $^3J_3$ = 7.4 Hz, ^4J = 1.4 Hz, 1 H, H-6), 2.90 (*virt.* td, $^3J_1 \approx {}^3J_2$ = 9.5 Hz, $^3J_3$ = 8.1 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 8.0 (q, CH_2CH_3), 8.3 (q, CH_2CH_3), 22.9 (t, C-4), 23.0 (t, C-5), 24.9 (t, CH_2CH_3), 30.2 (t, CH_2CH_3), 34.6 (t, C-8), 39.5 (t, C-3), 39.6 (d, C-1), 42.8 (s, C-7), 43.8 (d, C-6), 216.5 (s, C-2).

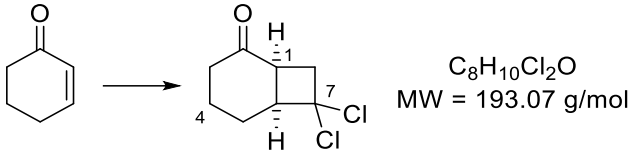
MS (EI, 70 eV): m/z (%) = 180 (9) $[M]^+$, 151 (14) $[M–C_2H_5]^+$, 97 (100) $[C_6H_9O]^+$, 84 (36) $[C_6H_{12}]^+$, 69 (42), 55 (25) $[C_4H_7]^+$, 41 (14).

HRMS (EI, 70 eV): calcd for $C_{12}H_{20}O$ $[M]^+$: 180.1509; found: 180.1508;
calcd for $C_{11}{}^{13}CH_{20}O$ $[M]^+$: 181.1542; found: 181.1547.

Chiral GC: τ_R (minor) = 134.3 min, τ_R (major) = 136.1 min, [60 °C (1 min), 105 °C (30 °C/min), 105 °C (127.5 min), 135 °C (3 °C/min), 200 °C (20 °C/min), 200 °C (3 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +113 (c = 1.05, CH_2Cl_2) [90% *ee*].

(1*S*,6*S*)-7,7-Dichlorobicyclo[4.2.0]octan-2-one (279)



238 **279**

Racemic [2+2] Photocycloaddition:

Following GP10, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and 1,1-dichloroethylene (801 µL, 969 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (9.20 mL) for 15 hours. After applying WP2 with eluent-mixture (P/Et_2O = 6/1), ketone *rac*-**279** (12.6 mg, 65.2 µmol, 33%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and 1,1-dichloroethylene (801 µL, 969 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (9.20 mL). After applying WP2 with eluent-mixture (P/Et_2O = 6/1), ketone **279** (26.4 mg, 137 µmol, 68%, 83% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.43 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2951 (m, sp^3-CH), 2876 (w, sp^3-CH), 1705 (vs, C=O), 706 (s, sp^3-CCl).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.81-1.90 (m, 1 H, *H*H-4), 1.93-2.06 (m, 2 H, H-5), 2.12-2.22 (m, 1 H, H*H*-4), 2.32-2.48 (m, 2 H, H-3), 3.10-3.24 (m, 3 H, H-1, H-8), 3.52-3.61 (m, 1 H, H-6).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 21.7 (t, C-4), 24.1 (t, C-5), 39.0 (d, C-1), 39.1 (t, C-3), 48.6 (t, C-8), 55.8 (d, C-6), 85.6 (s, C-7), 210.7 (s, C-2).

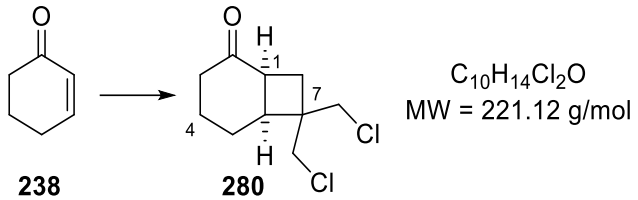
MS (EI, 70 eV): m/z (%) = 192 (6) $[M]^+$, 157 (24) $[M–Cl]^+$, 121 (16) $[M–Cl_2]^+$, 96 (36) $[M–C_2H_2Cl_2]^+$, 68 (100), 54 (30).

HRMS (EI, 70 eV): calcd for $C_8H_{10}O^{35}Cl$ $[M–Cl]^+$: 157.0415; found: 157.0404.

Chiral GC: τ_R (major) = 12.1 min, τ_R (minor) = 12.3 min, [60 °C (0 min), 170 °C (30 °C/min), 170 °C (8.4 min), 240 °C (30 °C/min), 240 °C (3 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +112 (c = 1.31, CH_2Cl_2) [83% *ee*].

(1*S*,6*S*)-7,7-Bis(chloromethyl)bicyclo[4.2.0]octan-2-one (280)



Racemic [2+2] Photocycloaddition:

Following GP10, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and 3-chloro-2-(chloromethyl)-prop-1-ene (1.06 mL, 1.25 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (8.94 mL) for 22 hours. After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 5/1, long) [*n.b.*: Three days of stirring over basic alumina are required], ketone *rac*-**280** (15.0 mg, 67.8 µmol, 34%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and 3-chloro-2-(chloromethyl)-prop-1-ene (1.06 mL, 1.25 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (8.94 mL). After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 5/1, long) [*n.b.*: Three days of stirring over basic alumina are required], ketone **280** (30.7 mg, 139 µmol, 69%, 92% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.35 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2944 (w, sp^3-CH), 2869 (w, sp^3-CH), 1700 (vs, C=O), 1437 (s), 1273 (m), 725 (vs, sp^3-CCl).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.62 (dddd, ^2J = 13.8 Hz, $^3J_1$ = 10.9 Hz, $^3J_2$ = 9.2 Hz, $^3J_3$ = 2.9 Hz, 1 H, *H*H-5), 1.77-1.87 (m, 1 H, *H*H-4), 1.90-2.05 (m, 2 H, H*H*-4, H*H*-5), 2.15 (*virt.* ddt, ^2J = 12.9 Hz, ^3J = 7.6 Hz, $^4J_1 \approx {}^4J_2$ = 0.9 Hz, 1 H, *H*H-8), 2.23 (ddd,

^2J = 12.9 Hz, ^3J = 10.0 Hz, ^4J = 1.9 Hz, 1 H, H*H*-8), 2.32-2.45 (m, 2 H, H-3), 2.72-2.79 (m, 1 H, H-6), 2.97 (*virt.* td, $^3J_1 \approx {}^3J_2$ = 9.8 Hz, $^3J_3$ = 7.6 Hz, 1 H, H-1), 3.67 (s, 2 H, CH_2Cl), 3.75-3.81 (m, 2 H, CH_2Cl).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.5 (t, C-4), 22.7 (t, C-5), 31.0 (t, C-8), 38.3 (d, C-1), 39.2 (t, C-3), 42.1 (d, C-6), 45.2 (s, C-7), 45.9 (t, CH_2Cl), 49.8 (t, CH_2Cl), 213.8 (s, C-2).

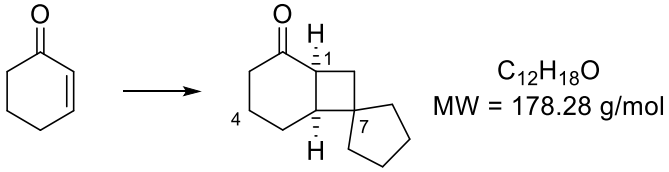
MS (EI, 70 eV): m/z (%) = 220 (4) $[M]^+$, 185 (15) $[M–Cl]^+$, 149 (27) $[M–Cl_2]^+$, 96 (36) $[C_6H_8O]^+$, 79 (24), 68 (100) $[C_5H_8]^+$, 55 (22) $[C_4H_7]^+$, 41 (9).

HRMS (EI, 70 eV): calcd for $C_{10}H_{14}O^{35}Cl_2$ $[M]^+$: 220.0416; found: 220.0416;
calcd for $C_9{}^{13}CH_{14}O^{35}Cl_2$ $[M]^+$: 221.0450; found: 221.0448.

Chiral GC: τ_R (major) = 33.6 min, τ_R (minor) = 33.7 min, [60 °C (0.5 min), 200 °C (4 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +142 (c = 1.03, CH_2Cl_2) [92% *ee*].

(1*S*,6*S*)-Spiro{bicyclo[4.2.0]octan-7,1'-cyclopentan}-2-one (281)



238 **281**

Racemic [2+2] Photocycloaddition:

Following GP10, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and methylenecyclopentane (1.06 mL, 821 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (8.94 mL) for 13 hours. After applying WP1 with eluent-mixtures (P/Et_2O = 6/1, short) and (P/Et_2O = 6/1, long), ketone *rac*-**281** (19.5 mg, 109 µmol, 55%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and methylenecyclopentane (1.06 mL, 821 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (8.94 mL). After applying WP1 with eluent-mixtures (P/Et_2O = 6/1, short) and (P/Et_2O = 6/1, long), ketone **281** (12.0 mg, 67.3 µmol, 34%, 30% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.55 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2936 (s, sp^3-CH), 2857 (m, sp^3-CH), 1699 (vs, C=O), 1451 (w, sp^3-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.32-1.40 (m, 1 H, 1 × H-cPent), 1.47-1.82 (m, 10 H, *H*H-4, H-5, 7 × H-cPent), 1.95-2.03 (m, 1 H, H*H*-4), 2.04-2.15 (m, 2 H, H-8), 2.28-2.42 (m, 2 H, H-3), 2.51-2.57 (m, 1 H, H-6), 2.94 (*virt.* dtd, $^3J_1$ = 9.4 Hz, $^3J_2 \approx {}^3J_3$ = 8.3 Hz, ^4J = 1.0 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.9 (t, C-4), 23.5 (t, C-cPent), 23.8 (t, C-cPent), 24.1 (t, C-5), 33.6 (t, C-cPent), 37.4 (t, C-8), 39.7 (t, C-3), 40.2 (t, C-cPent), 40.9 (d, C-1), 44.1 (d, C-6), 47.8 (s, C-7), 215.5 (s, C-2).

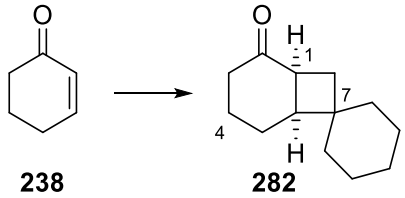
MS (EI, 70 eV): m/z (%) = 178 (12) $[M]^+$, 97 (100) $[M–C_6H_9]^+$, 79 (18), 67 (43), 54 (8), 41 (7).

HRMS (EI, 70 eV): calcd for $C_{12}H_{20}O$ $[M]^+$: 178.1352; found: 178.1355.

Chiral GC: τ_R (minor) = 143.7 min, τ_R (major) = 143.8 min, [60 °C (1 min), 105 °C (30 °C/min), 105 °C (127.5 min), 135 °C (3 °C/min), 200 °C (20 °C/min), 200 °C (3 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +37.9 (c = 1.05, CH_2Cl_2) [30% *ee*].

(1*S*,6*S*)-Spiro[bicyclo[4.2.0]octan-7,1'-cyclohexan]-2-one (282)



238 282

$C_{13}H_{20}O$
MW = 192.30 g/mol

Racemic [2+2] Photocycloaddition:

Following GP10, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and methylenecyclohexane (1.20 mL, 962 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (8.80 mL) for 15 hours. After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 6/1, long), ketone *rac*-**282** (21.2 mg, 110 µmol, 55%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and methylenecyclohexane (1.20 mL, 962 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (8.80 mL). After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 6/1, long), ketone **282** (19.2 mg, 99.8 µmol, 50%, 87% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.55 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2923 (vs, sp^3-CH), 2851 (s, sp^3-CH), 1701 (vs, C=O), 1446 (m, sp^3-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.21-1.58 (m, 10 H, 10 × H-cyHex), 1.61-1.69 (m, 1 H, *H*H-5), 1.70-1.80 (m, 2 H, *H*H-4, H*H*-5), 1.93-2.04 (m, 3 H, H*H*-4, H-8), 2.32-2.35 (m, 2 H, H-3), 2.40 (*virt.* dtd, $^3J_1$ = 9.0 Hz, $^3J_2 \approx {}^3J_3$ = 7.1 Hz, ^4J = 1.9 Hz, 1 H, H-6), 2.93 (*virt.* td, $^3J_1 \approx {}^3J_2$ = 9.5 Hz, $^3J_3$ = 8.0 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.5 (t, C-5), 22.9 (t, C-4), 23.1 (t, C-cyHex), 23.2 (t, C-cyHex), 26.2 (t, C-cyHex), 33.6 (t, C-cyHex), 35.2 (t, C-8), 38.8 (t, C-cyHex), 39.6 (t, C-3), 39.8 (d, C-1), 40.2 (s, C-7), 44.4 (d, C-6), 216.2 (s, C-2).

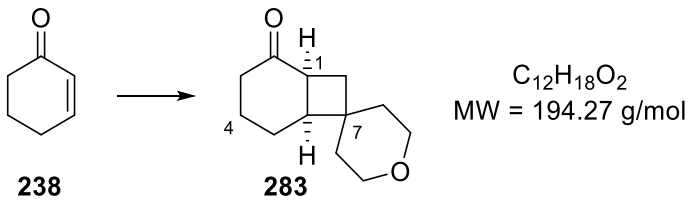
MS (EI, 70 eV): m/z (%) = 192 (14) $[M]^+$, 97 (100) $[M–C_7H_{11}]^+$, 81 (32) $[C_6H_9]^+$, 67 (18), 55 (10) $[C_4H_7]^+$, 41 (6).

HRMS (EI, 70 eV): calcd for $C_{13}H_{20}O$ $[M]^+$: 192.1509; found: 192.1508;
calcd for $C_{12}{}^{13}CH_{20}O$ $[M]^+$: 193.1542; found: 193.1544.

Chiral GC: τ_R (minor) = 55.4 min, τ_R (major) = 56.5 min, [60 °C (0.5 min), 120 °C (10 °C/min), 120 °C (52 min), 200 °C (15 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +91.7 (c = 1.13, CH_2Cl_2) [87% *ee*].

(1*S*,6*S*)-Tetrahydrospiro{bicyclo[4.2.0]octan-7,4'-pyran}-2-one (283)



Racemic [2+2] Photocycloaddition:

Following GP10, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and 4-methylenetetrahydro-2*H*-pyran (**257**) (981 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (9.02 mL) for 24 hours. After applying WP1 with eluent-mixtures (P/Et_2O = 1/1, short) and (P/Et_2O = 1/1, long), ketone *rac*-**283** (15.4 mg, 79.3 µmol, 40%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **238** (19.2 mg, 200 μmol, 1.00 equiv) and 4-methylenetetrahydro-2*H*-pyran (**257**) (981 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (9.02 mL). After applying WP1 with eluent-mixtures (P/Et_2O = 1/1, short) and (P/Et_2O = 1/1, long), ketone **283** (22.8 mg, 117 μmol, 59%, 82% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.11 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2931 (s, sp^3-CH), 2840 (m, sp^3-CH), 1699 (vs, C=O), 1229 (s, sp^3-CO), 1108 (vs, sp^3-CO), 839 (m).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.44 (dddd, ^2J = 13.4 Hz, $^3J_1$ = 5.0 Hz, $^3J_2$ = 3.0 Hz, ^4J = 1.6 Hz, 1 H, OCH_2CHH), 1.57-1.73 (m, 4 H, *H*H-5, OCH_2CHH, OCH_2CH_2), 1.74-1.84 (m, 2 H, *H*H-4, H*H*-5), 1.94-2.03 (m, 1 H, H*H*-4), 2.07-2.17 (m, 2 H, H-8), 2.33-2.38 (m, 2 H, H-3), 2.51 (*virt.* dtd, $^3J_1$ = 8.7 Hz, $^3J_2 \approx {}^3J_3$ = 7.2 Hz, ^4J = 1.3 Hz, 1 H, H-6), 2.94-3.01 (m, 1 H, H-1), 3.47 (ddd, ^2J = 11.7 Hz, $^3J_1$ = 9.2 Hz, $^3J_2$ = 3.0 Hz, 1 H, $OCHHCH_2$), 3.54 (ddd, ^2J = 11.7 Hz, $^3J_1$ = 9.2 Hz, $^3J_2$ = 3.0 Hz, 1 H, $OCHHCH_2$), 3.63 (*virt.* dt, ^2J = 11.7 Hz, $^3J_1 \approx {}^3J_2$ = 4.6 Hz, 1 H, $OCHHCH_2$), 3.69 (*virt.* dt, ^2J = 11.7 Hz, $^3J_1 \approx {}^3J_2$ = 4.6 Hz, 1 H, $OCHHCH_2$).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.3 (t, C-5), 22.9 (t, C-4), 33.8 (t, OCH_2CH_2), 34.6 (t, C-8), 38.0 (s, C-7), 38.6 (t, OCH_2CH_2), 39.6 (t, C-3), 39.7 (d, C-1), 44.6 (d, C-6), 64.7 (t, OCH_2CH_2), 64.9 (t, OCH_2CH_2), 215.4 (s, C-2).

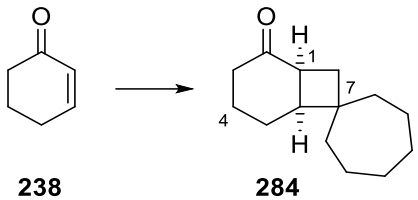
MS (EI, 70 eV): m/z (%) = 194 (17) $[M]^+$, 124 (9) $[C_8H_{12}O]^+$, 97 (100) $[C_6H_9O]^+$, 83 (15), 79 (19), 68 (44), 55 (11).

HRMS (EI, 70 eV): calcd for $C_{12}H_{18}O_2$ $[M]^+$: 194.1301; found: 194.1302;
calcd for $C_{11}{}^{13}CH_{18}O_2$ $[M]^+$: 195.1335; found: 195.1339.

Chiral GC: τ_R (major) = 107.4 min, τ_R (minor) = 108.1 min, [60 °C (0.5 min), 90 °C (10 °C/min), 150 °C (0.5 °C/min), 200 °C (10 °C/min), 200 °C (3 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +136 (c = 1.30, CH_2Cl_2) [82% *ee*].

(1*S*,6*S*)-Spiro{bicyclo[4.2.0]octan-7,1'-cycloheptan}-2-one (284)



238 284

$C_{14}H_{22}O$
MW = 206.23 g/mol

Racemic [2+2] Photocycloaddition:

Following GP10, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and methylenecycloheptane (**256**) (1.33 mL, 1.10 g, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (8.67 mL) for 22 hours. After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 4/1, long), ketone *rac*-**284** (27.3 mg, 132 µmol, 66%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and methylenecycloheptane (**256**) (1.33 mL, 1.10 g, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (8.67 mL). After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 4/1, long), ketone **284** (17.3 mg, 83.8 µmol, 42%, 85% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.50 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2921 (s, sp^3-CH), 2854 (m, sp^3-CH), 1700 (vs, C=O), 1457 (s, sp^3-CH), 822 (m).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.34-1.80 (m, 15 H, *H*H-4, H-5, 12 × H-cHept), 1.91-2.05 (m, 3 H, H*H*-4, H-8), 2.31-2.35 (m, 2 H, H-3), 2.43 (*virt.* tdd, $^3J_1 \approx {}^3J_2$ = 9.1 Hz, $^3J_3$ = 6.9 Hz, ^4J = 2.1 Hz, 1 H, H-6), 2.92 (*virt.* td, $^3J_1 \approx {}^3J_2$ = 9.5 Hz, $^3J_3$ = 8.2 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.7 (t, C-4), 23.0 (t, C-cHept), 23.1 (t, C-cHept), 23.3 (t, C-5), 28.3 (t, C-cHept), 28.4 (t, C-cHept), 36.3 (t, C-cHept), 36.8 (t, C-8), 39.5 (t, C-3), 39.6 (d, C-1), 41.8 (t, C-cHept), 42.9 (s, C-7), 45.4 (d, C-6), 216.3 (s, C-2).

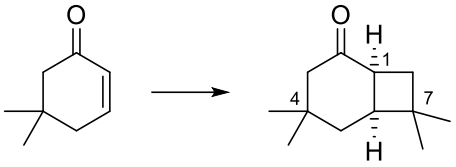
MS (EI, 70 eV): m/z (%) = 206 (9) $[M]^+$, 136 (5), 122 (8) $[C_8H_{10}O]^+$, 110 (12) $[C_8H_{14}]^+$, 97 (100) $[C_6H_9O]^+$, 82 (25) $[C_6H_{10}]^+$, 67 (21) $[C_5H_7]^+$, 55 (6).

HRMS (EI, 70 eV): calcd for $C_{14}H_{22}O$ $[M]^+$: 206.1665; found: 206.1653;
calcd for $C_{13}{}^{13}CH_{22}O$ $[M]^+$: 207.1699; found: 207.1685.

Chiral GC: τ_R (minor) = 111.5 min, τ_R (major) = 113.5 min, [60 °C (0.5 min), 120 °C (10 °C/min), 120 °C (109 min), 200 °C (15 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +105 (c = 1.30, CH_2Cl_2) [85% *ee*].

(1*S*,6*S*)-4,4,7,7-Tetramethylbicyclo[4.2.0]octan-2-one (285)



242 **285**

Racemic [2+2] Photocycloaddition:

Following GP10, enone **242** (24.8 mg, 200 µmol, 1.00 equiv) and isobutene (approx. 1 mL) were irradiated in dichloromethane (9.00 mL) for 22 hours. After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 10/1, long), ketone *rac*-**285** (20.8 mg, 115 µmol, 58%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **242** (24.8 mg, 200 µmol, 1.00 equiv) and isobutene (approx. 1 mL) were irradiated in dichloromethane (9.00 mL). After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 10/1, long), ketone **285** (26.1 mg, 145 µmol, 72%, 93% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.62 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2952 (s, sp^3-CH), 2929 (s, sp^3-CH), 2866 (m, sp^3-CH), 1697 (vs, C=O), 1457 (m, sp^3-CH), 1368 (m, sp^3-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.85 (s, 3 H, Me-4), 0.97 (s, 3 H, Me-7), 1.05 (s, 3 H, Me-4), 1.21 (s, 3 H, Me-7), 1.53 (dddd, ^2J = 13.7 Hz, ^3J = 7.7 Hz, $^4J_1$ = 2.7 Hz, $^4J_2$ = 0.8 Hz, 1 H, *H*H-5), 1.65 (dd, ^2J = 13.7 Hz, ^3J = 11.8 Hz, 1 H, H*H*-5), 1.95-1.99 (m, 2 H, H-8), 2.09 (ddd, ^2J = 16.5 Hz, $^4J_1$ = 2.7 Hz, $^4J_2$ = 1.4 Hz, 1 H, *H*H-3), 2.21 (*virt.* dt, ^2J = 16.5 Hz, $^4J_1 \approx {}^4J_2$ = 0.9 Hz, 1 H, H*H*-3), 2.30 (*virt.* dtd, $^3J_1$ = 11.8 Hz, $^3J_2 \approx {}^3J_3$ = 7.8 Hz, ^4J = 1.9 Hz, 1 H, H-6), 2.93 (*virt.* q, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 9.1 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 24.1 (q, Me-7), 25.6 (q, Me-4), 29.1 (q, Me-7), 31.8 (q, Me-4), 34.0 (s, C-4), 35.0 (s, C-7), 36.2 (t, C-5), 37.0 (t, C-8), 38.5 (d, C-1), 42.3 (d, C-6), 52.8 (t, C-3), 215.5 (s, C-2).

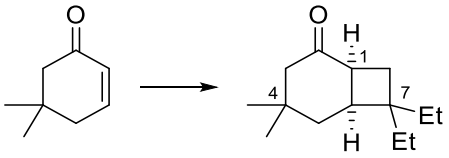
MS (EI, 70 eV): m/z (%) = 180 (17) $[M]^+$, 125 (100) $[M–C_4H_7]^+$, 110 (14) $[C_7H_{10}O]^+$, 95 (11) $[C_6H_7O]^+$, 68 (49), 55 (25) $[C_4H_7]^+$, 41 (19).

HRMS (EI, 70 eV): calcd for $C_{12}H_{20}O$ $[M]^+$: 180.1509; found: 180.1494.

Chiral GC: τ_R (major) = 25.9 min, τ_R (minor) = 27.5 min, [60 °C (0.5 min), 90 °C (10 °C/min), 150 °C (0.5 °C/min), 200 °C (10 °C/min), 200 °C (3 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +228 (c = 1.12, CH_2Cl_2) [93% *ee*].

(1*S*,6*S*)-7,7-Diethyl-4,4-dimethylbicyclo[4.2.0]octan-2-one (286)



$C_{14}H_{24}O$
MW = 208.35 g/mol

242 **286**

Racemic [2+2] Photocycloaddition:

Following GP10, enone **242** (24.8 mg, 200 µmol, 1.00 equiv) and 2-ethylbut-1-ene (**239**) (1.22 mL, 842 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (8.78 mL) for 22 hours. After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 10/1, long), ketone *rac*-**286** (26.2 mg, 126 µmol, 63%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **242** (24.8 mg, 200 µmol, 1.00 equiv) and 2-ethylbut-1-ene (**239**) (1.22 mL, 842 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (8.78 mL). After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 10/1, long), ketone **286** (27.2 mg, 131 µmol, 65%, 96% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.67 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2958 (s, sp^3-CH), 2933 (s, sp^3-CH), 2871 (m, sp^3-CH), 1698 (vs, C=O), 1459 (s, sp^3-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.69 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 0.79 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 0.88 (s, 3 H, Me-4), 1.04 (s, 3 H, Me-4), 1.29-1.45 (m, 2 H, CH_2CH_3), 1.49-1.62 (m, 3 H, *H*H-5, CH_2CH_3), 1.66 (dd, ^2J = 14.6 Hz, ^3J = 10.7 Hz, 1 H, H*H*-5), 1.80 (dd, ^2J = 11.4 Hz, ^3J = 9.2 Hz, 1 H, *H*H-8), 1.98 (ddd, ^2J = 11.4 Hz, ^3J = 9.9 Hz, ^4J = 2.8 Hz, 1 H, H*H*-8), 2.09 (ddd, ^2J = 16.8 Hz, $^4J_1$ = 2.6 Hz, $^4J_2$ = 1.3 Hz, 1 H, *H*H-3), 2.18

(d, ^2J = 16.8 Hz, 1 H, H*H*-3), 2.33-2.40 (m, 1 H, H-6), 2.85 (*virt.* q, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 9.2 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 8.2 (q, CH_2CH_3), 8.4 (q, CH_2CH_3), 25.2 (t, CH_2CH_3), 25.8 (q, Me-4), 29.0 (t, CH_2CH_3), 31.9 (q, Me-4), 33.9 (s, C-4), 34.2 (t, C-8), 35.5 (t, C-5), 38.3 (d, C-1), 40.6 (d, C-6), 41.6 (s, C-7), 52.7 (t, C-3), 216.0 (s, C-2).

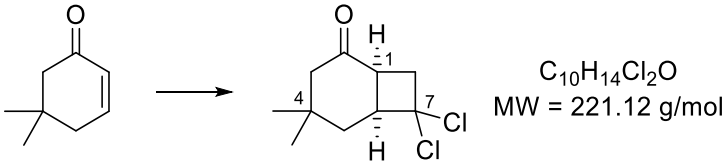
MS (EI, 70 eV): m/z (%) = 208 (10) $[M]^+$, 179 (7) $[M–C_2H_5]^+$, 138 (7), 125 (100) $[M–C_6H_{11}]^+$, 109 (8), 95 (7) $[C_6H_7O]^+$, 84 (13), 69 (25), 55 (17) $[C_4H_7]^+$, 41 (8).

HRMS (EI, 70 eV): calcd for $C_{14}H_{24}O$ $[M]^+$: 208.1822; found: 208.1803;
calcd for $C_{13}{}^{13}CH_{24}O$ $[M]^+$: 209.1855; found: 209.1843.

Chiral GC: τ_R (major) = 86.7 min, τ_R (minor) = 86.8 min, [60 °C (0.5 min), 90 °C (15 °C/min), 90 °C (80 min), 200 °C (15 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +202 (c = 1.00, CH_2Cl_2) [96% *ee*].

(1*S*,6*S*)-7,7-Dichloro-4,4-dimethylbicyclo[4.2.0]octan-2-one (287)



242 **287**

Racemic [2+2] Photocycloaddition:

Following GP10, enone **242** (24.8 mg, 200 µmol, 1.00 equiv) and 1,1-dichloroethylene (801 µL, 969 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (9.20 mL) for 17.5 hours. After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 6/1, long), ketone *rac*-**287** (27.3 mg, 123 µmol, 62%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **242** (24.8 mg, 200 µmol, 1.00 equiv) and 1,1-dichloroethylene (801 µL, 969 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (9.20 mL). After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 6/1, long), ketone **287** (21.3 mg, 96.3 µmol, 48%, 48% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.63 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2957 (m, sp^3-CH), 2871 (w, sp^3-CH), 1703 (vs, C=O), 725 (s, sp^3-CCl), 691 (s, sp^3-CCl).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.90 (s, 3 H, Me-4), 1.11 (s, 3 H, Me-4), 1.83 (dd, ^2J = 14.1 Hz, ^3J = 11.3 Hz, 1 H, *H*H-5), 1.92 (dddd, ^2J = 14.1 Hz, ^3J = 8.4 Hz, $^4J_1$ = 2.7 Hz, $^4J_2$ = 1.3 Hz, 1 H, H*H*-5), 2.18 (ddd, ^2J = 16.7 Hz, $^4J_1$ = 2.7 Hz, $^4J_2$ = 1.3 Hz, 1 H, *H*H-3), 2.28 (*virt.* dt, ^2J = 16.7 Hz, $^4J_1 \approx {}^4J_2$ = 0.9 Hz, 1 H, H*H*-3), 3.03 (ddd, ^2J = 13.0 Hz, ^3J = 9.5 Hz, ^4J = 1.1 Hz, 1 H, *H*H-8), 3.13 (ddd, ^2J = 13.0 Hz, ^3J = 9.0 Hz, ^4J = 4.1 Hz, 1 H, H*H*-8), 3.23 (*virt.* q, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 8.5 Hz, 1 H, H-1), 3.32-3.39 (m, 1 H, H-6).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 25.8 (q, Me-4), 31.4 (q, Me-4), 34.0 (s, C-4), 37.7 (t, C-5), 37.9 (d, C-1), 47.9 (t, C-8), 52.0 (t, C-3), 53.8 (d, C-6), 84.8 (s, C-7), 210.2 (s, C-2).

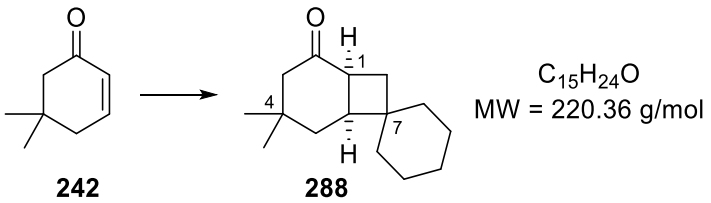
MS (EI, 70 eV): m/z (%) = 220 (7) $[M]^+$, 185 (17) $[M–Cl]^+$, 164 (3), 149 (7) $[C_{10}H_{13}O]^+$, 124 (19) $[C_8H_{12}O]^+$, 95 (14) $[C_2H_2Cl_2]^+$, 83 (15), 68 (100), 55 (18), 41 (10).

HRMS (EI, 70 eV): calcd for $C_{10}H_{14}O^{35}Cl_2$ $[M]^+$: 220.0416; found: 220.0415;
calcd for $C_9{}^{13}CH_{14}O^{35}Cl_2$ $[M]^+$: 221.0450; found: 221.0453.

Chiral GC: τ_R (major) = 16.3 min, τ_R (minor) = 16.4 min, [60 °C (0 min), 120 °C (30 °C/min), 120 °C (10 min), 240 °C (30 °C/min), 240 °C (2 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +92.6 (c = 1.21, CH_2Cl_2) [48% *ee*].

(1*S*,6*S*)-4,4-Dimethylspiro{bicyclo[4.2.0]octan-7,1'-cyclohexan}-2-one (288)



Racemic [2+2] Photocycloaddition:

Following GP10, enone **242** (24.8 mg, 200 µmol, 1.00 equiv) and methylenecyclohexane (1.20 mL, 962 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (8.80 mL) for 22 hours. After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 10/1, long), ketone *rac*-**288** (29.4 mg, 133 µmol, 67%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **242** (24.8 mg, 200 µmol, 1.00 equiv) and methylenecyclohexane (1.20 mL, 962 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (8.80 mL). After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 10/1, long), ketone **288** (29.2 mg, 133 µmol, 66%, 84% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.62 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2923 (vs, sp^3-CH), 2851 (s, sp^3-CH), 1696 (vs, C=O), 1448 (s, sp^3-CH), 1222 (w).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.87 (s, 3 H, Me-4), 1.04 (s, 3 H, Me-4), 1.19-1.39 (m, 5 H, 5 × H-cHex), 1.40-1.50 (m, 3 H, 3 × H-cHex), 1.52-1.62 (m, 3 H, *H*H-5, 2 × H-cHex), 1.66 (dd, ^2J = 13.5 Hz, ^3J = 11.8 Hz, 1 H, H*H*-5), 1.84 (dd, ^2J = 11.2 Hz, ^3J = 9.6 Hz, 1 H, *H*H-8), 2.00 (ddd, ^2J = 11.2 Hz, ^3J = 9.8 Hz, ^4J = 3.0 Hz, 1 H, H*H*-8), 2.09 (ddd, ^2J = 16.6 Hz, $^4J_1$ = 2.8 Hz, $^4J_2$ = 1.3 Hz, 1 H, *H*H-3), 2.19 (d, ^2J = 16.6 Hz, 1 H, H*H*-3), 2.30-2.38 (m, 1 H, H-6), 2.87 (*virt.* q, $^3J_1 \approx {}^3J_2 \approx {}^3J_3$ = 9.2 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 23.2 (t, C-cHex), 23.5 (t, C-cHex), 25.6 (q, Me-4), 26.2 (t, C-cHex), 31.8 (q, Me-4), 34.0 (t, C-cHex), 34.0 (s, C-4), 34.9 (t, C-8), 35.2 (t, C-5), 37.8 (t, C-cHex), 38.5 (d, C-1), 39.0 (s, C-7), 40.8 (d, C-6), 52.7 (t, C-3), 215.8 (s, C-2).

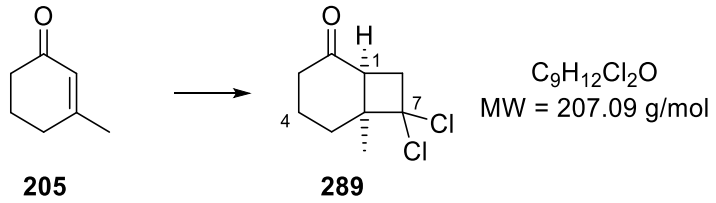
MS (EI, 70 eV): m/z (%) = 220 (14) $[M]^+$, 150 (6) $[C_{10}H_{14}O]^+$, 125 (100) $[C_8H_{13}O]^+$, 112 (5), 96 (9) $[C_7H_{18}]^+$, 81 (24), 67 (13), 55 (10), 41 (5).

HRMS (EI, 70 eV): calcd for $C_{15}H_{24}O$ $[M]^+$: 220.1822; found: 220.1821;
calcd for $C_{14}{}^{13}CH_{24}O$ $[M]^+$: 221.1855; found: 221.1858.

Chiral GC: τ_R (major) = 87.5 min, τ_R (minor) = 88.7 min, [60 °C (0.5 min), 90 °C (10 °C/min), 150 °C (0.5 °C/min), 200 °C (10 °C/min), 200 °C (3 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +175 (c = 1.21, CH_2Cl_2) [84% *ee*].

(1*S*,6*S*)-7,7-Dichloro-6-methylbicyclo[4.2.0]octan-2-one (289)



Racemic [2+2] Photocycloaddition:

Following GP10, enone **205** (22.0 mg, 200 µmol, 1.00 equiv) and 1,1-dichloroethylene (801 µL, 969 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (9.20 mL) for 17.5 hours. After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 6/1, long), ketone *rac*-**289** (10.5 mg, 50.7 µmol, 25%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **205** (22.0 mg, 200 µmol, 1.00 equiv) and 1,1-dichloroethlyene (801 µL, 969 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (9.20 mL). After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 6/1, long), ketone **289** (29.1 mg, 141 µmol, 70%, 77% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.50 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2950 (w, sp^3-CH), 2874 (w, sp^3-CH), 1703 (vs, C=O), 1460 (m, sp^3-CH), 717 (vs, sp^3-CCl).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.37 (d, ^4J = 0.8 Hz, 3 H, Me-6), 1.71-1.77 (m, 1 H, *H*H-5), 1.77-1.86 (m, 1 H, *H*H-4), 2.09-2.16 (m, 1 H, H*H*-4), 2.18-2.25 (m, 1 H, H*H*-5), 2.38-2.43 (m, 2 H, H-3), 2.82 (*virt.* t, $^3J_1 \approx {}^3J_2$ = 9.2 Hz, 1 H, H-1), 3.03 (br s, 1 H, *H*H-8), 3.05 (br s, 1 H, H*H*-8).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 21.6 (t, C-4), 23.7 (q, Me-6), 32.3 (t, C-5), 38.4 (t, C-3), 46.6 (t, C-8), 47.3 (d, C-1), 56.3 (s, C-6), 89.9 (s, C-7), 209.9 (s, C-2).

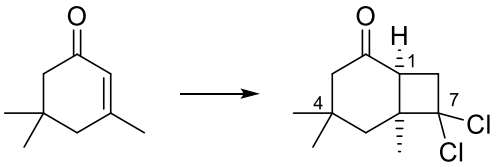
MS (EI, 70 eV): m/z (%) = 206 (2) $[M]^+$, 191 (1) $[M–CH_3]^+$, 171 (4) $[M–Cl]^+$, 135 (3) $[M–Cl_2]^+$, 110 (33) $[M–C_2H_2Cl_2]^+$, 82 (100) $[C_6H_{10}]^+$, 55 (6), 39 (4).

HRMS (EI, 70 eV): calcd for $C_9H_{12}O^{35}Cl_2$ $[M]^+$: 206.0260; found: 206.0247.

Chiral GC: τ_R (minor) = 35.4 min, τ_R (major) = 35.5 min, [60 °C (0 min), 120 °C (30 °C/min), 120 °C (30 min), 240 °C (30 °C/min), 240 °C (3 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +81.9 (c = 1.05, CH_2Cl_2) [77% *ee*].

(1*S*,6*S*)-7,7-Dichloro-4,4,6-trimethylbicyclo[4.2.0]octan-2-one (290)



290

$C_{11}H_{16}Cl_2O$
MW = 235.15 g/mol

Racemic [2+2] Photocycloaddition:

Following GP10, isophorone (27.6 mg, 200 µmol, 1.00 equiv) and 1,1-dichloroethylene (801 µL, 969 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (9.20 mL) for 17 hours. After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 6/1, long), ketone *rac*-**290** (23.4 mg, 99.5 µmol, 50%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, isophorone (27.6 mg, 200 µmol, 1.00 equiv) and 1,1-dichloroethylene (801 µL, 969 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (9.20 mL). After applying WP1 with eluent-mixtures (P/Et_2O = 4/1, short) and (P/Et_2O = 6/1, long), ketone **290** (38.3 mg, 163 µmol, 81%, 87% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.60 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2958 (m, sp^3-CH), 2872 (w, sp^3-CH), 1703 (vs, C=O), 1457 (m, sp^3-CH), 905 (s), 727 (vs, sp^3-CCl).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.97 (s, 3 H, Me-4), 1.12 (s, 3 H, Me-6), 1.45 (s, 3 H, Me-4), 1.54 (dd, ^2J = 14.6 Hz, ^4J = 2.5 Hz, 1 H, *H*H-5), 2.13 (ddd, ^2J = 15.6 Hz, $^4J_1$ = 2.5 Hz, $^4J_2$ = 1.3 Hz, 1 H, *H*H-3), 2.34 (d, ^2J = 14.6 Hz, 1 H, H*H*-5), 2.42 (d, ^2J = 15.6 Hz, 1 H, H*H*-3), 2.80 (*virt.* t, $^3J_1 \approx {}^3J_2$ = 8.7 Hz, 1 H, H-1), 3.00 (dd, ^2J = 12.9 Hz, ^3J = 8.3 Hz, 1 H, *H*H-8), 3.05 (dd, ^2J = 12.9 Hz, ^3J = 9.3 Hz, 1 H, H*H*-8).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 25.8 (q, Me-4), 27.7 (q, Me-4), 32.4 (q, Me-6), 35.2 (s, C-4), 44.0 (t, C-5), 46.9 (d, C-1), 47.1 (t, C-8), 50.8 (t, C-3), 55.7 (s, C-6), 91.6 (s, C-7), 210.2 (s, C-2).

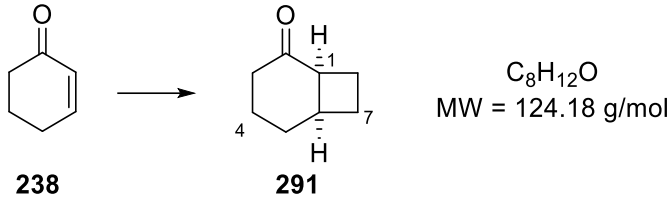
MS (EI, 70 eV): m/z (%) = 234 (1) $[M]^+$, 219 (1) $[M–CH_3]^+$, 199 (1) $[M–Cl]^+$, 138 (18) $[M–C_2H_2Cl_2]^+$, 95 (2) $[C_2H_2Cl_2]^+$, 82 (100), 55 (5).

HRMS (EI, 70 eV): calcd for $C_{11}H_{16}O^{35}Cl_2$ $[M]^+$: 234.0573; found: 234.0576.

Chiral GC: τ_R (major) = 32.3 min, τ_R (minor) = 32.5 min, [60 °C (0.5 min), 120 °C (15 °C/min), 120 °C (25 min), 200 °C (10 °C/min), 200 °C (7 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +135 (c = 1.04, CH_2Cl_2) [87% *ee*].

(1*S*,6*R*)-Bicyclo[4.2.0]octan-2-one (291)



238 **291**

Racemic [2+2] Photocycloaddition:

Following GP10, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 22 hours. After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone *rac*-**291** (12.0 mg, 96.6 µmol, 48%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone **291** (16.4 mg, 132 µmol, 66%, 80% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.50 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.51-1.57 (m, 1 H, *H*H-5), 1.71-1.80 (m, 2 H, H*H*-5, *H*H-7), 1.81-1.89 (m, 1 H, *H*H-4), 1.92-2.06 (m, 2 H, H*H*-4, H*H*-7), 2.13-2.28 (m, 3 H, *H*H-3, H-8), 2.42 (*virt.* dddt, ^2J = 15.9 Hz, $^3J_1$ = 6.3 Hz, $^3J_2$ = 4.5 Hz, $^4J_1 \approx {}^4J_2$ = 0.9 Hz, 1 H, H*H*-3), 2.83-2.89 (m, 1 H, H-1), 2.90-2.98 (m, 1 H, H-6).

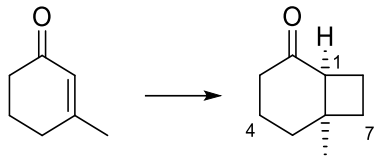
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.0 (t, C-4), 23.8 (t, C-8), 24.8 (t, C-7), 27.5 (t, C-5), 36.4 (d, C-6), 40.6 (t, C-3), 45.4 (d, C-1), 215.8 (s, C-2).

Chiral GC: τ_R (major) = 15.8 min, τ_R (minor) = 16.1 min, [60 °C (0.5 min), 200 °C (4 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +120 (c = 1.08, CH_2Cl_2) [80% *ee*].

The analytical data obtained matched those reported in the literature.[301]

(1*S*,6*R*)-6-Methylbicyclo[4.2.0]octan-2-one (231)



205 **231**

$C_9H_{14}O$
MW = 138.41 g/mol

Racemic [2+2] Photocycloaddition:

Following GP10, enone **205** (22.0 mg, 200 μmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 22 hours. After applying WP2 with eluent-mixture (P/Et_2O = 6/1), ketone *rac*-**231** (17.9 mg, 130 μmol, 65%) was obtained as a colorless oil.

Racemic [2+2] Photocycloaddition for the Starting Material of (±)-Grandisol (*rac*-**15**):

Following GP10, enone **205** (132 mg, 1.20 mmol, 1.00 equiv) and ethylene (approx. 6 mL) were irradiated in dichloromethane (60.0 mL) for 24 hours. After applying WP2 with eluent-mixture (P/Et_2O = 6/1), ketone *rac*-**231** (128 mg, 926 μmol, 77%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **205** (22.0 mg, 200 μmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 with eluent-mixture (P/Et_2O = 6/1), ketone **231** (19.6 mg, 142 μmol, 71%, 86% *ee*) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition for the Starting Material of (–)-Grandisol (**15**):

Following GP11, enone **205** (132 mg, 1.20 mmol, 1.00 equiv) and ethylene (approx. 6 mL) were irradiated in dichloromethane (60.0 mL). After applying WP2 with eluent-mixture (P/Et_2O = 6/1), ketone **231** (135 mg, 977 μmol, 81%, 86% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.53 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.22 (s, 3 H, Me-6), 1.49 (ddd, ^2J = 13.5 Hz, $^3J_1$ = 9.4 Hz, $^3J_2$ = 3.6 Hz, 1 H, *H*H-5), 1.66-1.76 (m, 2 H, H*H*-5, *H*H-7), 1.81-1.91 (m, 2 H, *H*H-4, H*H*-7), 1.93-2.07 (m, 2 H, H*H*-4, *H*H-8), 2.18-2.28 (m, 2 H, *H*H-3, H*H*-8), 2.45 (ddd, ^2J = 16.6 Hz, $^3J_1$ = 7.0 Hz, $^3J_2$ = 5.1 Hz, 1 H, H*H*-3), 2.53 (*virt.* ddt, $^3J_1$ = 10.5 Hz, $^3J_2$ = 6.8 Hz, $^4J_1 \approx {}^4J_2$ = 1.1 Hz, 1 H, H-1).

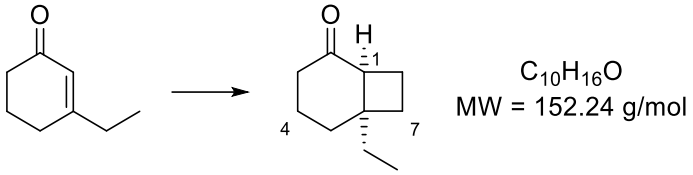
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 20.5 (t, C-8), 21.2 (t, C-4), 29.0 (q, Me-6), 31.2 (t, C-7), 35.2 (t, C-5), 39.6 (t, C-3), 40.8 (s, C-6), 51.5 (d, C-1), 215.3 (s, C-2).

Chiral GC: τ_R (major) = 15.9 min, τ_R (minor) = 16.6 min, [60 °C (0.5 min), 200 °C (4 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +139 (c = 1.12, CH_2Cl_2) [86% *ee*].

The analytical data obtained matched those reported in the literature.[209]

(1*S*,6*R*)-6-Ethylbicyclo[4.2.0]octan-2-one (292)



243 **292**

Racemic [2+2] Photocycloaddition:

Following GP10, enone **243** (24.8 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 22 hours. After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone *rac*-**292** (26.6 mg, 175 µmol, 87%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **243** (24.8 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone **292** (22.4 mg, 147 µmol, 74%, 85% *ee*) was obtained as a colorless oil. Starting material **243** (2.60 mg, 20.9 µmol, 10%) was partially recovered.

TLC: R_f = 0.57 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2958 (s, sp^3-CH), 2933 (s, sp^3-CH), 2877 (m, sp^3-CH), 2854 (m, sp^3-CH), 1699 (vs, C=O), 1460 (m, sp^3-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.84 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 1.47-1.55 (m, 3 H, *H*H-5, CH_2CH_3), 1.60 (dddd, ^2J = 13.9 Hz, $^3J_1$ = 6.9 Hz, $^3J_2$ = 3.4 Hz, ^4J = 0.9 Hz, 1 H, H*H*-5), 1.76-1.80 (m, 2 H, H-7), 1.82-1.91 (m, 1 H, *H*H-4), 1.94-2.06 (m, 2 H, H*H*-4, *H*H-8), 2.15-2.26 (m, 2 H, *H*H-3, H*H*-8), 2.48 (dt, ^2J = 16.9 Hz, ^3J = 5.6 Hz, 1 H, H*H*-3), 2.55 (dd, $^3J_1$ = 10.3 Hz, $^3J_2$ = 6.9 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 8.3 (q, $CH_2\mathit{C}H_3$), 20.6 (t, C-8), 20.8 (t, C-4), 28.6 (t, C-7), 31.8 (t, C-5), 34.1 (t, $\mathit{C}H_2CH_3$), 39.6 (t, C-3), 44.0 (s, C-6), 50.1 (d, C-1), 215.4 (s, C-2).

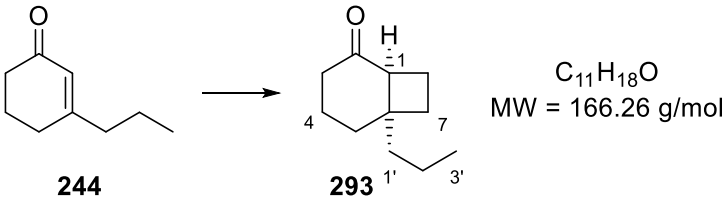
MS (EI, 70 eV): m/z (%) = 152 (8) $[M]^+$, 137 (4) $[M–CH_3]^+$, 124 (58) $[M–C_2H_4]^+$, 109 (6) $[M–C_3H_7]^+$, 96 (100) $[M–C_4H_9]^+$, 81 (23), 67 (35) $[C_5H_7]^+$, 55 (31) $[C_4H_7]^+$, 41 (17).

HRMS (EI, 70 eV): calcd for $C_{10}H_{16}O$ $[M]^+$: 152.1196; found: 152.1198.

Chiral GC: τ_R (major) = 18.6 min, τ_R (minor) = 19.3 min, [60 °C (0.5 min), 200 °C (4 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +110 (c = 1.12, CH_2Cl_2) [85% *ee*].

(1*S*,6*R*)-6-Propylbicyclo[4.2.0]octan-2-one (293)



Racemic [2+2] Photocycloaddition:

Following GP10, enone **244** (27.6 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 18 hours. After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone *rac*-**293** (27.9 mg, 168 µmol, 84%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **244** (27.6 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone **293** (27.8 mg, 167 µmol, 84%, 83% *ee*) was obtained as a colorless oil. Starting material **244** (1.60 mg, 11.6 µmol, 6%) was partially recovered.

TLC: R_f = 0.59 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2955 (s, sp^3-CH), 2930 (s, sp^3-CH), 2871 (m, sp^3-CH), 1699 (vs, C=O), 1458 (m, sp^3-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.91 (t, ^3J = 7.3 Hz, 3 H, H-3'), 1.21-1.30 (m, 2 H, H-2'), 1.43-1.55 (m, 3 H, *H*H-5, H-1'), 1.61 (dddd, ^2J = 14.0 Hz, $^3J_1$ = 7.1 Hz, $^3J_2$ = 3.5 Hz, ^4J = 0.9 Hz, 1 H, H*H*-5), 1.74-1.82 (m, 2 H, H-7), 1.82-1.90 (m, 1 H, *H*H-4),

1.93-2.05 (m, 2 H, H*H*-4, *H*H-8), 2.14-2.26 (m, 2 H, *H*H-3, H*H*-8), 2.47 (*virt.* dt, ^2J = 16.9 Hz, $^3J_1 \approx {}^3J_2$ = 5.6 Hz, 1 H, H*H*-3), 2.55 (dd, $^3J_1$ = 10.4 Hz, $^3J_2$ = 7.1 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 14.9 (q, C-3'), 17.3 (t, C-2'), 20.8 (t, C-8), 20.9 (t, C-4), 29.2 (t, C-7), 32.4 (t, C-5), 39.6 (t, C-3), 43.7 (s, C-6), 44.3 (t, C-1'), 50.5 (d, C-1), 215.3 (s, C-2).

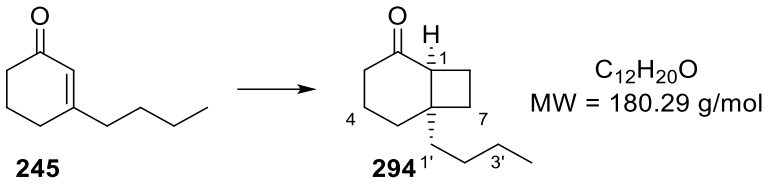
MS (EI, 70 eV): m/z (%) = 166 (7) $[M]^+$, 151 (3) $[M–CH_3]^+$, 138 (61) $[M–C_2H_4]^+$, 123 (43) $[M–C_3H_7]^+$, 110 (40) $[M–C_4H_8]^+$, 95 (21) $[C_6H_7O]^+$, 82 (100), 67 (26), 55 (24) $[C_4H_7]^+$, 41 (2).

HRMS (EI, 70 eV): calcd for $C_{11}H_{18}O$ $[M]^+$: 166.1352; found: 166.1349;
calcd for $C_{10}{}^{13}CH_{18}O$ $[M]^+$: 167.1386; found: 167.1389.

Chiral GC: τ_R (major) = 20.4 min, τ_R (minor) = 21.0 min, [60 °C (0.5 min), 200 °C (4 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +104 (c = 1.50, CH_2Cl_2) [83% *ee*].

(1*S*,6*R*)-6-Butylbicyclo[4.2.0]octan-2-one (294)



Racemic [2+2] Photocycloaddition:

Following GP10, enone **245** (30.5 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 22 hours. After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone *rac*-**294** (31.3 mg, 174 µmol, 87%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **245** (30.5 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone **294** (28.5 mg, 158 µmol, 79%, 80% *ee*) was obtained as a colorless oil. Starting material **245** (4.10 mg, 26.9 µmol, 13%) was partially recovered.

TLC: R_f = 0.60 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2954 (s, sp^3-CH), 2927 (s, sp^3-CH), 2858 (m, sp^3-CH), 1701 (vs, C=O), 1458 (m, sp^3-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.89 (t, ^3J = 7.3 Hz, 3 H, H-4'), 1.16-1.25 (m, 2 H, H-2'), 1.25-1.34 (m, 2 H, H-3'), 1.44-1.55 (m, 3 H, *H*H-5, H-1'), 1.61 (dddd, ^2J = 14.0 Hz, $^3J_1$ = 7.2 Hz, $^3J_2$ = 3.4 Hz, ^4J = 0.9 Hz, 1 H, H*H*-5), 1.75-1.81 (m, 2 H, H-7), 1.81-1.90 (m, 1 H, *H*H-4), 1.93-2.06 (m, 2 H, H*H*-4, *H*H-8), 2.15-2.26 (m, 2 H, *H*H-3, H*H*-8), 2.47 (ddd, ^2J = 16.9 Hz, $^3J_1$ = 6.2 Hz, $^3J_2$ = 5.0 Hz, 1 H, H*H*-3), 2.55 (dd, $^3J_1$ = 10.4 Hz, $^3J_2$ = 7.1 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 14.3 (q, C-4'), 20.7 (t, C-8), 20.9 (t, C-4), 23.4 (t, C-3'), 26.3 (t, C-2'), 29.2 (t, C-7), 32.3 (t, C-5), 39.6 (t, C-3), 41.7 (t, C-1'), 43.6 (s, C-6), 50.5 (d, C-1), 215.3 (s, C-2).

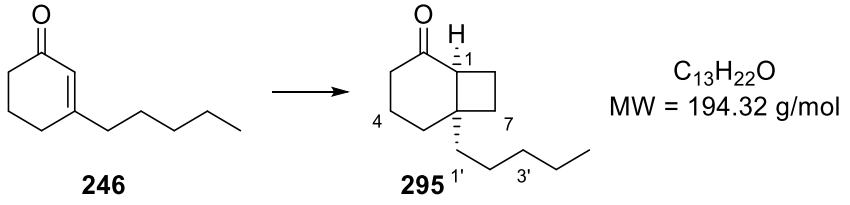
MS (EI, 70 eV): m/z (%) = 180 (5) $[M]^+$, 165 (1) $[M–CH_3]^+$, 152 (19) $[M–C_2H_4]^+$, 137 (5) $[M–C_3H_7]^+$, 123 (38) $[M–C_4H_9]^+$, 110 (53) $[C_7H_{10}O]^+$, 95 (17) $[C_6H_7O]^+$, 82 (100), 67 (20), 55 (18) $[C_4H_7]^+$, 41 (11).

HRMS (EI, 70 eV): calcd for $C_{12}H_{20}O$ $[M]^+$: 180.1509; found: 180.1502.

Chiral GC: τ_R (major) = 22.8 min, τ_R (minor) = 23.2 min, [60 °C (0.5 min), 200 °C (4 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +87.8 (c = 1.18, CH_2Cl_2) [80% *ee*].

(1*S*,6*R*)-6-Pentylbicyclo[4.2.0]octan-2-one (295)



Racemic [2+2] Photocycloaddition:

Following GP10, enone **246** (33.3 mg, 200 μmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 22 hours. After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone *rac*-**295** (33.7 mg, 173 μmol, 88%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **246** (33.3 mg, 200 μmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 with eluent-mixture

(P/Et_2O = 4/1), ketone **295** (30.8 mg, 159 μmol, 79%, 82% *ee*) was obtained as a colorless oil. Starting material **246** (2.10 mg, 12.6 μmol, 6%) was partially recovered.

TLC: R_f = 0.63 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2953 (m, sp^3-CH), 2926 (s, sp^3-CH), 2857 (m, sp^3-CH), 1701 (vs, C=O), 1459 (m, sp^3-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.88 (t, ^3J = 7.1 Hz, 3 H, H-5'), 1.18-1.35 (m, 6 H, H-2', H-3', H-4'), 1.43-1.56 (m, 3 H, *H*H-5, H-1'), 1.61 (dddd, ^2J = 14.0 Hz, $^3J_1$ = 7.2 Hz, $^3J_2$ = 3.5 Hz, ^4J = 0.9 Hz, 1 H, H*H*-5), 1.76-1.81 (m, 2 H, H-7), 1.81-1.90 (m, 1 H, *H*H-4), 1.94-2.05 (m, 2 H, H*H*-4, *H*H-8), 2.15-2.26 (m, 2 H, *H*H-3, H*H*-8), 2.48 (*virt.* dt, ^2J = 16.9 Hz, $^3J_1 \approx {}^3J_2$ = 5.6 Hz, 1 H, H*H*-3), 2.55 (dd, $^3J_1$ = 10.3 Hz, $^3J_2$ = 7.1 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 14.2 (q, C-5'), 20.7 (t, C-8), 20.9 (t, C-4), 22.8 (t, C-4'), 23.8 (t, C-2'), 29.2 (t, C-7), 32.4 (t, C-5), 32.5 (t, C-3'), 39.6 (t, C-3), 41.9 (t, C-1'), 43.7 (s, C-6), 50.5 (d, C-1), 215.3 (s, C-2).

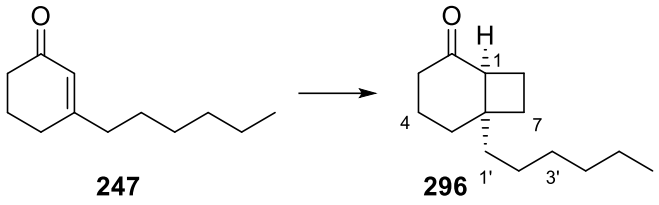
MS (EI, 70 eV): m/z (%) = 194 (7) $[M]^+$, 166 (22) $[M–C_2H_4]^+$, 151 (5) $[M–C_3H_7]^+$, 138 (13) $[M–C_4H_9]^+$, 123 (59) $[M–C_5H_{11}]^+$, 110 (83) $[C_7H_{10}O]^+$, 95 (35) $[C_6H_7O]^+$, 82 (100), 67 (24), 55 (23), 41 (14).

HRMS (EI, 70 eV): calcd for $C_{13}H_{22}O$ $[M]^+$: 194.1665; found: 194.1666;
calcd for $C_{12}{}^{13}CH_{22}O$ $[M]^+$: 195.1669; found: 195.1702.

Chiral GC: τ_R (major) = 25.5 min, τ_R (minor) = 25.8 min, [60 °C (0.5 min), 200 °C (4 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +83.6 (c = 1.12, CH_2Cl_2) [82% *ee*].

(1*S*,6*R*)-6-Hexylbicyclo[4.2.0]octan-2-one (296)



Racemic [2+2] Photocycloaddition:

Following GP10, enone **247** (36.1 mg, 200 μmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 22 hours. After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone *rac*-**296** (37.1 mg, 178 μmol, 89%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **247** (36.1 mg, 200 μmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone **296** (32.9 mg, 158 μmol, 79%, 81% *ee*) was obtained as a colorless oil. Starting material **247** (4.10 mg, 22.7 μmol, 11%) was partially recovered.

TLC: R_f = 0.60 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2953 (s, sp^3-CH), 2924 (vs, sp^3-CH), 2855 (s, sp^3-CH), 1701 (vs, C=O), 1459 (m, sp^3-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.84-0.92 (m, 3 H, H-6'), 1.18-1.34 (m, 8 H, H-2', H-3', H-4', H-5'), 1.45-1.55 (m, 3 H, *H*H-5, H-1'), 1.58-1.65 (m, 1 H, H*H*-5), 1.76-1.82 (m, 2 H, H-7), 1.82-1.90 (m, 1 H, *H*H-4), 1.94-2.05 (m, 2 H, H*H*-4, *H*H-8), 2.15-2.27 (m, 2 H, *H*H-3, H*H*-8), 2.48 (*virt.* dt, ^2J = 16.9 Hz, $^3J_1 \approx {}^3J_2$ = 5.6 Hz, 1 H, H*H*-3), 2.55 (dd, $^3J_1$ = 10.4 Hz, $^3J_2$ = 7.1 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 14.2 (q, C-6'), 20.8 (t, C-8), 20.9 (t, C-4), 22.8 (t, C-5'), 24.1 (t, C-2'), 29.2 (t, C-7), 30.0 (t, C-3'), 32.0 (t, C-4'), 32.4 (t, C-5), 39.6 (t, C-3), 42.0 (t, C-1'), 43.7 (s, C-6), 50.5 (d, C-1), 215.3 (s, C-2).

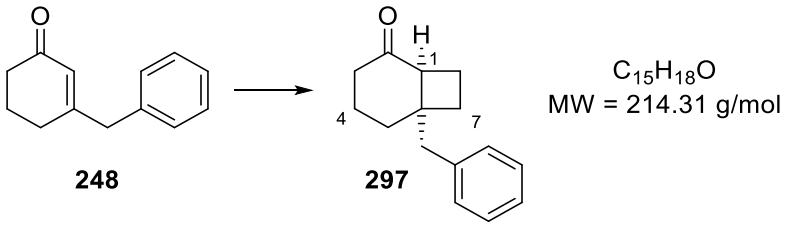
MS (EI, 70 eV): m/z (%) = 208 (10) $[M]^+$, 193 (1) $[M–CH_3]^+$, 180 (26) $[M–C_2H_4]^+$, 165 (5) $[M–C_3H_7]^+$, 151 (6) $[M–C_4H_9]^+$, 138 (24) $[M–C_5H_{10}]^+$, 123 (72) $[M–C_6H_{13}]^+$, 110 (100) $[C_7H_{10}O]^+$, 95 (40) $[C_6H_7O]^+$, 82 (99), 67 (32), 55 (30) $[C_4H_7]^+$, 41 (19).

HRMS (EI, 70 eV): calcd for $C_{14}H_{24}O$ $[M]^+$: 208.1822; found: 208.1809;
calcd for $C_{13}{}^{13}CH_{24}O$ $[M]^+$: 209.1855; found: 209.1843.

Chiral GC: τ_R (major) = 28.2 min, τ_R (minor) = 28.5 min, [60 °C (0.5 min), 200 °C (4 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +77.4 (c = 1.50, CH_2Cl_2) [81% *ee*].

(1*S*,6*R*)-6-Benzylbicyclo[4.2.0]octan-2-one (297)



Racemic [2+2] Photocycloaddition:

Following GP10, enone **248** (37.3 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 22 hours. After applying WP2 with eluent-mixture (P/Et_2O = 3/1), ketone *rac*-**297** (37.1 mg, 173 µmol, 87%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **248** (37.3 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 with eluent-mixture (P/Et_2O = 3/1), ketone **297** (32.6 mg, 152 µmol, 76%, 58% *ee*) was obtained as a colorless oil. Starting material **248** (6.60 mg, 35.4 µmol, 18%) was partially recovered.

TLC: R_f = 0.51 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3027 (w, sp^2-CH), 2931 (m, sp^3-CH), 2863 (w, sp^3-CH), 1696 (vs, C=O), 756 (s, sp^2-CH), 701 (vs, sp^2-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.58-1.66 (m, 2 H, H-5), 1.73-1.82 (m, 2 H, *H*H-4, *H*H-7), 1.90-2.00 (m, 1 H, H*H*-4), 2.00-2.10 (m, 2 H, H*H*-7, *H*H-8), 2.13-2.24 (m, 2 H, *H*H-3, H*H*-8), 2.46 (ddd, ^2J = 16.8 Hz, $^3J_1$ = 7.4 Hz, $^3J_2$ = 5.2 Hz, 1 H, H*H*-3), 2.74-2.84 (m, 3 H, H-1, CH_2Ph), 7.12-7.16 (m, 2 H, 2 × H-*o*-Ph), 7.20-7.25 (m, 1 H, H-*p*-Ph), 7.25-7.31 (m, 2 H, 2 × H-*m*-Ph).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 20.8 (t, C-8), 20.9 (t, C-4), 29.5 (t, C-7), 32.2 (t, C-5), 39.3 (t, C-3), 44.5 (s, C-6), 47.2 (t, *C*H_2Ph), 50.1 (d, C-1), 126.4 (d, C-*p*-Ph), 128.3 (d, 2 C, 2 × C-*m*-Ph), 129.9 (d, 2 C, 2 × C-*o*-Ph), 138.4 (s, C-*i*-Ph), 214.4 (s, C-2).

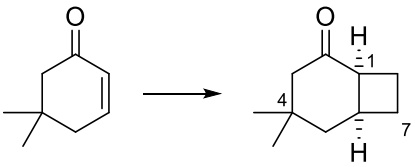
MS (EI, 70 eV): m/z (%) = 214 (12) $[M]^+$, 196 (3), 186 (100) $[M–C_2H_4]^+$, 168 (15), 158 (79), 144 (36), 129 (87), 123 (39) $[M–C_7H_7]^+$, 115 (19), 105 (7), 91 (66) $[C_7H_7]^+$, 79 (12), 67 (18), 55 (21), 41 (9).

HRMS (EI, 70 eV): calcd for $C_{15}H_{18}O$ $[M]^+$: 214.1352; found: 214.1340;
calcd for $C_{14}{}^{13}CH_{18}O$ $[M]^+$: 215.1386; found: 215.1379.

Chiral GC: τ_R (major) = 38.9 min, τ_R (minor) = 39.1 min, [60 °C (0.5 min), 150 °C (15 °C/min), 150 °C (30 min), 200 °C (15 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +50.1 (c = 1.40, CH_2Cl_2) [58% *ee*].

(1*S*,6*S*)-4,4-Dimethylbicyclo[4.2.0]octan-2-one (298)



$C_{10}H_{16}O$
MW = 152.24 g/mol

242 **298**

Racemic [2+2] Photocycloaddition:

Following GP10, enone **242** (24.8 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 22 hours. After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone *rac*-**298** (21.4 mg, 141 µmol, 70%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **242** (24.8 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone **298** (23.7 mg, 156 µmol, 78%, 82% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.60 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2952 (s, sp^3-CH), 2867 (m, sp^3-CH), 1697 (vs, C=O), 1461 (m, sp^3-CH), 1247 (m).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.83 (s, 3 H, Me-4), 1.05 (s, 3 H, Me-4), 1.48-1.57 (m, 1 H, *H*H-7), 1.61 (dd, ^2J = 13.8 Hz, ^3J = 10.5 Hz, 1 H, *H*H-5), 1.77 (ddd, ^2J = 13.8 Hz, ^3J = 7.7 Hz, ^4J = 2.6 Hz, 1 H, H*H*-5), 2.08 (ddd, ^2J = 15.9 Hz, $^4J_1$ = 2.6 Hz, $^4J_2$ = 1.5 Hz, 1 H, *H*H-3), 2.18-2.36 (m, 4 H, H*H*-3, H*H*-7, H-8), 2.63-2.73 (m, 1 H, H-6), 2.90-2.99 (m, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 24.3 (t, C-8), 25.7 (t, C-7), 25.7 (q, Me-4), 31.3 (q, Me-4), 33.5 (d, C-6), 34.8 (s, C-4), 41.6 (t, C-5), 43.5 (d, C-1), 52.5 (t, C-3), 214.6 (s, C-2).

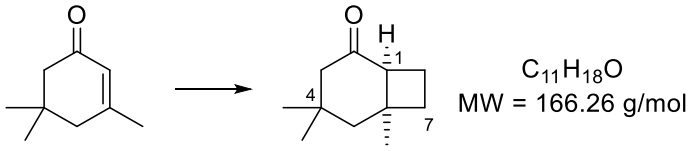
MS (EI, 70 eV): m/z (%) = 152 (51) $[M]^+$, 137 (20) $[M–CH_3]^+$, 124 (10) $[M–C_2H_4]^+$, 109 (18) $[M–C_3H_7]^+$, 96 (43) $[M–C_4H_{10}]^+$, 83 (77), 68 (93) $[C_5H_8]^+$, 55 (100) $[C_4H_7]^+$, 41 (32) $[C_3H_5]^+$.

HRMS (EI, 70 eV): calcd for $C_{10}H_{16}O$ $[M]^+$: 152.1196; found: 152.1197.

Chiral GC: τ_R (major) = 13.4 min, τ_R (minor) = 13.6 min, [60 °C (0 min), 120 °C (30 °C/min), 120 °C (10 min), 240 °C (30 °C/min), 240 °C (2 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +187 (c = 1.61, CH_2Cl_2) [82% *ee*].

(1*S*,6*S*)-4,4,6-Trimethylbicyclo[4.2.0]octan-2-one (299)



299

Racemic [2+2] Photocycloaddition:

Following GP10, isophorone (27.6 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 22 hours. After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone *rac*-**299** (28.1 mg, 169 µmol, 85%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, isophorone (27.6 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone **299** (22.8 mg, 137 µmol, 69%, 87% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.65 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.91 (s, 3 H, Me-4), 1.05 (s, 3 H, Me-4), 1.24 (s, 3 H, Me-6), 1.52 (dd, ^2J = 14.3 Hz, ^4J = 1.9 Hz, 1 H, *H*H-5), 1.75-1.86 (m, 3 H, H*H*-5, H-7), 2.04-2.14 (m, 2 H, *H*H-3, *H*H-8), 2.20 (dddd, ^2J = 11.9 Hz, $^3J_1$ = 9.7 Hz, $^3J_2$ = 8.8 Hz, $^3J_3$ = 4.8 Hz, 1 H, H*H*-8), 2.37 (d, ^2J = 14.4 Hz, 1 H, H*H*-3), 2.57 (*virt.* t, $^3J_1 \approx {}^3J_2$ = 8.8 Hz, 1 H, H-1).

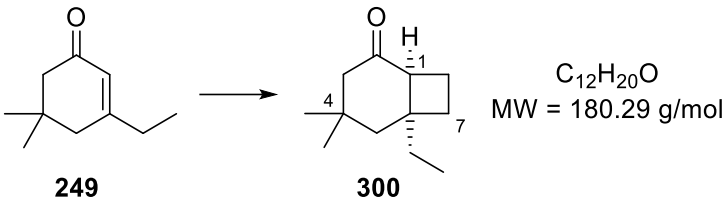
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 20.8 (t, C-8), 28.7 (q, Me-4), 30.9 (q, Me-6), 31.1 (q, Me-4), 35.1 (t, C-7), 35.7 (s, C-4), 40.8 (s, C-6), 48.4 (t, C-5), 50.9 (d, C-1), 52.0 (t, C-3), 214.9 (s, C-2).

Chiral GC: τ_R (major) = 17.0 min, τ_R (minor) = 17.2 min, [60 °C (0.5 min), 200 °C (4 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +169 (c = 1.19, CH_2Cl_2) [87% *ee*].

The analytical data obtained matched those reported in the literature.[302]

(1*S*,6*S*)-6-Ethyl-4,4-dimethylbicyclo[4.2.0]octan-2-one (300)



249 **300**

Racemic [2+2] Photocycloaddition:

Following GP10, enone **249** (30.5 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 22 hours. After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone *rac*-**300** (35.0 mg, 194 µmol, 97%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **249** (30.5 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone **300** (28.0 mg, 155 µmol, 78%, 80% *ee*) was obtained as a colorless oil. Starting material **249** (2.50 mg, 16.4 µmol, 8%) was partially recovered.

TLC: R_f = 0.64 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2957 (s, sp^3-CH), 2875 (m, sp^3-CH), 1700 (vs, C=O), 1460 (m, sp^3-CH), 1280 (m).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.85 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3), 0.91 (s, 3 H, Me-4), 1.05 (s, 3 H, Me-4), 1.47-1.63 (m, 4 H, H-5, CH_2CH_3), 1.70-1.84 (m, 2 H, H-7), 2.04-2.14 (m, 2 H, *H*H-3, *H*H-8), 2.19 (dddd, ^2J = 12.0 Hz, $^3J_1$ = 9.8 Hz, $^3J_2$ = 9.0 Hz, $^3J_3$ = 5.4 Hz, 1 H, H*H*-8), 2.35 (d, ^2J = 14.1 Hz, 1 H, H*H*-3), 2.53 (*virt.* ddq, $^3J_1$ = 9.8 Hz, $^3J_2$ = 7.3 Hz, $^4J_1 \approx {}^4J_2$ = 1.1 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 8.3 (q, $CH_2\mathit{C}H_3$), 20.9 (t, C-8), 29.5 (q, Me-4), 30.7 (q, Me-4), 31.4 (t, C-7), 35.1 (t, $\mathit{C}H_2CH_3$), 35.7 (d, C-4), 44.5 (t, C-5), 44.5 (s, C-6), 49.7 (d, C-1), 52.5 (t, C-3), 215.3 (s, C-2).

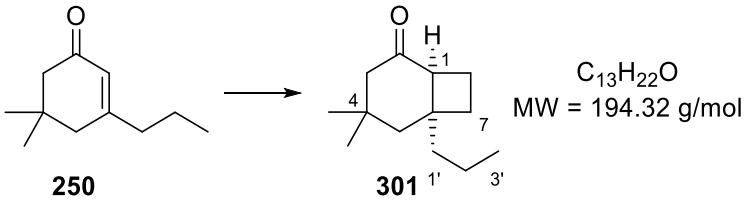
MS (EI, 70 eV): m/z (%) = 180 (2) $[M]^+$, 152 (27) $[M–C_2H_5]^+$, 96 (100), 81 (11), 67 (13), 55 (16), 41 (7).

HRMS (EI, 70 eV): calcd for $C_{12}H_{20}O$ $[M]^+$: 180.1509; found: 180.1502.

Chiral GC: τ_R (major) = 14.8 min, τ_R (minor) = 14.9 min, [60 °C (0 min), 120 °C (30 °C/min), 120 °C (10 min), 240 °C (30 °C/min), 240 °C (2 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +123 (c = 1.28, CH_2Cl_2) [80% *ee*].

(1*S*,6*S*)-4,4-Dimethyl-6-propylbicyclo[4.2.0]octan-2-one (301)



Racemic [2+2] Photocycloaddition:

Following GP10, enone **250** (33.3 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 22 hours. After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone *rac*-**301** (34.6 mg, 178 µmol, 89%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **250** (33.3 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone **301** (25.3 mg, 130 µmol, 65%, 55% *ee*) was obtained as a colorless oil. Starting material **250** (7.20 mg, 43.3 µmol, 22%) was partially recovered.

TLC: R_f = 0.66 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2954 (s, sp^3-CH), 2932 (s, sp^3-CH), 2871 (m, sp^3-CH), 1699 (vs, C=O), 1484 (m, sp^3-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.91 (t, ^3J = 7.3 Hz, 3 H, H-3'), 0.91 (s, 3 H, Me-4), 1.05 (s, 3 H, Me-4), 1.20-1.37 (m, 2 H, H-2'), 1.44 (ddd, ^2J = 13.2 Hz, $^3J_1$ = 11.3 Hz, $^3J_2$ = 5.1 Hz, 1 H, *H*H-1'), 1.54 (ddd, ^2J = 13.2 Hz, $^3J_1$ = 11.3 Hz, $^3J_2$ = 4.7 Hz, 1 H, H*H*-1'),

1.57-1.65 (m, 2 H, H-5), 1.71-1.78 (m, 1 H, *H*H-7), 1.78-1.86 (m, 1 H, H*H*-7), 2.04-2.15 (m, 2 H, *H*H-3, *H*H-8), 2.20 (*virt.* dtd, ^2J = 11.8 Hz, $^3J_1 \approx {}^3J_2$ = 9.5 Hz, $^3J_3$ = 5.2 Hz, 1 H, H*H*-8), 2.35 (d, ^2J = 14.1 Hz, 1 H, H*H*-3), 2.51-2.56 (m, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 14.8 (q, C-3'), 17.3 (t, C-2'), 21.1 (t, C-8), 29.5 (q, Me-4), 30.7 (q, Me-4), 32.1 (t, C-7), 35.8 (s, C-4), 44.2 (s, C-6), 45.0 (t, C-5), 45.3 (t, C-1'), 50.1 (d, C-1), 52.4 (t, C-3), 215.2 (s, C-2).

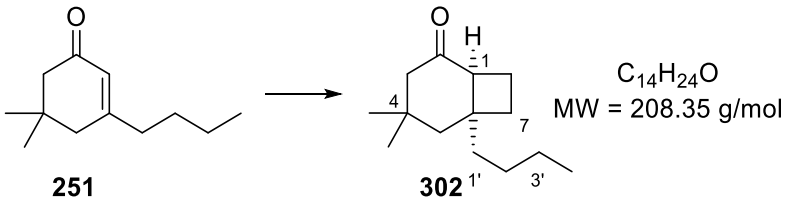
MS (EI, 70 eV): m/z (%) = 194 (3) $[M]^+$, 179 (4) $[M–CH_3]^+$, 166 (35) $[M–C_2H_4]^+$, 151 (17) $[M–C_3H_7]^+$, 138 (6), 123 (5) $[C_8H_{11}O]^+$, 110 (66), 82 (100), 67 (16), 55 (31) $[C_4H_7]^+$.

HRMS (EI, 70 eV): calcd for $C_{13}H_{22}O$ $[M]^+$: 194.1665; found: 194.1646.

Chiral GC: τ_R (major) = 33.1 min, τ_R (minor) = 33.5 min, [60 °C (0 min), 120 °C (30 °C/min), 120 °C (30 min), 240 °C (30 °C/min), 240 °C (3 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +92.8 (c = 1.21, CH_2Cl_2) [55% *ee*].

(1*S*,6*S*)-6-Butyl-4,4-dimethylbicyclo[4.2.0]octan-2-one (302)



251 **302**

Racemic [2+2] Photocycloaddition:

Following GP10, enone **251** (36.1 mg, 200 μmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 22 hours. After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone *rac*-**302** (38.2 mg, 183 μmol, 92%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **251** (36.1 mg, 200 μmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone **302** (33.6 mg, 161 μmol, 81%, 59% *ee*) was obtained as a colorless oil. Starting material **251** (2.90 mg, 16.1 μmol, 8%) was partially recovered.

TLC: R_f = 0.70 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2954 (s, sp^3-CH), 2929 (s, sp^3-CH), 2860 (m, sp^3-CH), 1700 (vs, C=O), 1459 (m, sp^3-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.90 (t, ^3J = 7.2 Hz, 3 H, H-4'), 0.92 (s, 3 H, Me-4), 1.05 (s, 3 H, Me-4), 1.16-1.35 (m, 4 H, H-2', H-3'), 1.42-1.49 (m, 1 H, *H*H-1'), 1.53-1.65 (m, 3 H, H*H*-1', H-5), 1.71-1.85 (m, 2 H, H-7), 2.05-2.14 (m, 2 H, *H*H-3, *H*H-8), 2.20 (dddd, ^2J = 11.9 Hz, $^3J_1$ = 9.9 Hz, $^3J_2$ = 9.1 Hz, $^3J_3$ = 5.2 Hz, 1 H, H*H*-8), 2.35 (d, ^2J = 14.1 Hz, 1 H, H*H*-3), 2.51-2.56 (m, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 14.3 (q, C-4'), 21.1 (t, C-8), 23.3 (t, C-3'), 26.3 (t, C-2'), 29.5 (q, Me-4), 30.7 (q, Me-4), 32.1 (t, C-7), 35.8 (s, C-4), 42.7 (t, C-1'), 44.2 (s, C-6), 45.0 (t, C-5), 50.1 (d, C-1), 52.4 (t, C-3), 215.2 (s, C-2).

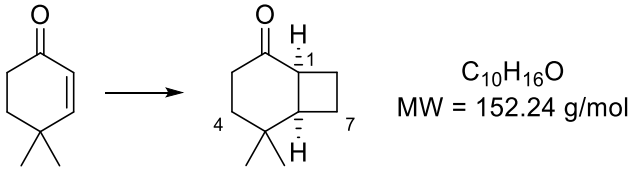
MS (EI, 70 eV): m/z (%) = 208 (2) $[M]^+$, 180 (12) $[M–C_2H_4]^+$, 165 (5) $[M–C_3H_7]^+$, 151 (13) $[M–C_4H_9]^+$, 138 (31), 124 (9) $[C_8H_{12}O]^+$, 109 (6) $[C_7H_9O]^+$, 95 (8), 82 (100), 67 (9), 55 (15), 41 (6).

HRMS (EI, 70 eV): calcd for $C_{14}H_{24}O$ $[M]^+$: 208.1822; found: 208.1808;
calcd for $C_{13}{}^{13}CH_{24}O$ $[M]^+$: 209.1855; found: 209.1845.

Chiral GC: τ_R (major) = 35.2 min, τ_R (minor) = 35.3 min, [60 °C (0 min), 120 °C (30 °C/min), 120 °C (30 min), 240 °C (30 °C/min), 240 °C (3 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +94.1 (c = 1.11, CH_2Cl_2) [59% *ee*].

(1*S*,6*R*)-5,5-Dimethylbicyclo[4.2.0]octan-2-one (303)



303

Racemic [2+2] Photocycloaddition:

Following GP10, 4,4-dimethylcyclohex-2-en-1-one (24.8 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 22 hours. After applying WP2 (three days of isomerization over basic alumina was required) with eluent-mixture (P/Et_2O = 4/1), ketone *rac*-**303** (10.9 mg, 71.6 µmol, 36%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, 4,4-dimethylcyclohex-2-en-1-one (24.8 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 (three days of isomerization over basic alumina was required) with eluent-mixture (P/Et_2O = 4/1), ketone **303** (19.0 mg, 125 µmol, 62%, 70% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.62 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2954 (m, sp^3-CH), 2866 (m, sp^3-CH), 1702 (vs, C=O), 1471 (w, sp^3-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.83 (s, 3 H, Me-5), 1.04 (s, 3 H, Me-5), 1.56 (dddd, ^2J = 13.8 Hz, $^3J_1$ = 5.9 Hz, $^3J_2$ = 2.9 Hz, ^4J = 2.0 Hz, 1 H, *H*H-4), 1.73-1.87 (m, 2 H, H-7), 1.92 (*virt.* td, $^2J \approx {}^3J_1$ = 13.8 Hz, $^3J_2$ = 4.7 Hz, 1 H, H*H*-4), 1.98-2.04 (m, 1 H, *H*H-8), 2.09 (*virt.* ddt, ^2J = 11.4 Hz, $^3J_1$ = 10.1 Hz, $^3J_2 \approx {}^3J_3$ = 8.8Hz, 1 H, H*H*-8), 2.32 (dddd, ^2J = 16.1 Hz, $^3J_1$ = 4.7 Hz, $^3J_2$ = 2.9 Hz, ^4J = 0.7 Hz, 1 H, *H*H-3), 2.41 (dddd, ^2J = 16.1 Hz, $^3J_1$ = 13.8 Hz, $^3J_2$ = 5.9 Hz, ^4J = 0.8 Hz, 1 H, H*H*-3), 2.52-2.59 (m, 1 H, H-6), 2.72-2.78 (m, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.8 (t, C-8), 23.3 (t, C-7), 25.9 (q, Me-5), 26.1 (q, Me-5), 30.4 (s, C-5), 34.1 (t, C-4), 37.3 (t, C-3), 45.0 (d, C-1), 48.0 (d, C-6), 216.7 (s, C-2).

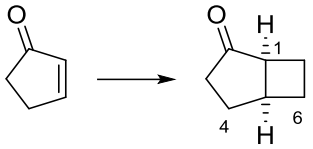
MS (EI, 70 eV): m/z (%) = 152 (35) $[M]^+$, 137 (24) $[M–CH_3]^+$, 123 (30) $[M–C_2H_4]^+$, 109 (26) $[M–C_3H_7]^+$, 96 (100) $[C_6H_8O]^+$, 81 (77), 67 (57), 55 (66) $[C_4H_7]^+$, 41 (52) $[C_3H_5]^+$.

HRMS (EI, 70 eV): calcd for $C_{10}H_{16}O$ $[M]^+$: 152.1196; found: 152.1204.

Chiral GC: τ_R (minor) = 13.7 min, τ_R (major) = 13.9 min, [60 °C (0 min), 120 °C (30 °C/min), 120 °C (10 min), 240 °C (30 °C/min), 240 °C (2 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +56.8 (c = 1.73, CH_2Cl_2) [70% *ee*].

(1*S*,5*S*)-Bicyclo[3.2.0]heptan-2-one (304)



$C_7H_{10}O$
MW = 110.16 g/mol

235 **304**

Racemic [2+2] Photocycloaddition:

Following GP10, enone **235** (16.4 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 22 hours [*n.b.*: irradiation was performed at λ = 350 nm]. After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone *rac*-**304** (3.10 mg, 28.1 µmol, 14%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **235** (16.4 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 with eluent-mixture (P/Et_2O = 4/1), ketone **304** (10.1 mg, 91.7 µmol, 46%, 90% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.51 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.83-1.94 (m, 3 H, *H*H-4, *H*H-6, *H*H-7), 2.06 (dddd, ^2J = 13.5 Hz, $^3J_1$ = 10.9 Hz, $^3J_2$ = 9.4 Hz, $^3J_3$ = 7.4 Hz, 1 H, H*H*-4), 2.29-2.47 (m, 3 H, *H*H-3, H*H*-6, H*H*-7), 2.66-2.76 (m, 2 H, H*H*-3, H-5), 3.00-3.08 (m, 1 H, H-1).

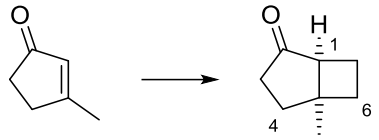
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.3 (t, C-7), 25.0 (t, C-6), 28.2 (t, C-4), 35.5 (d, C-1), 37.0 (t, C-3), 45.1 (d, C-5), 223.7 (s, C-2).

Chiral GC: τ_R (minor) = 7.9 min, τ_R (major) = 8.3 min, [60 °C (0 min), 120 °C (30 °C/min), 120 °C (10 min), 240 °C (30 °C/min), 240 °C (2 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +329 (c = 1.42, CH_2Cl_2) [90% *ee*].

The analytical data obtained matched those reported in the literature.[303]

(1*S*,5*S*)-5-Methylbicyclo[3.2.0]heptan-2-one (233)



$C_8H_{12}O$
MW = 124.18 g/mol

233

Racemic [2+2] Photocycloaddition:

Following GP10, 3-methylcyclopent-2-en-1-one (19.2 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL) for 22 hours [*n.b.*: Irradiation was performed at $\lambda = 350$ nm]. After applying WP2 with eluent-mixture ($P/Et_2O = 4/1$), ketone *rac*-**233** (7.80 mg, 62.8 µmol, 31%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, 3-methylcyclopent-2-en-1-one (19.2 mg, 200 µmol, 1.00 equiv) and ethylene (approx. 1 mL) were irradiated in dichloromethane (10.0 mL). After applying WP2 with eluent-mixture ($P/Et_2O = 4/1$), ketone **233** (5.20 mg, 41.9 µmol, 21%, 93% *ee*) was obtained as a colorless oil. Starting material (12.4 mg, 129 µmol, 65%) was partially recovered.

TLC: $R_f = 0.58$ ($P/Et_2O = 1/1$) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.30 (s, 3 H, Me-5), 1.70 (ddd, $^2J = 13.2$ Hz, $^3J_1 = 11.0$ Hz, $^3J_2 = 9.2$ Hz, 1 H, *H*H-4), 1.77 (dddd, $^2J = 11.2$ Hz, $^3J_1 = 8.8$ Hz, $^3J_2 = 5.0$ Hz, $^3J_3 = 2.9$ Hz, 1 H, *H*H-7), 1.88-1.96 (m, 2 H, H*H*-4, *H*H-6), 2.04-2.10 (m, 1 H, H*H*-6), 2.29-2.34 (m, 1 H, H-1), 2.34-2.43 (m, 2 H, *H*H-3, H*H*-7), 2.68-2.76 (m, 1 H, H*H*-3).

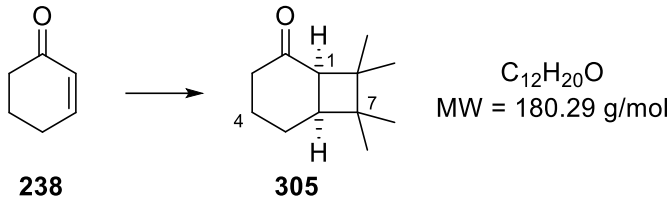
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 19.0 (t, C-7), 26.1 (q, Me-5), 30.9 (t, C-6), 35.7 (t, C-4), 38.6 (t, C-3), 42.7 (s, C-5), 50.5 (d, C-1), 223.2 (s, C-2).

Chiral GC: τ_R (major) = 12.8 min, τ_R (minor) = 13.4 min, [60 °C (0.5 min), 200 °C (4 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25} = +284$ ($c = 0.86$, CH_2Cl_2) [93% *ee*].

The analytical data obtained matched those reported in the literature.[221]

(1*R*,6*S*)-7,7,8,8-Tetramethylbicyclo[4.2.0]octan-2-one (305)



Racemic [2+2] Photocycloaddition:

Following GP10, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and 2,3-dimethyl-2-butene (1.19 mL, 842 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (8.81 mL) for 15 hours. After applying WP1 with eluent-mixtures (P/Et_2O = 6/1, short) and (P/Et_2O = 6/1, long), ketone *rac*-**305** (20.6 mg, 114 µmol, 57%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **238** (19.2 mg, 200 µmol, 1.00 equiv) and 2,3-dimethyl-2-butene (1.19 mL, 842 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (8.81 mL). After applying WP1 with eluent-mixtures (P/Et_2O = 6/1, short) and (P/Et_2O = 6/1, long), ketone **305** (5.00 mg, 27.7 µmol, 14%, 46% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.53 (P/Et_2O = 1/1) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2940 (s, sp^3-CH), 2867 (m, sp^3-CH), 1693 (vs, C=O), 1369 (s, sp^3-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 0.91 (s, 3 H, Me-7), 1.02 (s, 3 H, Me-8), 1.04 (s, 3 H, Me-8), 1.09 (s, 3 H, Me-7), 1.53 (*virt.* qdd, $^2J \approx {}^3J_1 \approx {}^3J_2$ = 12.8 Hz, $^3J_3$ = 4.5 Hz, ^4J = 2.7 Hz, 1 H, *H*H-4), 1.60-1.69 (m, 1 H, *H*H-5), 1.79-1.86 (m, 1 H, H*H*-5), 1.94 (*virt.* dddt, ^2J = 13.5 Hz, $^3J_1$ = 5.9 Hz, $^3J_2$ = 4.6 Hz, $^3J_3 \approx {}^3J_4$ = 2.9 Hz, 1 H, H*H*-4), 2.09 (dddd, ^2J = 18.3 Hz, $^3J_1$ = 12.6 Hz, $^3J_2$ = 5.9 Hz, ^4J = 1.1 Hz, 1 H, *H*H-3), 2.18 (ddd, $^3J_1$ = 11.1 Hz, $^3J_2$ = 9.4 Hz, $^3J_3$ = 7.9 Hz, 1 H, H-6), 2.38 (dddd, ^2J = 18.3 Hz, $^3J_1$ = 6.3 Hz, $^3J_2$ = 3.2 Hz, ^4J = 1.7 Hz, 1 H, H*H*-3), 2.71 (*virt.* dq, ^3J = 9.4 Hz, $^4J_1 \approx {}^4J_2 \approx {}^4J_3$ = 0.9 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 19.1 (q, Me-7), 22.0 (t, C-4), 23.1 (q, Me-8), 24.1 (t, C-5), 26.4 (q, Me-8), 27.3 (q, Me-7), 39.7 (s, C-7), 41.3 (t, C-3), 42.5 (d, C-6), 44.5 (s, C-8), 50.6 (d, C-1), 214.5 (s, C-2).

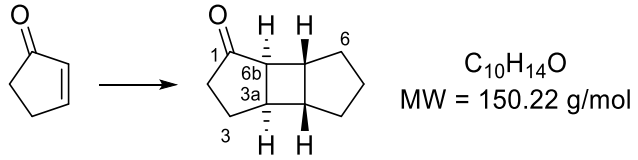
MS (EI, 70 eV): m/z (%) = 180 (13) $[M]^+$, 98 (58) $[M–C_6H_{10}]^+$, 83 (100) $[C_6H_{11}]^+$, 69 (26), 55 (14), 41 (13).

HRMS (EI, 70 eV): calcd for $C_{12}H_{20}O$ $[M]^+$: 180.1509; found: 180.1509.

Chiral GC: τ_R (major) = 15.0 min, τ_R (minor) = 15.1 min, [60 °C (0 min), 120 °C (30 °C/min), 120 °C (10 min), 240 °C (30 °C/min), 240 °C (2 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +56.0 (c = 1.25, CH_2Cl_2) [46% *ee*].

(3a*R*,3b*S*,6a*R*,6b*S*)-Octahydrocyclobuta[1,2:3,4]di[5]annulen-1(2*H*)-one (5)



235 **5**

Racemic [2+2] Photocycloaddition:

Following GP10, enone **235** (16.4 mg, 200 µmol, 1.00 equiv) and cyclopentene (881 µL, 681 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (9.12 mL) for 23 hours. After applying WP1 with eluent-mixtures (P/Et_2O = 6/1, short) and (P/Et_2O = 6/1, long), ketone *rac*-**5** (15.7 mg, 105 µmol, 52%) was obtained as a colorless oil.

Enantioselective [2+2] Photocycloaddition:

Following GP11, enone **235** (16.4 mg, 200 µmol, 1.00 equiv) and cyclopentene (881 µL, 681 mg, 10.0 mmol, 50.0 equiv) were irradiated in dichloromethane (9.12 mL). After applying WP1 with eluent-mixtures (P/Et_2O = 6/1, short) and (P/Et_2O = 6/1, long), ketone **5** (3.70 mg, 24.6 µmol, 12%, 86% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.54 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.44-1.59 (m, 2 H, H-4), 1.63-1.68 (m, 1 H, *H*H-6), 1.69-1.74 (m, 1 H, H*H*-6), 1.74-1.79 (m, 1 H, *H*H-5), 1.79-1.86 (m, 1 H, H*H*-5), 1.92 (*virt.* ddt, ^2J = 13.2 Hz, $^3J_1$ = 9.4 Hz, $^3J_2 \approx {}^4J$ = 1.7 Hz, 1 H, *H*H-3), 2.04 (dddd, ^2J = 13.2 Hz, $^3J_1$ = 12.4 Hz, $^3J_2$ = 8.9 Hz, $^3J_3$ = 7.6 Hz, 1 H, H*H*-3), 2.11 (*virt.* dt, $^3J_1$ = 6.5 Hz, $^3J_2 \approx {}^4J$ = 2.2 Hz, 1 H, H-6b), 2.21-2.26 (m, 1 H, *H*H-2), 2.26-2.31 (m, 1 H, H-3a), 2.46-2.52 (m, 2 H, H-3b, H-6a), 2.72 (ddd, ^2J = 17.7 Hz, $^3J_1$ = 12.4 Hz, $^3J_2$ = 9.4 Hz, 1 H, H*H*-2).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 24.8 (t, C-5), 28.4 (t, C-3), 33.2 (t, C-6), 33.3 (t, C-4), 36.4 (t, C-2), 38.7 (d, C-3a), 40.5 (d, C-6a), 43.2 (d, C-3b), 49.0 (d, C-6b), 222.9 (s, C-1).

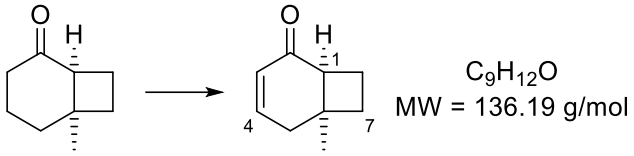
Chiral GC: τ_R (minor) = 15.4 min, τ_R (major) = 15.5 min, [60 °C (0 min), 120 °C (30 °C/min), 120 °C (10 min), 240 °C (30 °C/min), 240 °C (2 min)], Cyclosil-B.

Specific Rotation: $[\alpha]_D^{25}$ = +670 (c = 0.20, CH_2Cl_2) [86% *ee*].

The analytical data obtained matched those reported in the literature.[304]

6.3.12 Synthesis of (–)-Grandisol

(1*S*,6*S*)-6-Methylbicyclo[4.2.0]oct-3-en-2-one (306)



231 **306**

According to a modified literature procedure:[246] Dimethylsulfoxide (33.4 µL, 36.7 mg, 470 µmol, 10.0 mol%) was added to a solution of ketone **231** (650 mg, 4.70 mmol, 1.00 equiv) and palladium(II) trifluoroacetate (78.2 mg, 235 µmol, 5.00 mol%) in acetic acid (24 mL, 200 mM) at room temperature. The reaction vessel was evacuated and purged with oxygen three times. The reaction mixture was heated at 80 °C and was subsequently vigorously stirred for 19 hours under an oxygen atmosphere (balloon). After cooling to room temperature, the suspension was filtered through a short plug of Celite in order to remove precipitated palladium and washed with small portions of diethyl ether. The filtrate was washed with saturated aqueous sodium hydrogen carbonate solution (2 × 80 mL) [*caution*: carbon dioxide evolution], dried with brine (80 mL) and over sodium sulfate. After filtration, the solution was concentrated in vacuo. After purification of the residue by column chromatography (silica, P/Et_2O = 1/1), enone **306** (324 mg, 2.38 mmol, 51%, 86% *ee*) was obtained as a pale yellow oil and ketone **231** (177 mg, 1.28 mmol, 27%, 86% *ee*) was recovered.

TLC: R_f = 0.39 (P/Et_2O = 1/1) [$KMnO_4$, UV].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.31 (s, 3 H, Me-6), 1.69 (dddd, ^2J = 11.3 Hz, $^3J_1$ = 8.9 Hz, $^3J_2$ = 4.4 Hz, ^4J = 2.5 Hz, 1 H, *H*H-7), 1.89 (*virt.* ddt, ^2J = 11.8 Hz, $^3J_1$ = 9.2 Hz, $^3J_2 \approx {}^3J_3$ = 4.4 Hz, 1 H, *H*H-8), 2.08-2.21 (m, 2 H, *H*H-5, H*H*-7), 2.25 (ddd, ^2J = 19.5 Hz, ^3J = 4.9 Hz, ^4J = 1.9 Hz, 1 H, H*H*-5), 2.50 (*virt.* ddt, ^2J = 11.8 Hz, $^3J_1$ = 10.1 Hz, $^3J_2 \approx {}^3J_3$ = 8.6 Hz, 1 H, H*H*-8), 2.57-2.62 (m, 1 H, H-1), 6.15 (*virt.* dt, ^3J = 10.4 Hz, $^4J_1 \approx {}^4J_2$ = 2.2 Hz, 1 H, H-3), 6.90 (ddd, $^3J_1$ = 10.4 Hz, $^3J_2$ = 4.9 Hz, $^3J_3$ = 3.4 Hz, 1 H, H-4).

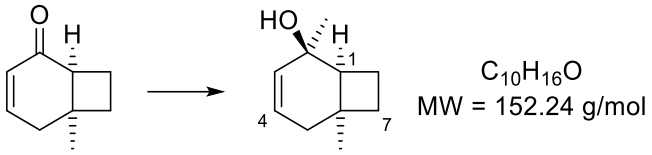
^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.9 (t, C-8), 28.3 (q, Me-6), 32.0 (t, C-7), 36.0 (t, C-5), 37.1 (s, C-6), 48.6 (d, C-1), 129.3 (d, C-3), 148.8 (d, C-4), 202.1 (s, C-2).

Chiral GC: τ_R (major) = 18.5 min, τ_R (minor) = 18.9 min, [60 °C (0.5 min), 200 °C (4 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +25.9 (c = 2.70, CH_2Cl_2) [86% *ee*].

The analytical data obtained matched those reported in the literature.[209]

(1*S*,2*R*,6*S*)-2,6-Dimethylbicyclo[4.2.0]oct-3-en-2-ol (307)



306 **307**

According to a modified literature procedure:[209] A solution of methyllithium (1.60 M in hexane, 2.07 mL, 3.30 mmol, 1.50 equiv) was added dropwise by a syringe pump (0.1 mL/min) to a solution of ketone **306** (300 mg, 2.20 mmol, 1.00 equiv) in diethyl ether (14 mL, 160 mM) at 0 °C. The reaction mixture was stirred for one hour and was subsequently slowly quenched by dropwise addition of water (0.5 mL) followed by brine (10 mL). The layers were separated and the organic layer was dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. No purification with column chromatography was performed since the product is unstable on silica. After desiccation, crude alcohol **307** (293 mg, 1.92 mmol, 96%, 86% *ee*) was obtained as a pale yellow solid. A recrystallization from pentane (50 mg/mL) at –14 °C afforded alcohol **307** (138 mg, 906 μmol, 45%, 96% *ee*) as colorless needles. Recrystallization was repeated with concentrated mother liquor [50 mg/mL] and yielded alcohol **5** (69.2 mg, 455 μmol, 23%, 96% *ee*) as colorless needles.

Mp: 86 °C (P).

TLC: R_f = 0.33 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, C_6D_6, 298 K): δ [ppm] = 1.01 (s, 3 H, Me-6), 1.08 (s, 3 H, Me-2), 1.17 (br s, 1 H, OH-2), 1.47-1.55 (m, 1 H, *H*H-7), 1.55-1.66 (m, 3 H, *H*H-5, H*H*-7, *H*H-8), 1.70 (dd, ^2J = 16.8 Hz, ^3J = 6.4 Hz, 1 H, H*H*-5), 1.73-1.81 (m, 1 H, H*H*-8), 2.01-2.07 (m, 1 H, H-1), 5.67 (ddd, $^3J_1$ = 10.0 Hz, $^3J_2$ = 6.4 Hz, $^3J_3$ = 2.5 Hz, 1 H, H-4), 5.87 (ddd, ^3J = 10.0 Hz, $^4J_1$ = 3.3 Hz, $^4J_2$ = 1.6 Hz, 1 H, H-3).

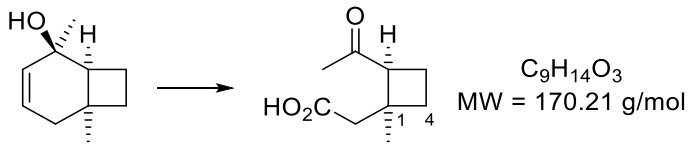
^{13}C NMR (126 MHz, C_6D_6, 300 K): δ [ppm] = 17.6 (t, C-8), 27.6 (q, Me-2), 30.9 (q, Me-6), 32.7 (t, C-7), 35.5 (s, C-6), 36.4 (t, C-5), 51.5 (d, C-1), 70.9 (s, C-2), 126.0 (d, C-4), 136.9 (d, C-3).

Chiral GC: τ_R (major) = 13.7 min, τ_R (minor) = 14.0 min, [60 °C (0.5 min), 200 °C (4 °C/min), 200 °C (5 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{25}$ = +109 (c = 2.42, CH_2Cl_2) [96% *ee*].

The analytical data obtained matched those reported in the literature.[209]

2-[(1*S*,2*S*)-2-Acetyl-1-methylcyclobutyl]acetic acid (308)



307 **308**

According to a modified literature procedure:[209] A solution of ruthenium(III) chloride hydrate (8.00 mg, 35.5 μmol, 0.03 equiv) in water (4 mL, 9.00 mM) was added to a solution of alcohol **307** (200 mg, 1.31 mmol, 1.00 equiv) and sodium perchlorate (1.55 g, 7.23 mmol, 5.50 equiv) in chloroform (2.6 mL, previously filtered through basic alumina) and acetonitrile (2.6 mL, total 250 mM). The reaction mixture was vigorously stirred at room temperature for five hours. Water was added until the colorless precipitate was completely dissolved and it was acidified with a small portion of aqueous hydrochloric acid solution (1.00 M). After extraction with dichloromethane (3 × 10 mL), the combined organic layers were dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. After purification of the residue by column chromatography (silica, P/Et_2O/AcOH = 5/1/0.06 → 4/1/0.05), and removal of residual acetic acid with azeotropic distillation (toluene), ketone **308** (77.5 mg, 455 μmol, 54%, 96% *ee*) was obtained as a pale yellow oil.

TLC: R_f = 0.38 (P/Et_2O/AcOH = 1/1/0.02) [CAM].

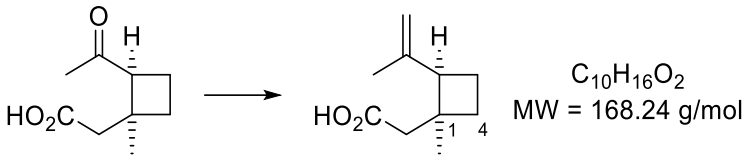
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.39 (s, 3 H, Me-1), 1.78 (*virt.* dt, ^2J = 11.1 Hz, $^3J_1 \approx {}^3J_2$ = 8.6 Hz, 1 H, *H*H-4), 1.92 (*virt.* dtd, ^2J = 11.5 Hz, $^3J_1 \approx {}^3J_2$ = 8.5 Hz, $^3J_3$ = 4.4 Hz, 1 H, *H*H-3), 2.00 (dddd, ^2J = 11.1 Hz, $^3J_1$ = 9.4 Hz, $^3J_2$ = 4.4 Hz, ^4J = 0.9 Hz, 1 H, H*H*-4), 2.10 (s, 3 H, COMe), 2.21 (*virt.* ddt, ^2J = 11.5 Hz, $^3J_1$ = 9.4 Hz, $^3J_2 \approx {}^3J_3$ = 8.3 Hz, 1 H, H*H*-3), 2.46 (d, ^2J = 15.6 Hz, 1 H, C*H*HCO$_2$H), 2.54 (dd, ^2J = 15.6 Hz, ^4J = 0.9 Hz, 1 H, CH*H*CO$_2$H), 3.08 (t, ^3J = 8.3 Hz, 1 H, H-2), 10.94 (br s, 1 H, CH_2CO_2H).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 17.7 (t, C-3), 27.8 (q, Me-1), 30.6 (t, C-4), 31.0 (q, CO*Me*), 39.8 (t, *C*H_2CO_2H), 41.3 (s, C-1), 55.1 (d, C-2), 177.6 (s, CH_2*C*O_2H), 209.5 (s, *C*OMe).

Specific Rotation: $[\alpha]_D^{24}$ = +36.2 (c = 2.65, CH_2Cl_2) [96% *ee*].

The analytical data obtained matched those reported in the literature.[209]

2-[(1*S*,2*R*)-1-Methyl-2-(prop-1-en-2-yl)cyclobutyl]acetic acid (309)



308 **309**

According to a modified literature procedure:[209] A solution of *n*-butyllithium (2.50 M in hexane, 418 µL, 1.05 mmol, 2.50 equiv) was added dropwise to a suspension of methyltriphenylphosphonium bromide (374 mg, 1.05 mmol, 2.50 equiv) in tetrahydrofuran (5.81 mL, 180 mM) at 0 °C. The reaction mixture was stirred for one hour. A solution of ketone **308** (71.2 mg, 418 µmol, 1.00 equiv) in tetrahydrofuran (523 µL, 800 mM) was added dropwise to the ylid solution at 0 °C. The reaction solution was allowed to warm to room temperature and was subsequently stirred for two hours. The reaction mixture was poured into water (20 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined and dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. After purification of the residue by column chromatography (silica, P/Et_2O = 1/1), acid **309** (52.2 mg, 310 µmol, 74%, 96% *ee*) was obtained as a crystalline colorless solid.

Mp: 49 °C.

TLC: R_f = 0.28 (P/Et_2O = 1/1) [$KMnO_4$].

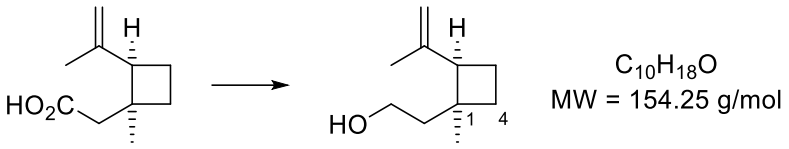
^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.32 (d, ^4J = 0.7 Hz, 3 H, Me-1), 1.66 (*virt.* dt, $^4J_1$ = 1.5 Hz, $^4J_2 \approx {}^4J_3$ = 0.8 Hz, 3 H, C*H*$_3$CCH$_2$), 1.68-1.77 (m, 1 H, *H*H-4), 1.81-1.88 (m, 1 H, *H*H-3), 1.93-2.03 (m, 2 H, H*H*-3, H*H*-4), 2.05 (dd, ^2J = 14.7 Hz, ^4J = 1.5 Hz, 1 H, C*H*HCO$_2$H), 2.55 (d, ^2J = 14.7 Hz, 1 H, CH*H*CO$_2$H), 2.63 (*virt.* dddt, $^3J_1$ = 9.5 Hz, $^3J_2$ = 8.6 Hz, $^4J_1$ = 1.7 Hz, $^4J_2 \approx {}^4J_3$ = 0.9 Hz, 1 H, H-2), 4.67 (*virt.* dquint, ^2J = 3.0 Hz, $^4J_1 \approx {}^4J_2$ = 0.9 Hz, 1 H, CH$_3$CC*H*H), 4.86 (dq, ^2J = 3.0 Hz, ^4J = 1.5 Hz, 1 H, CH$_3$CCH*H*), 11.00 (br s, 1 H, CH$_2$CO$_2$*H*).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 19.0 (t, C-3), 23.3 (q, *C*H_3CCH_2), 28.2 (q, Me-1), 29.2 (t, C-4), 38.7 (t, *C*H_2CO_2H), 41.4 (s, C-1), 52.1 (d, C-2), 110.6 (t, CH_3*C*CH_2), 144.6 (s, CH_3*C*CH_2), 179.1 (s, CH_2*C*O_2H).

Specific Rotation: $[\alpha]_D^{24}$ = –49.2 (c = 2.28, CH_2Cl_2) [96% *ee*].

The analytical data obtained matched those reported in the literature.[209]

2-[(1*S*,2*R*)-1-Methyl-2-(prop-1-en-2-yl)cyclobutyl]ethan-1-ol, (–)-grandisol (15)



309 **15**

According to a modified literature procedure:[209] A solution of acid **309** (45.2 mg, 269 µmol, 1.00 equiv) in diethyl ether (537 µL, 500 mM) was added dropwise to a suspension of lithiumaluminum hydride (20.4 mg, 537 µmol, 2.00 equiv) in diethyl ether (1.1 mL, 500 mM) at 0 °C. The resulting mixture was allowed to warm to room temperature and was subsequently stirred for four hours. The excess lithiumaluminum hydride was quenched at 0 °C by dropwise addition of methanol until no evolution of gas could be observed. The mixture was treated with aqueous hydrochloric acid solution (1.00 M, 1.00 mL) and diluted with brine (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over sodium sulfate. After filtration, the solution was concentrated in vacuo. Without further purification, alcohol **15** (39.5 mg, 256 µmol, 95%, 96% *ee*) was obtained as a colorless oil.

TLC: R_f = 0.36 (P/Et_2O = 1/1) [$KMnO_4$].

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.17 (d, ^4J = 1.2 Hz, 3 H, Me-1), 1.40-1.48 (m, 1 H, C*H*HCH_2OH), 1.57-1.70 (m, 5 H, H-4, C*H*$_3$$CCH_2$), 1.72-1.84 (m, 2 H, *H*H-3, CH*H*CH_2OH), 1.97 (*virt.* dtdd, ^2J = 11.5 Hz, $^3J_1 \approx {}^3J_2$ = 10.3 Hz, $^3J_3$ = 8.9 Hz, ^4J = 1.4 Hz, 1 H, H*H*-3), 2.55 (*virt.* t, $^3J_1 \approx {}^3J_2$= 9.1 Hz, 1 H, H-2), 3.62-3.73 (m, 2 H, CH_2C*H*$_2$OH), 4.65 (*virt.* tq, $^2J \approx {}^4J_1$ = 1.8 Hz, $^4J_2$ = 0.9 Hz, 1 H, CH_3CC*H*H), 4.84 (dq, ^2J = 2.9 Hz, ^4J = 1.4 Hz, 1 H, CH_3CCH*H*).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 19.3 (t, C-3), 23.4 (q, *C*H_3CCH_2), 28.5 (q, Me-1), 29.4 (t, C-4), 37.0 (t, *C*H_2CH_2OH), 41.4 (s, C-1), 52.6 (d, C-2), 60.1 (t, CH_2*C*H_2OH), 109.9 (t, CH_3C*C*H_2), 145.4 (s, CH_3*C*CH_2).

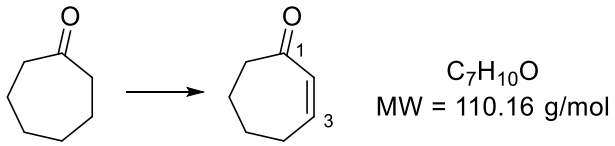
Chiral GC: τ_R (minor) = 80.6 min, τ_R (major) = 81.9 min, [60 °C (0.5 min), 75 °C (10 °C/min), 75 °C (77 min), 110 °C (3 °C/min), 180 °C (10 °C/min), 180 °C (3 min)], Lipodex E.

Specific Rotation: $[\alpha]_D^{24} = -13.2$ (c = 3.02, CH_2Cl_2) [96% *ee*].

The analytical data obtained matched those reported in the literature.[209]

6.3.13 Synthesis of Irradiation Precursors for *Cis-Trans* Isomerizations

Cyclohept-2-en-1-one (315)



320 **315**

Following GP12, ketone **320** (5.00 g, 44.6 mmol, 1.00 equiv) was converted with bromine (2.28 mL, 7.12 g, 44.6 mmol, 1.00 equiv) in ethylene glycol (45 mL). After work-up and column chromatography, enone **315** (1.25 g, 11.3 mmol, 25%) was obtained as a pale yellow oil.

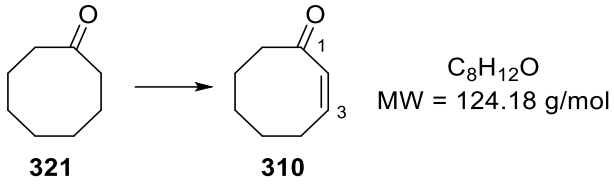
TLC: R_f = 0.56 (P/EtOAc = 3/1) [$KMnO_4$].

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.76-1.82 (m, 2 H, H-6), 1.82-1.90 (m, 2 H, H-5), 2.48 (dtd, $^3J_1$ = 6.8 Hz, $^3J_2$ = 5.4 Hz, ^4J = 1.7 Hz, 2 H, H-4), 2.59-2.64 (m, 2 H, H-7), 6.04 (dtt, ^3J = 12.1 Hz, $^4J_1$ = 1.7 Hz, $^4J_2$ = 0.7 Hz, 1 H, H-2), 6.60 (dt, ^3J = 12.1 Hz, ^3J = 5.4 Hz, 1 H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 21.9 (t, C-6), 26.3 (t, C-5), 30.4 (t, C-4), 43.7 (t, C-7), 132.7 (d, C-2), 146.5 (d, C-3), 204.5 (s, C-1).

The analytical data obtained matched those reported in the literature.[305]

Cyclooct-2-en-1-one (310)



Following GP12, ketone **321** (5.62 g, 44.6 mmol, 1.00 equiv) was converted with bromine (2.28 mL, 7.12 g, 44.6 mmol, 1.00 equiv) in ethylene glycol (45 mL). After work-up and column chromatography, enone **310** (888 mg, 7.15 mmol, 16%) was obtained as a pale yellow oil.

TLC: R_f = 0.62 (P/EtOAc = 3/1) [$KMnO_4$].

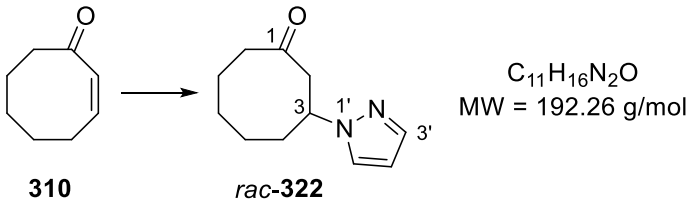
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.54-1.61 (m, 2 H, H-6), 1.61-1.67 (m, 2 H, H-5), 1.78-1.86 (m, 2 H, H-7), 2.51 (tdd, $^3J_1$ = 7.0 Hz, $^3J_2$ = 5.6 Hz, ^4J = 1.5 Hz, 2 H, H-4), 2.63-2.68 (m, 2 H, H-8), 6.01 (dtt, ^3J = 12.4 Hz, $^4J_1$ = 1.5 Hz, $^4J_2$ = 0.5 Hz, 1 H, H-2), 6.35 (dt, $^3J_1$ = 12.4 Hz, $^3J_2$ = 7.0 Hz, 1 H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.7 (t, C-7), 23.3 (t, C-5), 25.3 (t, C-6), 28.7 (t, C-4), 42.9 (t, C-8), 132.5 (d, C-2), 141.7 (d, C-3), 206.2 (s, C-1).

The analytical data obtained matched those reported in the literature.[254]

6.3.14 *Cis*/*Trans*-Isomerization Reactions

3-(1*H*-Pyrazol-1-yl)cyclooctan-1-one (*rac*-322)



Racemic *Cis*/*Trans*-Isomerization:

A solution of enone **310** (22.4 mg, 180 µmol, 1.00 equiv) and pyrazole (36.8 mg, 540 µmol, 3.00 equiv) in dichloromethane (3.50 mL, 50.0 mM) was irradiated in a phototube at room temperature at λ = 350 nm. After 24 hours, the solvent was removed in vacuo and the residue was purified by column chromatography (silica, cHex/EtOAc = 4/1). The ketone *rac*-**322** (33.7 mg, 175 µmol, 97%) was obtained as a colorless solid.

Enantioselective *Cis*/*Trans*-Isomerization:

A solution of enone **310** (12.4 mg, 100 μmol, 1.00 equiv) in dichloromethane (1-3 mL) was transferred to a heat-gun dried *Duran* phototube and the vessel was washed twice with small portions of dichloromethane. Then, a solution of the activated oxazaborolidine catalyst **50'** (22.5 mg, 50.0 μmol, 50.0 mol%) in dichloromethane (1-3 mL) was transferred to the solution and the vessel was washed with small portions of dichloromethane. Dichloromethane was added until a concentration of 20 mM was reached. The solution was cooled to –75 °C within 30 minutes and was subsequently irradiated at λ = 350 nm for four hours. The light source was switched off and a solution of pyrazole (68.1 mg, 1.00 mmol, 10.0 equiv) in dichloromethane (2.00 mL, 500 mM) pre-cooled at 0 °C was added dropwise. After complete addition, the resulting solution was homogenized, cooled to –78 °C, and was allowed to warm to room temperature over night. The solvent was removed and the residue was purified by column chromatography (silica, cHex/EtOAc = 4/1) affording ketone *rac*-**322** (17.7 mg, 92.1 μmol, 92%, 0% *ee*) as a colorless solid.

Mp: 67 °C.

TLC: R_f = 0.42 (CH_2Cl_2/MeOH = 98/2) [$KMnO_4$].

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3111 (m, sp^2-CN), 2938 (m, sp^3-CH), 2876 (w, sp^3-CH), 1686 (s, C=O), 1401 (s, sp^2-CN), 1283 (s, sp^2-CN), 762 (vs, sp^2-CH).

^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ [ppm] = 1.28-1.38 (m, 1 H, *H*H-5), 1.51-1.60 (m, 1 H, *H*H-6), 1.63-1.77 (m, 2 H, H*H*-5, H*H*-6), 1.87-1.94 (m, 1 H, *H*H-7), 2.00-2.12 (m, 2 H, H-4), 2.13-2.24 (m, 1 H, H*H*-7), 2.45-2.49 (m, 2 H, H-8), 2.65 (ddd, ^2J = 12.2 Hz, ^3J = 3.5 Hz, ^4J = 1.3 Hz, 1 H, *H*H-2), 3.37 (*virt.* t, $^2J \approx {}^3J$ = 12.0 Hz, 1 H, H*H*-2), 4.54-4.61 (m, 1 H, H-3), 6.21-6.22 (m, 1 H, H-4'), 7.41 (dd, ^3J = 2.4 Hz, ^4J = 0.8 Hz, 1 H, H-5'), 7.50 (dd, ^3J = 1.9 Hz, ^4J = 0.8 Hz, 1 H, H-3').

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ [ppm] = 22.0 (t, C-5), 23.6 (t, C-7), 27.7 (t, C-6), 33.8 (t, C-4), 43.8 (t, C-8), 47.1 (t, C-2), 61.0 (d, C-3), 105.3 (d, C-4'), 127.4 (d, C-5'), 139.3 (d, C-3'), 212.9 (s, C-1).

MS (EI, 70 eV): m/z (%) = 192 (19) $[M]^+$, 164 (20) $[M–CO]^+$, 149 (20), 135 (26), 121 (30), 107 (27), 95 (97), 81 (99), 69 (100) $[C_3H_5N_2]^+$, 55 (50) $[C_4H_7]^+$, 41 (40) $[C_3H_5]^+$.

HRMS (EI, 70 eV): calcd for $C_{11}H_{16}ON_2$ $[M]^+$: 192.1257; found: 192.1260;
calcd for $C_{10}{}^{13}CH_{16}ON_2$ $[M]^+$: 193.1291; found: 193.1299.

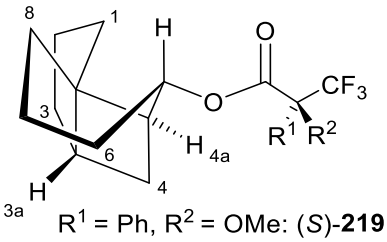
Chiral HPLC: τ_{R1} = 5.4 min, τ_{R2} = 7.1 min, [H_2O/MeCN = 80/20 → 0/100, 30 min], Chiralpak AD-RH, 150×4.6.

7. Appendices

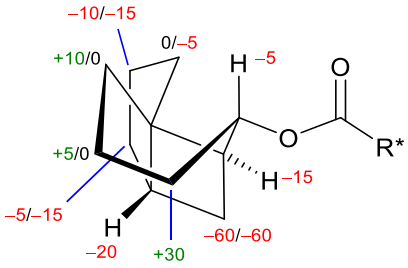
7.1 *Mosher* Analysis of Ketones (*S*)-219 and (*R*)-219

Proton	δ_S [ppm]	δ_R [ppm]	$\Delta\delta^{SR}$ [ppm]	$\Delta\delta^{SR}$ [Hz]
H-6	1.90	1.84	+0.06	+30
H_B-8	1.41	1.39	+0.02	+10
H_A-7	1.87	1.86	+0.01	+5
H_B-7	1.65	1.65	0	0
H_A-1	1.62	1.62	0	0
H_A-8	1.60	1.60	0	0
H_A-3	1.58	1.59	–0.01	–5
H_B-1	1.18	1.19	–0.01	–5
H-5	5.27	5.28	–0.01	–5
H_B-2	1.78	1.80	–0.02	–10
H-4a	2.35	2.38	–0.03	–15
H_B-3	1.48	1.51	–0.03	–15
H_A-2	1.90	1.93	–0.03	–15
H-3a	2.26	2.30	–0.04	–20
H_A-4	2.02	2.14	–0.12	–60
H_B-4	1.22	1.34	–0.12	–60

In the case of overlaying signals, HSQC crosspeaks were used for exact assignment.



R^1 = Ph, R^2 = OMe: (*S*)-**219**
R^1 = OMe, R^2 = Ph: (*R*)-**219**



$\Delta\delta^{SR} = \delta_S - \delta_R$

Mosher analysis was conducted according to a literature procedure and confirms the above shown absolute configuration.[193]

7.2 DFT Calculations

7.2.1 Thermodynamic Calculations

Derivation of equation (1) starting from the equation for the calculation of enantiomeric excesses:

$$ee = \frac{k_S - k_R}{k_S + k_R} \leftrightarrow (k_S + k_R)ee = k_S - k_R \leftrightarrow k_S \times ee - k_S + k_R \times ee + k_R = 0$$

$$k_S(ee - 1) + k_R(ee + 1) = 0 \leftrightarrow \frac{k_S}{k_R} + \frac{(ee + 1)}{(ee - 1)} = 0 \leftrightarrow \frac{k_S}{k_R} = -\frac{(ee + 1)}{(ee - 1)}$$

Derivation of equation (2) starting from the thermodynamic *Eyring*'s equation[306] for absolute reaction rates, assuming a transmission coefficient of unity:

$$k_{S\ or\ R} = \frac{k_b T}{h} \times e^{-\frac{\Delta G^{\neq}_{S\ or\ R}}{RT}}$$

$$\frac{k_S}{k_R} = \frac{e^{-\frac{\Delta G^{\neq}_S}{RT}}}{e^{-\frac{\Delta G^{\neq}_R}{RT}}} \leftrightarrow \frac{k_S}{k_R} = e^{\frac{\Delta G^{\neq}_R - \Delta G^{\neq}_S}{RT}} \leftrightarrow \ln\left(\frac{k_S}{k_R}\right) = \frac{\Delta\Delta G^{\neq}_{RS}}{RT} \leftrightarrow \Delta\Delta G^{\neq}_{RS} = \mathrm{R} \times \mathrm{T} \times \ln\left(\frac{k_S}{k_R}\right)$$

Calculation of k_S/k_R and $\Delta\Delta G_{RS}^{\neq}$ for catalyst **176** (*ee* = 75%):

$$\frac{k_S}{k_R} = -\frac{(0.75 + 1)}{(0.75 - 1)} = -(-7) = 7$$

$$\Delta\Delta G^{\neq}_{RS} = \mathrm{R} \times \mathrm{T} \times \ln\left(\frac{k_S}{k_R}\right) = 8.314\frac{J}{mol\ K} \times 198.15\ K\ \times \ln(7) = 3.21\frac{kJ}{mol}$$

Calculation of k_S/k_R and $\Delta\Delta G_{RS}^{\neq}$ for catalyst **193** (*ee* = –29%):

$$\frac{k_S}{k_R} = -\frac{(-0.29 + 1)}{(-0.29 - 1)} = -(-0.55) = 0.55$$

$$\Delta\Delta G^{\neq}_{RS} = \mathrm{R} \times \mathrm{T} \times \ln\left(\frac{k_S}{k_R}\right) = 8.314\frac{J}{mol\ K} \times 198.15\ K\ \times \ln(0.55) = -0.98\frac{kJ}{mol}$$

7.2.2 Calculated Structures of Complex 205·176'

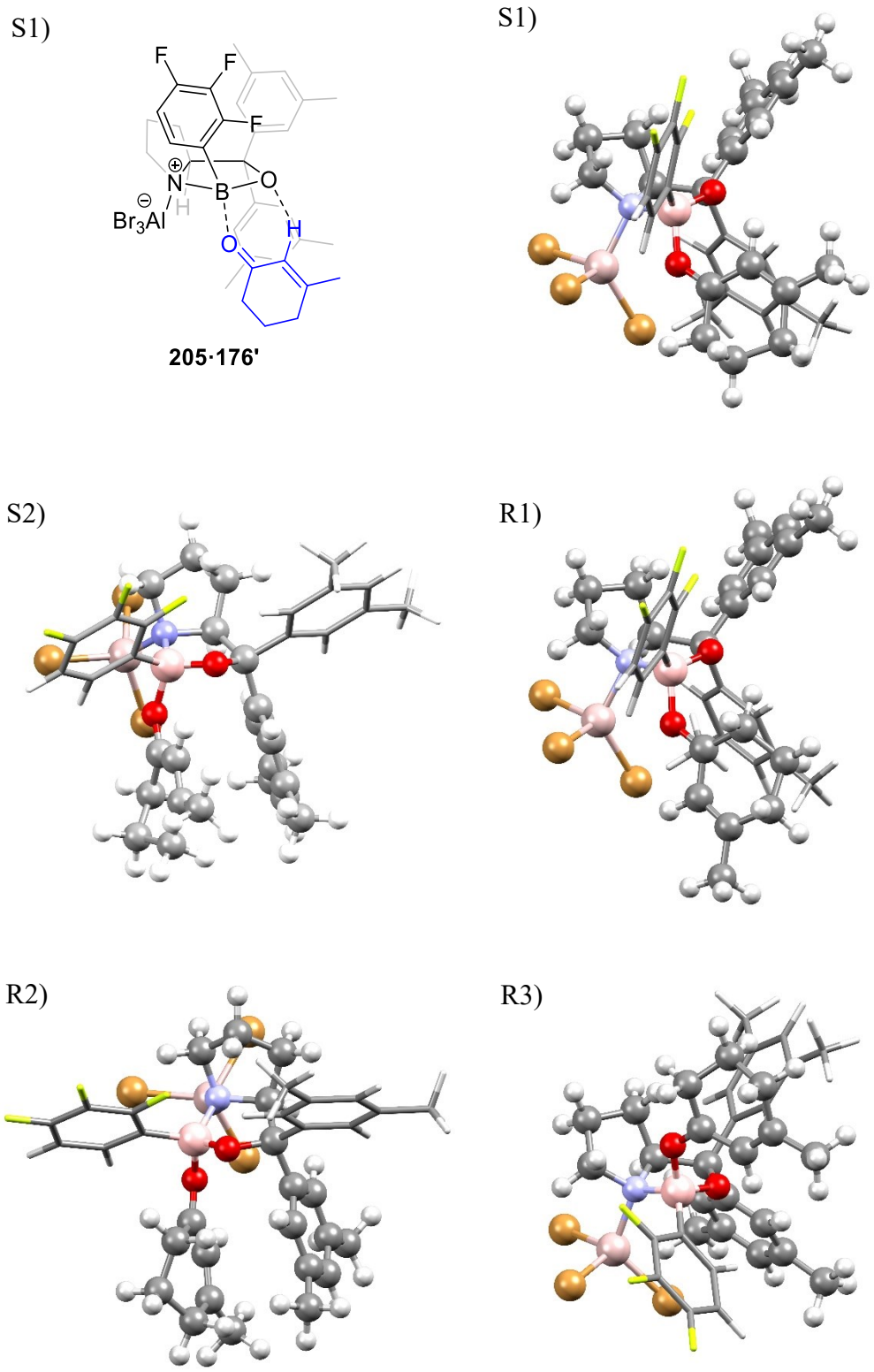


Figure 28. Putative model of the complex **205·176'**. Structures of different complexes as per DFT calculations (B3LYP-D3BJ/cc-pVTZ, PCM = CH_2Cl_2, T = 198 K). Structures S1) and S2) lead to the (*S*) configurated photoadduct and R1), R2) and R3) to the (*R*) configurated photoadduct, respectively.

7.2.3 Calculated Structures of Complex 205·193'

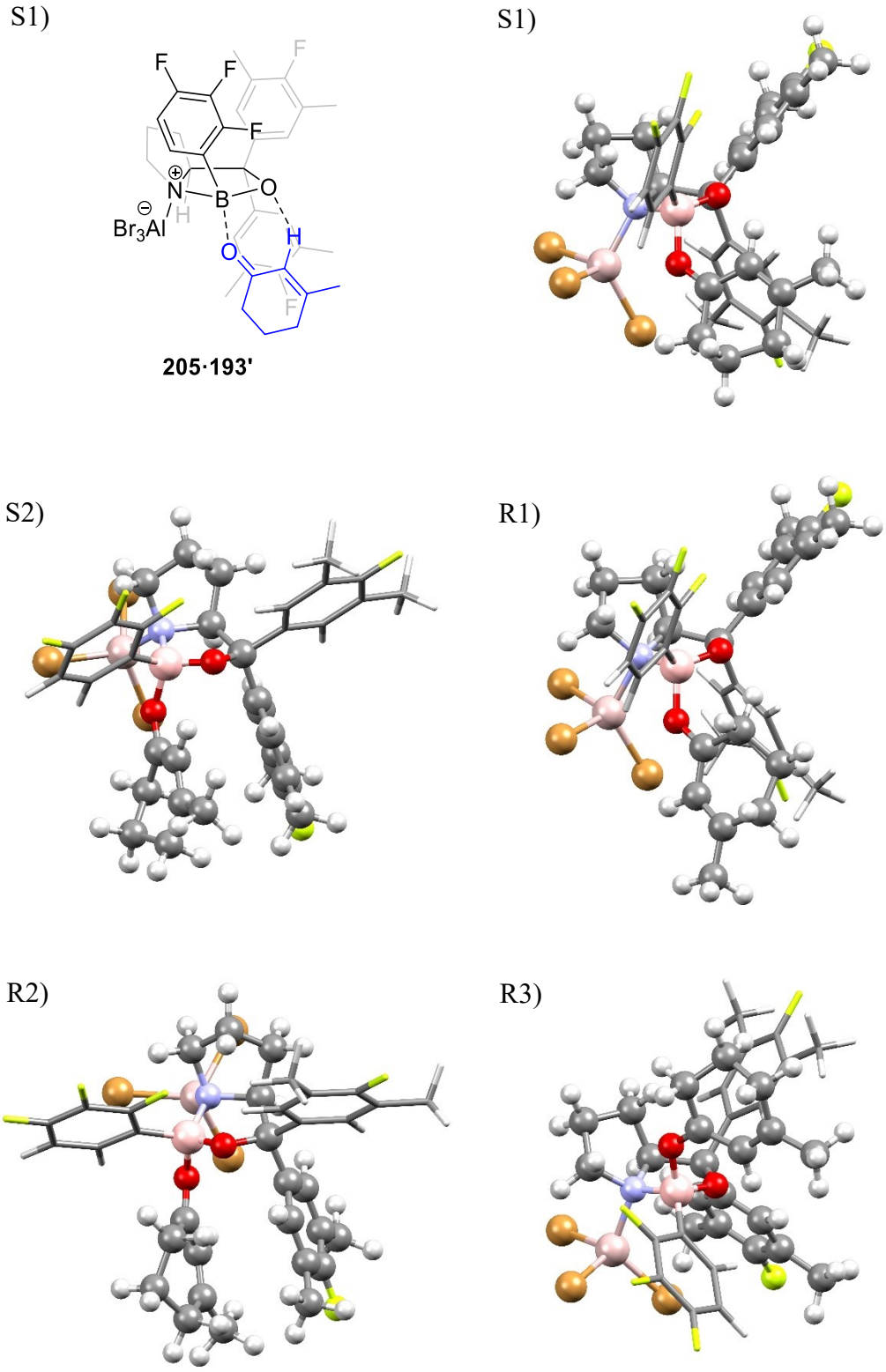
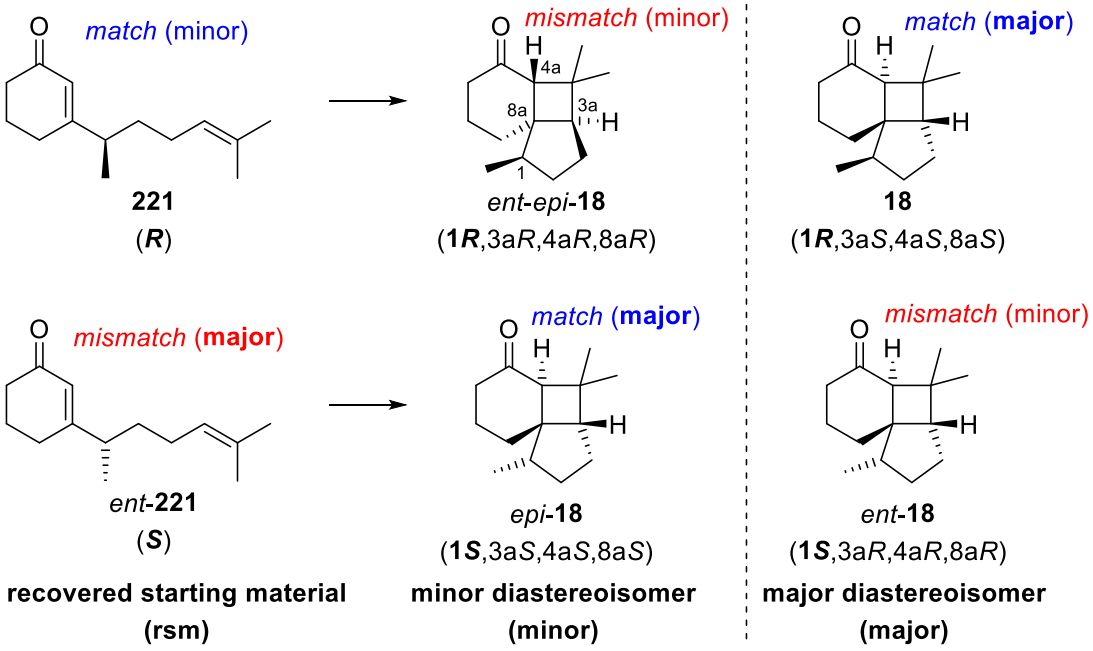


Figure 29. Putative model of the complex **205·193'**. Structures of different complexes as per DFT calculations (B3LYP-D3BJ/cc-pVTZ, PCM = CH_2Cl_2, T = 198 K). Structures S1) and S2) lead to the (*S*) configurated photoadduct and R1), R2) and R3) to the (*R*) configurated photoadduct, respectively.

7.3 Calculations for the Parallel Kinetic Resolution

Following a procedure reported by *Kagan*:[201,202]



enantiomeric excesses with original ***R*** configuration in major products: positive values
enantiomeric excesses with original ***S*** configuration in major products: negative values

ee_{rsm} (–) ee_{minor} (–) ee_{major} (+)

Formulae:

$$C = \frac{(1+dr)ee_{rsm}}{dr(ee_{rsm} - ee_{minor}) + ee_{rsm} - ee_{major}} \quad (4)$$

$$dr = \frac{x_{minor}}{x_{major}} \quad (5)$$

$$s = \frac{\ln[(1-C)(1-ee_{rsm})]}{\ln[(1-C)(1+ee_{rsm})]} \quad (6)$$

Table 8 (Entry 1): Catalyst **50**, ee_{rsm} = –10%, ee_{minor} = –23%, ee_{major} = +42%, d.r. = 0.19

$$C = \frac{(1+0.19)(-0.10)}{0.19(-0.10-(-0.23)) + (-0.10) - 0.42} = 0.24$$

$$s = \frac{\ln[(1 - 0.24)(1 - 0.10)]}{\ln[(1 - 0.24)(1 + 0.10)]} = 2.12$$

Table 8 (Entry 2): Catalyst **176**, ee_{rsm} = –11%, ee_{minor} = –35%, ee_{major} = +27%, d.r. = 0.22

$$C = \frac{(1 + 0.22)(-0.11)}{0.22(-0.11 - (-0.35)) + (-0.11) - 0.27} = 0.41$$

$$s = \frac{\ln[(1 - 0.41)(1 - 0.11)]}{\ln[(1 - 0.41)(1 + 0.11)]} = 1.52$$

Calculation of the hypothetical simple kinetic resolution of *rac*-**221**:

$$C = \frac{ee_{rsm}}{ee_{rsm} + ee_{product}} \qquad (7)$$

$$C = \frac{ee_{rsm}}{ee_{rsm} + ee_{product}} \leftrightarrow ee_{rsm} = \frac{C \times ee_{product}}{1 - C}$$

Assumption: C = 24%, $ee_{product}$ = 90% results in ee_{rsm} = 28%

$$ee_{rsm} = \frac{0.24 \times 0.90}{1 - 0.24} = 0.28$$

ee_{rsm} = 28% and C = 24% result in a selectivity factor of 25.

$$s = \frac{\ln[(1 - 0.24)(1 - 0.28)]}{\ln[(1 - 0.24)(1 + 0.28)]} = 25$$

Assumption: C = 41%, $ee_{product}$ = 90% results in ee_{rsm} = 63%

$$ee_{rsm} = \frac{0.41 \times 0.90}{1 - 0.41} = 0.63$$

ee_{rsm} = 63% and C = 41% result in a selectivity factor of 35.

$$s = \frac{\ln[(1 - 0.41)(1 - 0.63)]}{\ln[(1 - 0.41)(1 + 0.63)]} = 36$$

8. Abbreviations

(dF)(CF_3)ppy	3,5-difluoro-2-[5-(trifluoromethyl)pyridin-2-yl]phenyl
Å	Ångström
Ac	acetyl
ATR	attenuated total reflection
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
calcd	calculated
cHex	cyclohexane
COSY	correlation spectroscopy
d.r.	diastereomeric ratio
de	diastereomeric excess
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*'-dimethylpropylenurea
DMSO	dimethyl sulfoxide
dtbbpy	4,4'-di-*tert*-butyl-2,2'-bipyridine
ee	enantiomeric excess
EI	electron ionization
equiv	equivalents
ESI	electronspray ionization
E_T	triplet energy
Et	ethyl
Et_2O	diethyl ether
GC	gas chromatography
GP	general procedure
h	Planck's constant
h	hour
HFIP	hexafluoro-*iso*-propanol

HFX	hexafluoro-*m*-xylene
HH	head-to-head
HMBC	heteronuclear multiple-bond correlation spectroscopy
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
HT	head-to-tail
$h\nu$	denotes irradiation with photons of a specific wavelength
i	*iso*
i.e.	*id est* (that is)
IC	internal conversion
^{i}Pr	*iso*-propyl
IR	infrared
ISC	intersystem crossing
J	coupling constant
k_B	Boltzmann's constant
LUMO	lowest unoccupied molecular orbital
m	*meta*-
MeOH	methanol
min	minutes
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves/mass spectrometry
MTBE	methyl *tert*-butyl ether
n.b.	*nota bene* (note well)
nHex	*n*-hexane
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
o	*ortho*-

OAc	acetate
OTf	trifluoromethanesulfonate
p	*para*-
P	pentane
PET	photoelectron transfer
Ph	phenyl
PKR	parallel kinetic resolution
ppm	parts per million
ppy	2-(pyridin-2-yl)phenyl
quant	quantitative
R	ideal gas constant
r.t.	room temperature
rac	racemic
rsm	recovered starting material
S_0	singlet ground-state
S_1	singlet excited state
SOMO	singly occupied molecular orbital
t	*tert*
T	temperature
T_1	triplet excited state
TBAF	tetra-*n*-butylammonium fluoride
^{t}Bu	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TST	transition state theory
TTET	triplet-triplet energy transfer
UV	ultraviolet
Vis	visible

WP	work-up procedure
ΔE	electronic energy
ΔG	*Gibb*'s free energy
ε	molar extinction coefficient
λ	wavelength
τ_R	retention time

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