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Unusual Rearrangements Triggered by Hypervalent λ^3- Iodane Reagents

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In this work, relative configurations of racemates are represented by bars (bold and dashed), absolute and relative configurations of optical pure or optical enriched compounds in wedge form (bold or dashed lines).

Abstract

This dissertation focused mainly on hypervalent iodane catalyzed synthese of novel heterocyclic compounds and ring expansion with hypervalent fluoroiodane reagents. On the one hand, a facile diastereoselective one-pot synthese of heterocyclic compounds from corresponding *N*-allylhydroxamic acids **99** was achieved via unusual rearrangement catalyzed by iodine pre-catalyst **59**. On the other hand, hypervalent iodane **42a** mediated fluorination of cyclobutanols **102** to get a-fluoro cyclopentanones **106** in high yield involving a metathesis /fluorination/1, 2-aryl shift /semi-pinacol reaction was realized.

Focusing first on highly diastereoselective one-pot facile synthesis of heterocyclic compounds in moderate to good yields has been investigated. Two heterocyclic rings constructed consecutively in one-pot which *N*-allylhydroxamic acids **99** were firstly converted into *in-situ* generated ketonitrones **101** using hypervalent iodine pre-catalyst **59** and reacted with different dipolarophiles in one-pot via [3+2] cycloaddition to afford the second ring in high diastereoselectivity. Three different dipolarophiles were used to trap the intermediate ketonitrones **101**. In comparison with phenyl isocyanate **107** and 2-(trimethyl silyl) aryl triflate **109**, dimethyl acetylenedicarboxylate (DMAD) **108** reacted with the intermediate ketonitrones **101** in high diastereoselectivity in moderate to good yields.

The next aim was to realize the hypervalent iodane **42a** mediated unusual rearrangement cascade reaction for the construction of a-fluoro cyclopentanones **106** with high yield. The methodology featured the ready availability of the starting materials, high yield, and mild reaction conditions. Further expansion of the substrate scope and transformation of the corresponding products **106** are currently ongoing.

Contents

I. Theoretical Background

1. Introduction

In 1811, the industrial chemist B. Courtois firstly isolated the iodine from the ash of seaweed, and then English chemist Sir Humphry Davy and French physical chemist Louis-Joseph Gay-Lussac further identified the element iodine almost at the same time around 1813.[1] About 100 hundred years later, tincture of iodine was first introduced as a way for rapid disinfection of the human skin in the surgical field by Antonio Grossich, an Istrian-born surgeon. However, only since the middle of 19th century, organoiodine compounds have been utilized in varies reactions, e.g. Hofmann alkylations, Wurtz couplings, and Williamson ether synthese.[2]

Iodine often occurs with an oxidation state of -1 in the monovalent compound, because iodine has seven valence electrons in the fifth shell with the electron configuration of [Kr] $4d^{10}5s^{2}5p^{5}$, so that the iodine is eager to get one electron from the other element to form a full octet. Besides that, the bond between the iodine and the first-row element is comparatively weak respectively, including carbon, that the dissociation energy of typical carbon–iodine bond is around 55 kcal/mol. However, iodine can constitute stable polycoordinate, multivalent compounds; due to iodine is the most polarizable, largest, yet least electronegative among the conventional halogens. The formation of stable polycoordinate high-valent compounds is another property of the iodine atom, even in a value state of up to 7, and the most popular hypervalent iodine organic compounds are I (III) and I (V) species, such as hypervalent λ^3 or λ^5-iodane compounds.

The chemist Willgerodt synthesized the first hypervalent λ^3-iodane (Iodine (III)) compound $PhICl_2$ **1b**[3] in 1886, and then $PhI(OAc)_2$ **5a**, [4] as well as the first iodonium salt[5] $Ar_2I{+}HSO_4^-$ **7a** and even many others was rapidly realized subsequently. As a result that there were nearly 500 such compounds until Willgerodt[6] published the review of his whole

previous work in 1914 on hypervalent iodine species. The most studied hypervalent λ^3-iodane species were diaryliodonium[7] salts **7** in 1977, which were used in lithography and as polymerization initiators. However, the attention of scientists to hypervalent λ^3-iodane compounds has changed gradually, from iodonium salt **7** to (dihaloiodo)arene **1** in the following centuries.

Studies on hypervalent organic iodine compounds have experienced a revival since the early 1980s, probably for the reason that the similarity of chemical properties and reactivities between hypervalent λ^3-iodane species and those of thallium (III), lead (IV), osmium (VIII), mercury (II) and chromium (VI) derivatives, yet without the toxicity and environmental issues. Main types of hypervalent λ^3-iodane compounds are shown in (Figure 1).

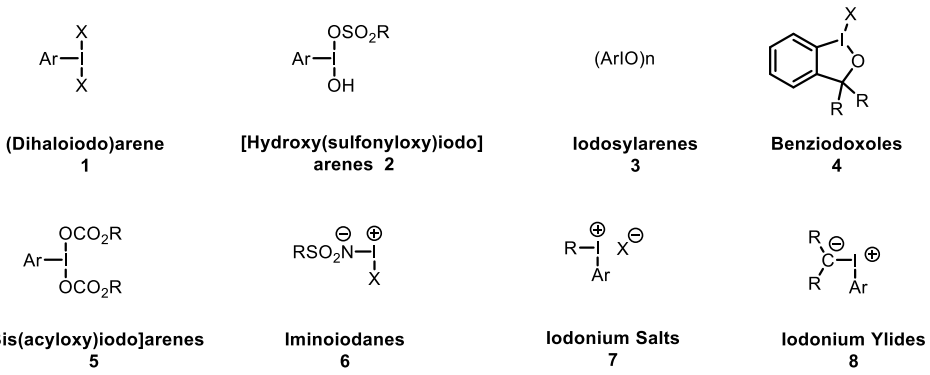


Figure 1. Main hypervalent λ^3-iodanes reagents.

Iodine in oxidation states are known as a wide variety of structural classes, instead of the common -1. These hypervalent iodane species differ in the number of ligands (L), the number of valence electrons surrounding the central iodine atom, and their chemical nature. According to the Martin-Arduengo N-X-L designation,[8] the prevalent hypervalent λ^3-iodane compounds for organic chemistry are generally two structural types as follows (Figure 2).

Figure 2. Typical structural types of λ^3-iodanes.

The two types of λ^3-iodanes, such as **9** and **10,** are the common classification of the hypervalent iodane compounds, which conventionally considered as derivatives of trivalent iodine. The structural part of hypervalent iodine compounds have been discussed in many reviews and books.[9-12] **10** has an approximately T-shaped structure, structures of iodines of **10** are distorted trigonal bipyramids, the most electronegative groups in the axial positions, while the equatorial positions have the least electronegative group of two electron pairs.

On the basis of the number of carbon ligands, surrounding the iodine atom of structures **9-10**.[9] The λ^3-iodane organic compounds are classified into three typical types: (1) iodane with one carbon ligand in structural types **9** or **10**; (2) iodane (iodonium salts) with two carbons ligands in structural types **9** or **10**, (3) iodane with three carbons ligands in structural type **10**.

The first type of hypervalent iodane compounds are represented by a lot of organic iodosyl compounds **3** (RIO), and their derivatives **1 - 5** (RIX_2, where X is any non-carbon ligand). The second type includes many iodonium salts **6 - 8** ($R_2I^+X^-$). The third type with three carbon ligands are the least important for synthetic organic chemistry among the three types of hypervalent iodane compounds, and are also the least investigated consequently, because of their low thermal stability (Figure 1).

2. State of Knowledge

2.1. Hypervalent λ^3-iodane mediated halogenations

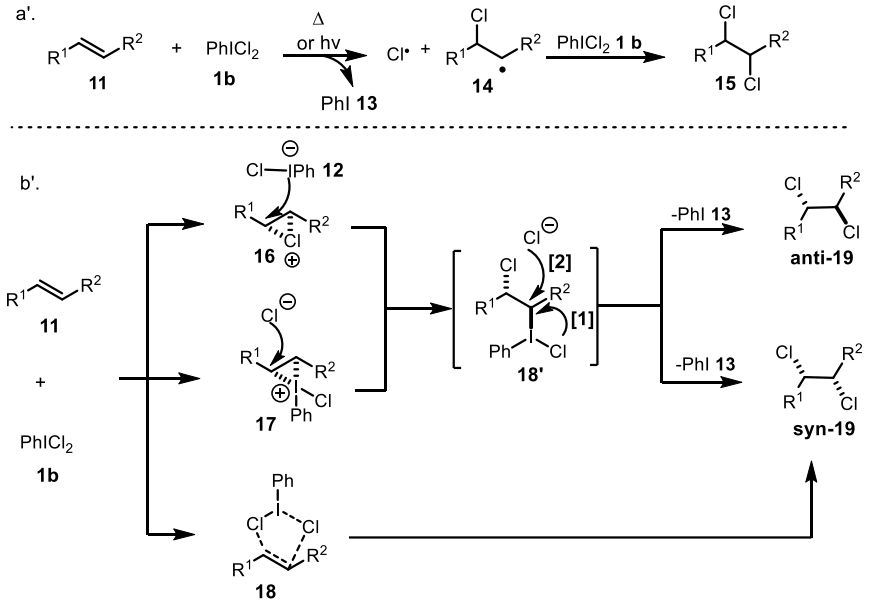
Halogen-containing compounds[13] play increasing important roles in medicinal, material science and agricultural chemistry, because of the readily transformation of halogenated products into other functionalization compounds. Electrophilic halofunctionalizations[14] of organic molecules, especially, the halogenation of alkenes are one of the most popular reliable methods for the functionalization of substrates. In recent decades, an efficient, environmental-friendly and non-metallic methodology of versatile hypervalent λ^3-iodane chemistry was explored as an alternative to the standard, well-established halogenation methodologies, with the result that the development of hypervalent λ^3-iodane chemistry has tremendously realized in many reactions, such as oxidations of alcohols,[15-24] cyclization, and atom-transfer reactions.[19]

2.1.1. Stoichiometric chlorinations and brominations of alkenes

Dichloroiodobenzene ($PhICl_2$) **1b**, a yellow unstable solid, which has been initially isolated in 1886 by Willgerodt,[3] is the first example of the hypervalent iodine(III) reagent, and it is known for its ability thoroughly dichlorinate olefins under mild conditions. however, it is hard to be available commercially, because of its instability, such as being storable at -20^{o}C only for less than two weeks, as well as it has to be prepared under harsh conditions, such as organic syntheses between the iodobenzene and the toxic chlorine gas[25, 26] or *in situ* generated chlorine gas through strong oxidants with chloride sources.[27] And $PhICl_2$ **1b** reagents undergo rapid and reversible dissociation to Cl_2 and the corresponding aryl iodide in polar solvents, such as acetic acid, nitromethane.[25-30]

In 2015, Denmark et al[31] discussed a two-stage mechanism involving haliranium ion intermediate formation, or alkene dihalogen complex and nucleophilic attack of halide ion subsequently. And then Gulder et al summarized and further elaborated the mechanism of the

dichlorinationin the review, [32] that several previously proposed mechanistic intermediates could happen in alkene dichlorinations, depending on the reaction conditions, which was shown as follows:

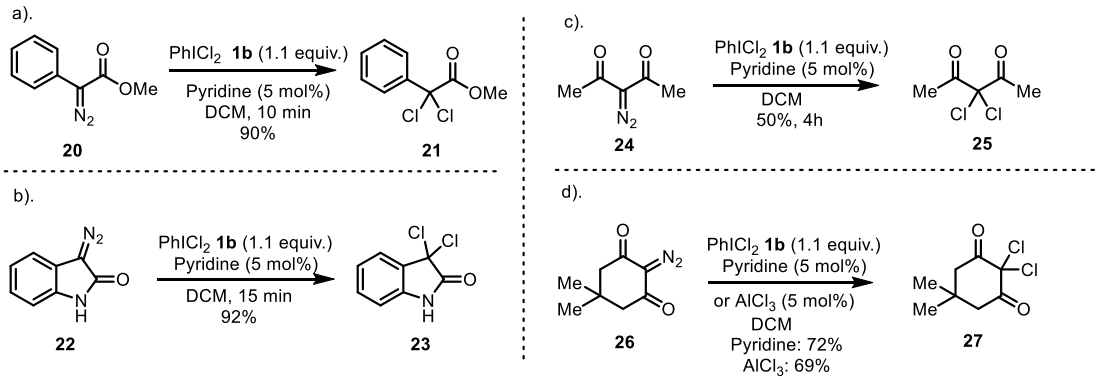


Scheme 1. a') Dichlorinations of alkenes **11** with $PhICl_2$ **1b** in refluxing carbon tetrachloride[33] through a radical mechanism; b') The ionic pathways for alkene dichlorinations [34-36] with $PhICl_2$ **1b**.

The radical mechanism has initially been proposed by Bloomfield,[37] it was proposed that $Cl^{\cdot}$ was the initial radical species; however, $Ph(Cl)I^{\cdot}$ might also be appeared in the process. At the same time, a related question has also arisen in ionic mechanisms with $PhICl_2$ **1b** as to whether $Cl^{\cdot}$ or Ph(Cl)I, was the active nucleophile (Scheme 1a').[38]

As for the ionic mechanism, there were three proposed pathways to get anti- or syn-dichlorination products **19**. At first, chloronium cations **16** were formed between the alkenes **11** and $PhICl_2$ **1b**, which were then attacked by iodine atoms of the **12** to afford *anti*-configured phenyliodonium adducts **18'**. The other similar pathway was that the intermediate species **18**' were generated by the attack of the chlorine anions with iodonium cations **17**, and then two possible scenarios may further occur subsequently, the one type was that the reaction of free chlorine anions with the phenyliodonium adducts **18'**, while the other one was that the chlorines, connecting with iodines, kicked out the iodine groups affording the mixture of anti- and syn-**19**.

The third type mechanism involved a collaborative transfer of two chlorine atoms might tranfer to the alkene **11** from monomeric $PhICl_2$ **1b**, via a 5-membered cyclic transition state **18**, followed by reductive elimination with stereo-retentive (Scheme 1b').

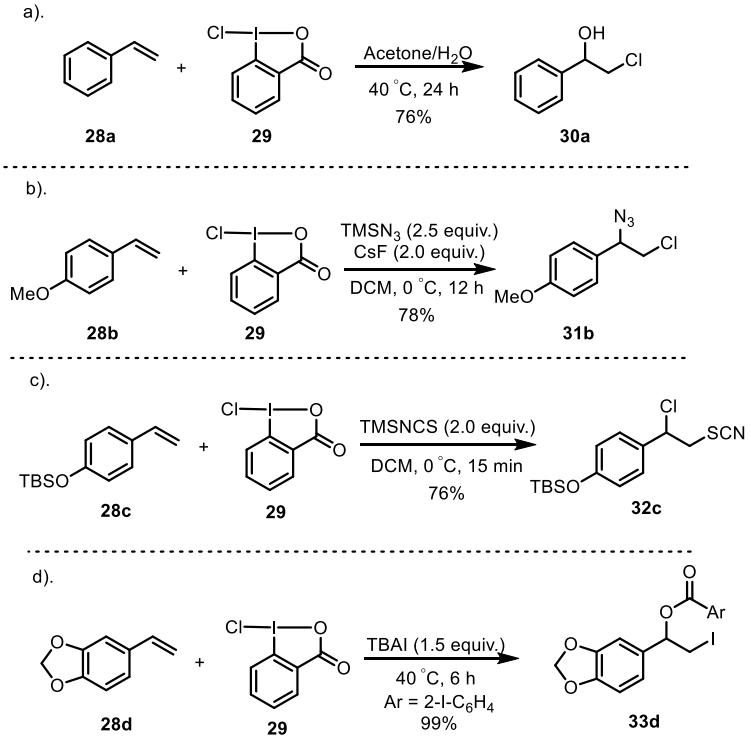


Scheme 2. Typical examples of hypervalent λ^3-iodane mediated dichlorination reactions: a). Using diazoacetate derivatives in the dichlorination reaction; b). Chlorination of N-functionalized 3-diazo-2-oxindole derivatives; c). Chlorination of acyclic diazo-dicarbonyl compounds with $PhICl_2$ **1b**; d). Chlorination of cyclic diazodicarbonyl compounds with $PhICl_2$ **1b**.

Murphy et al.[39-41] reported a series of hypervalent λ^3-iodane mediated dichlorination reactions (Scheme 2, a-d). They converted the diazo functional group of simple, monostabilized acyclic and cyclic diazoesters **20**, **22**, **24**, **26** into *gem*-dihalides **21**, **23**, **25**, **27** with Lewis base or Lewis acid catalysis. Diazo-*β*-dicarbonyls were chose as substrates, due to the significant stabilization of diazo compounds gained by substitution with strongly electron-withdrawing groups, based on diazo compounds were commonly highly reactive and unstable species,. The α-diazo-β-dicarbonyls have increased thermal, catalytic, and Lewis or Brønsted acids stability, compared with pure diazo carbonyl compounds. What they found that the activations of the hypervalent λ^3-dichloroiodanes by Lewis acids or Lewis bases was the key to trigger rapid transformation to the dihalogenated products in good isolated yields in several minutes.

Difunctionalizations of alkenes has been useful tools for the synthesis of organic molecules, because two functional-groups could be invited into organic frameworks at one time.

Hamashima and Egami et al.[42] reported the development of hypervalent chloro-iodane reagent 1-chloro-1,2-benziodoxol-3-(1H)-one **29** in difunctionalization of alkenes with a variety of nucleophiles (Scheme 3). Various reactions of styrene derivatives **28** with **29**, containing oxychlorination,[43-46] azidochlorination,[47-50] chlorothiocyanation,[51] and even iodoesterification were studied.[52-54]



Scheme 3. Difunctionalization of alkenes using hypervalent λ^3-iodane reagents: a). Oxychlorination in acetone/water; b). Azidochlorination using **29** with $TMSN_3$; c). Chlorothiocyanation using **29** with TMSNCS; d). Iodoesterification using **29** with tetra-n-butylammonium iodide (TBAI).

Chlorohydrins have been important classes of substructures in organic synthesis.[43-46] At first, chlorohydrins **30a** was synthesized using the method of oxychlorination in the solvent of acetone and water, oxychlorination of styrenes **28a** with the chlorination reagents **29** was carried out in a mixture of acetone/H_2O as solvent, the chlorohydrin **30a** was formed at 40 ℃ although the reaction proceeded slowly, and good to excellent yields were generally obtained, followed with different styrene derivative substrates (Scheme 3a).

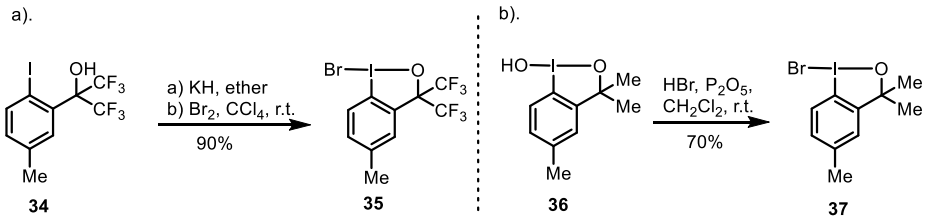
Next, trimethylsilyl azide ($TMSN_3$) , as an external nucleophile, was added to the reaction

mixture of **29** and the substrates **28b** in a non-protic solvent, in order to introduce nitrogen functional group into the molecular, and **29** acted as a moderate electrophilic chlorinating reagent in this reaction (Scheme 3b). The addition of fluoride ion generating azide anion was the crucial point to accelerate the desired azidochlorination reaction, and the reaction temperature was important to control the regioselectivity, poor regioselectivity was detected at 40 ℃, compared to that at room temperature.

Then the reaction was chlorothiocyanation of alkenes, which has rarely been reported before,[51] the combination of (Trimethylsilyl)isothiocyanate TMSNCS with **29** was reported in the same work, the addition of a fluoride ion source was not necessary for this reaction, unlike the azidochlorination. However, the ratio between **29** and TMSNCS was crucial for the formation of target products, due to dithiocyanation compounds occurred as by-products with an excess of TMSNCS reaction condition (Scheme 3c).

Finally, they found the combination of TBAI and **29** afforded the iodoesterification products **33d** in good to high yields, and other functional groups were also adapt to these reaction conditions (Scheme 3d).[52-54]

Not too much examples for stoichiometric brominations of alkenes have been reported, one reason is that (dibromoiodo) arenes cannot be isolated and are unstable compounds. and the other one is that, as far as we know, only two typical of monobromoiodanes (**35** and **37**), which have stabilized iodines in a five-membered ring, has been utilized in the known literatures (Scheme 4).[55]

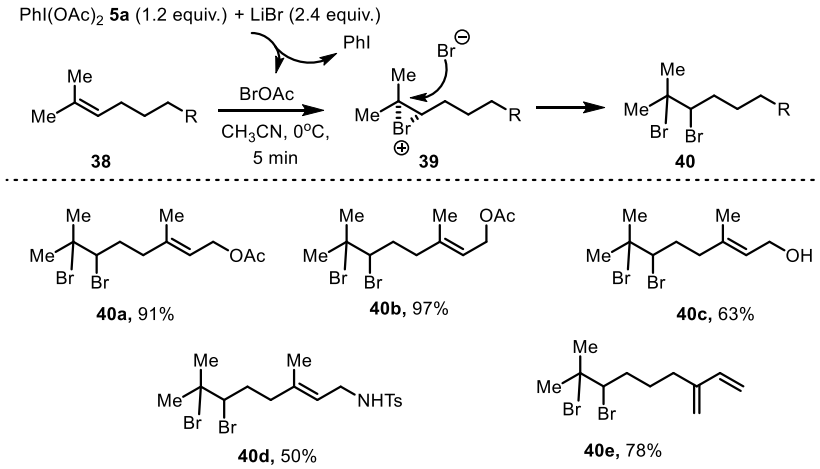


Scheme 4. The synthese of stable monobromoiodanes: a. preparations of **35**; b. formations of **37**.

Both of bromoiodanes **35** and **37** are separable, crystalline solids, the apical positions of the

iodine atom in 35, where stand two electron-withdrawing CF_3 make **35** is commonly more stable than **37**.[55] Bromoiodanes **35** and **36** have several applications in synthese as discerning free-radical brominating reagents, e.g., **35** and **37** can react with cyclohexenes to generate the corresponding allylic bromides in quantitative yields under photochemical conditions.

In 2018, Cariou et al[56] showed that electrophilic halogenations could be triggered by the combining hypervalent λ^3-iodane reagent derivatives with a suitable bromide salt (Scheme 5), because hypervalent λ^3-iodane reagents were able to oxidize the bromine anion smoothly into the corresponding bromonium ion, to promote brominations with increased selectivity.



Scheme 5. Dibromination of acyclic monoterpenoids **38** and the proposal mechanism.

They speculated that BrOAc was the actual reactive species in the dibromination, and then bromonium intermediate **39** was formed in the reaction between acyclic monoterpenoids **38** and generated new species BrOAc, followed by the nucleophilic attack of **39** by bromide ion to generate dibromo adductive derivatives **40** in good to high yields. In the meanwhile, BrOAc was obtained via the oxidation of lithium bromide by (diacetoxy) iodobenzene **5a** (Scheme 5).

2.1.2. Stoichiometric fluorinations of alkenes

Fluorinated compounds have significantly influence on the progress in science and technologies and are essential substrates in our daily life, because fluoride atoms can alter the physical and chemical characteristics of fluoro-containing molecules.[56] Many methods have been invented to synthesize the fluoro-containing molecules, such as the nucleophilic fluorination, but this method is subject to the fluoride anion low reactivity; electrophilic fluorination, accompanied by low selectivities and structurally simple substrates, the milestone is the invitation of easy-to-handle, stable N-fluoro reagents, but the preparation problems, which are expensive and often involve the fluorine gas, restrict their application in laboratory; as well as using transition-metal catalysts in the formation of fluoro-containing compounds. In this case, hypervalent fluoro λ^3-iodanes are used as metal-free, low-cost, alternative reagents. The general trivalent iodine derivatives include two structural types: the linear and cyclic λ^3-iodanes (Figure 3 a, b).[57]

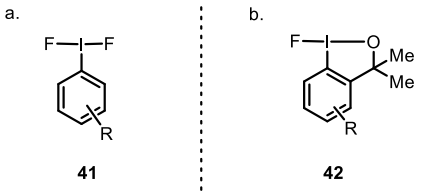


Figure 3. Typical structure of hypervalent λ^3-iodane reagents: a. linear λ^3-difluoroiodanes; b. cyclic λ^3-fluoroiodanes.

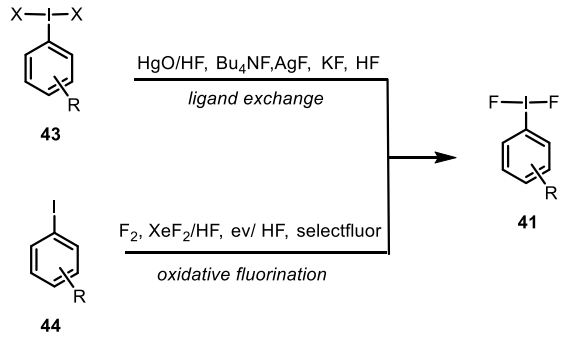
Both of radical and ionic mechanisms are possible in hypervalent λ^3-iodanes chemistry. However, the ionic pathways are in charge of fluoro-λ^3-iodanes mediated transformations. Many of the known hypervalent iodine reagents solely give electrophilic behavior with positive charges only at the iodine atoms, because of the point in the hypervalent iodane HOMO bonds associated with extended I-X bond lengths.

The preparations for the corresponding difluoroiodane analogues **41**, e.g., difluoroiodanes ($ArIF_2$) **41** are far less explored, although several hypervalent λ^3-iodane reagents have been developed, even some of them have already been commercially available now.[58-60] Several

causes trigger the difficulty of the synthese of $ArIF_2$ **41**:

a. Difluoroiodanes often need harsh reaction conditions, and complicated execution protocols;

b. Difluoroiodanes are hygroscopic and highly hydrolizable, so that their separation from hydrofluoric acid, and crystallization are complicated. In general, two systems could be utilized to get fluorinated hypervalent λ^3-iodanes; the first one is that a more stable hypervalent λ^3-iodanes reagents **43** (Scheme 6, top) act as precursors and are transformed into **41** via the fluorine anion nucleophilic attack of the electrophilic iodine atom. Varies inorganic or organic fluoride sources, are used in this ligand-exchange step, but the general method is hydrofluoric acid combining with additives, e.g., HgO.[61-65]

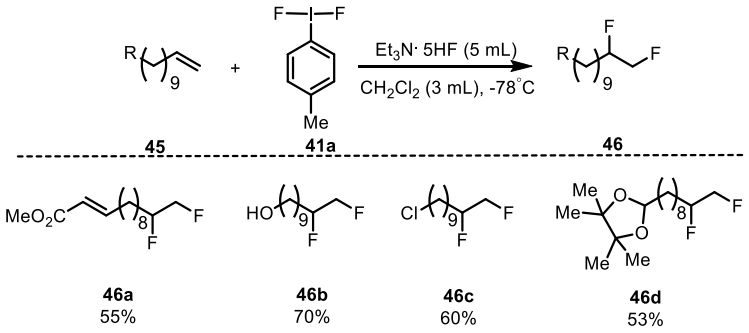


Scheme 6. Typical systems for the preparation of difluoro λ^3-iodanes **41** derivatives.

The other one is that the oxidation of **44** by fluorine addition to afford **41** directly (Scheme 6, below).[65, 66]A practicable and general applicable synthetic system using selectfluor **94** to prepare (difluoroiodane)arenes has been reported by Shreeve et al.,[67] in this system, selectfluor **94** played as not only an oxidant, but also an F-delivering agent. And then the thermo-, moisture- and air-stable cyclic fluoroiodanes **42** are developed. **42** are readily prepared from inexpensive starting materials, and the fluorine atom is conveniently employed through ligand exchange exploited KF or $Et_3N{\cdot}3HF$. In the five-membered ring structure, the presentation of oxygen atom makes **42** a bench-stable electrophilic fluorination reagent, because that oxygen can stabilize the electron-deficient I (III) atom. These two typical fluorination reagents provide novel methodologies to the application of hypervalent iodanes as fluorinating agents, most of the reactions involving hypervalent iodanes reagents are electrophilic fluorinations, such as, a) α-fluorinations of carbonyl compounds;[61, 63, 68] b) alkyne functionalizations;[69-72] c) oxidative substitutions;[73] d) rearrangements;[74] e) aryl

fluorinations;[74] f) fluorocyclizations to vicinal;[75] g) geminal fluoro functionalizations. [75]

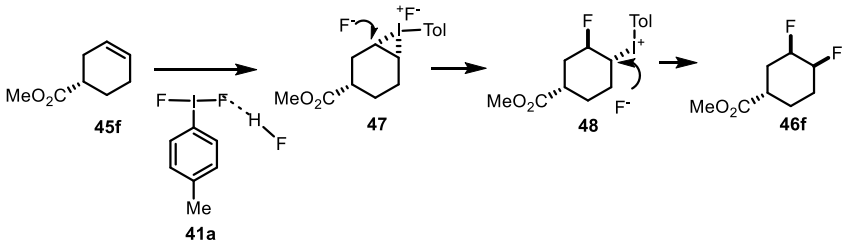
The known 1,2-difluorination examples are not as many as dichlorinations and dibrominations.[31] Hara et al. studied the reaction of the terminal alkenes **45** with fluoro-λ^3-iodane **41a** in 1998, and it has been the only vicinal difluorination for a long time (Scheme 7). [76]



Scheme 7. Fluoro-λ^3-iodane reagent **41a** mediated difluorination of **45**.

In this reaction, non-commercially available, highly concentrated $Et_3N{\cdot}5HF$ was used as an inevitable co-solvent, to activate the F-I-F structural motif, in **41a** via hydrogen bonding, in order to make the conversion of **45** happen under activated environment. What they found that **46** could not be obtained, or detected in a trace amount when $Et_3N{\cdot}5HF$ was replaced, by $Et_3N{\cdot}3HF$ or $Pyr{\cdot}9HF$. Several terminal alkene **45** derivatives were also suitable to this reaction system. [76]

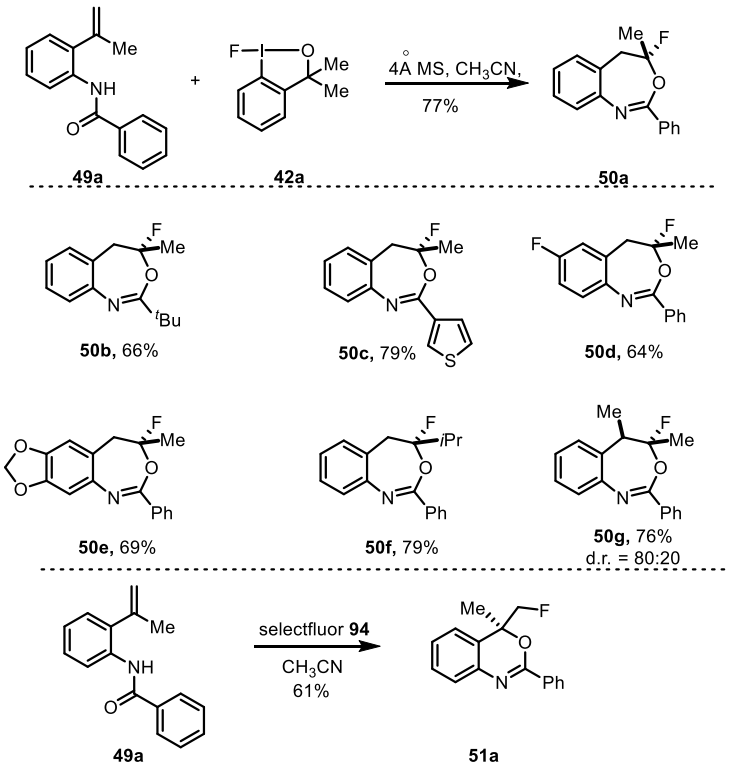
The cyclohexene **45f** as a special non-terminal alkene sample was used in this difluorination, the 1, 2-difluoro cyclohexane **46f** was exclusively generated as the *syn* addition product in 55% yield. Considering the high diastereoselectivity of this reaction, its proposal mechanism was shown as follows (Scheme 8): [76]



Scheme 8. Proposed mechanism of the *syn*-difunctionalization.

At first, the nucleophilic attack of the activated hypervalent iodine atom in **41a** by the double bond in **45f**, generating the iodiranium ion **47**, and then the three-membered heterocycle in the iodiranium ion **47** was ring-opened by fluoride ion and the intermediate **48** was formed. The second attack of **48** by another fluoride ion converted **48** into the product **46f**. [76]

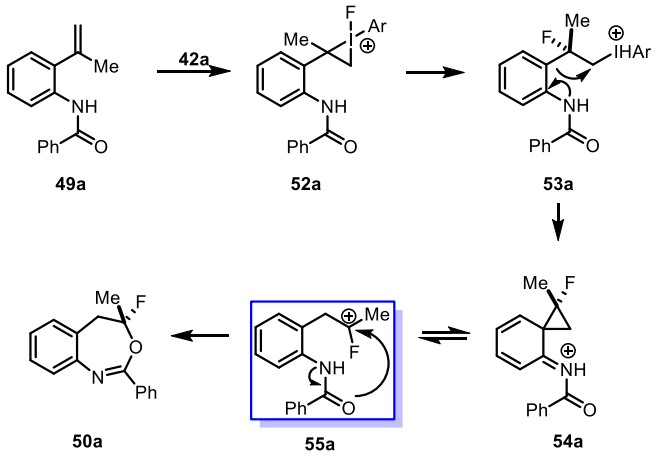
The generation of geminal difluorinated products, using phenyl substituted olefins as the starting materials, which were mediated by hypervalent iodane has been known for several years.[77] Gulder et al[78] established a fluorocyclization using *o*-styryl benzamides **49a** (Scheme 9). Treatment of **49a** with cyclic fluoro-iodane **42a**, gave merely the fluorinated 1, 3-benzoxazepines **50a**, through endo fluorocyclizations, as well as an orderly migration of vinyl methyl groups to the homobenzylic positions. This result was different that benzoxazines **51a** was formed, using other electrophilic F-sources, e.g., selectfluor **94** (Scheme 9). Benzoxazepines **50** were formed with high regioselectivities and (61-85%) good to excellent yield in CH_3CN.



Scheme 9. Chemical divergent fluorination of *o*-styryl benzamides **49a**.

This system provided a flexible methodology to furnish the seven-membered ring product **50**. In this reaction, varies (hetero) alkyl and aryl substituents at the amide **50b**-**50c** were tolerated, along with electron-withdrawing **50d** (F-) and electron-donating groups **50e** (-O-CH_2-O-) at the styrene ring. The carbon-carbon double bond was furnished with different alkyl moieties, making no significant difference on the reactivity (Scheme 9, **50a** vs **50f**). Even the substrate with three substituents on the double bond, such as **50g** was obtained in 76% yield, and in an moderate diastereomer control (d.r. = 80:20). In this case, the relative *cis* configuration of the two methyl groups in **50g** was maintained during this procedure.[78a]

Computational and experimental studies were conducted to understand the mechanism behind the unusual rearrangement, and a concept of *F*-carbocation **55a** has been explored in the report.[78b]



Scheme 10. Proposal mechanism for fluorination of *o*-styryl benzamides **49a**.

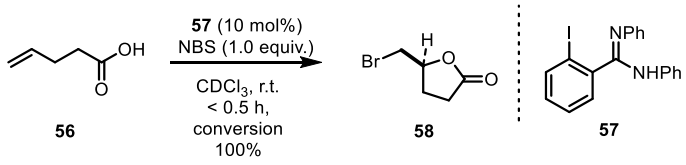
Firstly, the formation of the iodiranium ion **52a** came from the nucleophilic attack of the F-iodane reagent **42a** by the double bond of olefin **49a**, and further the opening of the three – member ring iodiramium ion **52a** by the intramolecular 1, 2-F atom migration on the benzylic side in high selectivity afforded the 1, 2-fluoroiodine intermediate **53a**, and then the cyclopropyl species **54a** was furnished through the 1, 2-intromolecular phenyl group shift. **54a** was in an equilibrium with the key intermediate α-fluoro carbocation **55a**,[162] and then nucleophilic attack of the oxygen afforded the benzoxazepine **50a** (Scheme 10).

2.2. Hypervalent λ^3-iodane catalyzed halogenations

Although the great achievements have been accomplished in the field of hypervalent λ^3-iodane mediated halogenations within the last decades, their application in halogenations area has been significantly hindered.[163] On the one hand, stoichiometric numbers of iodo-aryl waste products are formed during the progress of the reaction. On the other hand, these aromatic by-products are hard to separate from the desired target compounds, which require laborious and high-costly purification protocols. For large-scale, industrial processes,[80] and the particular impediment of reagent-based hypervalent iodane chemistry is the low atom economy. Besides, the corresponding non-cyclic hypervalent λ^3-iodane compounds are elusive, because of their high chemical instability, as well as these molecules are very easy to hydrolysis, thus limiting the application of linear λ^3-iodane halogenation reagents in halogenations, e.g. chlorinations, brominations, and fluorinations. The catalytic loading of these useful hypervalent iodanes might be considered as a perfect solution to these problems in halogenation area. However, reports on catalytic, suitable systems for the selective construction of carbon–halogen bonds[31],[14] are far less than the relevant oxygenations or nitrogenations, for examples that the Sharpless epoxidation,[79] or aminations.[81]

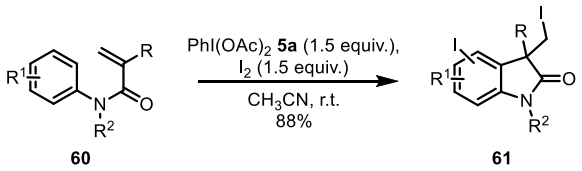
2.2.1. Catalytic chlorinations and brominations of alkenes

Braddock and co-workers[82] reported the usage of *ortho*-substituted iodobenzenes in organocatalytic bromination of alkenes in 2006. In this work, a catalytic cycle including I (I) and I (III) oxidation states bromination was developed, a conversion of pentenoic acid **56** into bromolactone **58** was observed with *N*-bromosuccinimide (NBS), and 10 mol% of the iodophenyl carbinol **57** in the mixture, 100% conversion of **56** was obtained (Scheme 11).



Scheme 11. Catalytic bromo-lactonization of **56** to generate **58**.

Halocarbocyclization offered an easily approach for the synthese of heterocycles. In 2011, Zhu et al [83] reported the first reaction of iodo-carbocyclization involving electron-deficient olefins (Scheme 12). 3, 3'-disubstituted oxindoles **61** was afforded from the iodoarylation of nitro-arylacrylamide derivatives **60** by using a combination of $PhI(OAc)_2$ **5a** and I_2. It was noteworthy that the unique cyclization mode proceeded through an unusual formal 5-exo-trig cyclization, compared to the general 6-endo-dig cyclization.

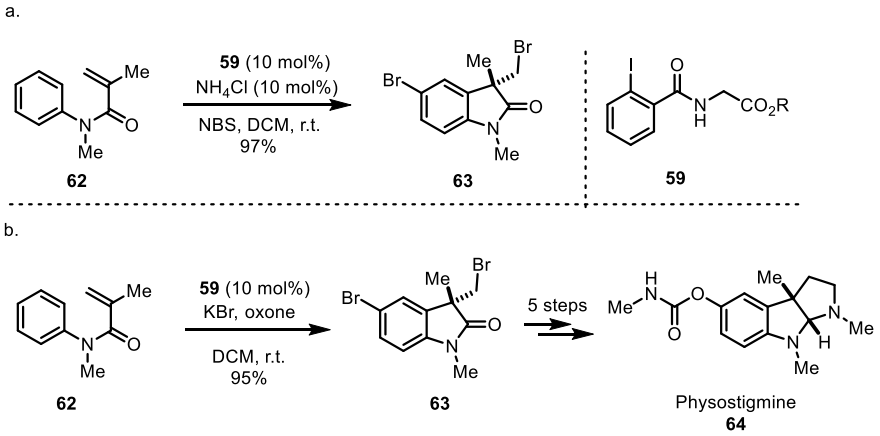


Scheme 12. λ^3-iodane catalyzed the synthese of oxindoles **61**.

In 2012, Gulder et al.[84] reported the bromocarbocyclization for the synthese of C-3 disubstituted oxoindoles **63**, by using *o*-iodobenzamide **59** as the precatalyst, a metal-free, diastereoselective procedure into heterocycles was realized (Scheme 13a). Under this conditions, a variety of structurally *N*-alkyl benzamides **62** derivatives were suitable to convert into heterocycles **63** in moderate to excellent yields (51-97%).

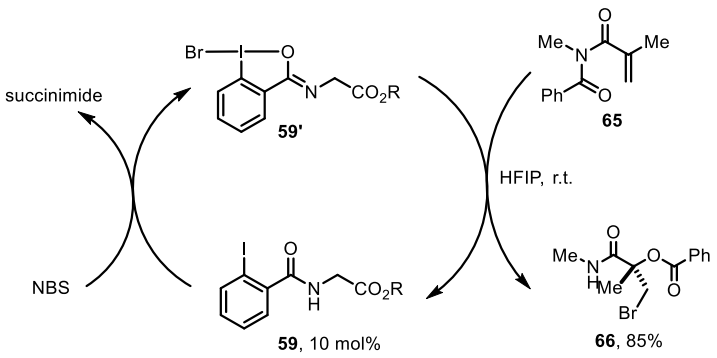
The efficient method for the synthese of these oxoindole derivatives was further improved by

inviting KBr together with oxone as the external oxidant,[84] which significantly increased the atom economy of the bromination reagents (Scheme 13b). By using this NBS-free protocol, a lot of substrates **62** were again transformed into the oxoindoles **63** in moderate to excellent yields (68-95%). Both methods were further demonstrated, with the total synthese of acetylcholinesterase inhibitor physostigmines **64**, which were realized in a short, efficient and diastereoselective pathway containing the hypervalent iodane-catalyzed bromocyclization as a significant step.



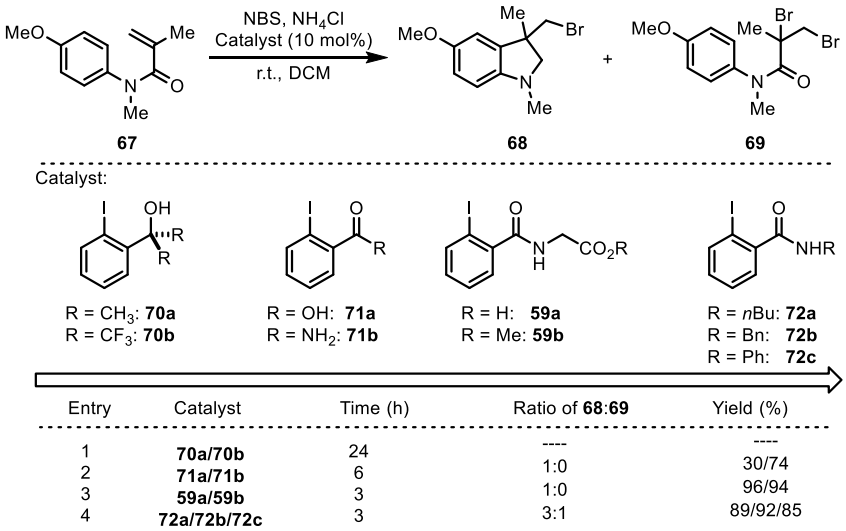
Scheme 13. Hypervalent iodanes catalyzed bromination: a). iodane **59** catalyzed bromocarbo-cyclization of methacrylamides **62**; b). iodane **59** catalyzed bromocyclization of methacrylamides **62** to oxoindoles **63**.

An iodane-catalyzed rearrangement of the imide analogues **62** instead of the *N*-alkyl methacrylamides **57** to *α,α*-dialkylated-*α*-hydroxy carboxylamides **63** were obtained in good to excellent yields (67-98%).[85] In this case, the carboxyl oxygen atom reacted as the nucleophile, intercepting the intermediate haliranium ion (Scheme 14). The selective formation of the hypervalent bromo-iodane species **59'**, realized by the oxidation of **59** using NBS, was proven by NMR and ESI-MS experiments. This reaction provided a piece of analytical evidence for the *in situ* formation of such a highly reactive Br–imine benziodoxolone species **59'**, which should be the actual halogenating reagent in these reactions.



Scheme 14. Hypervalent iodane-catalyzed bromination of imides **65**.

Further study showed that, the structure of the iodobenzene *pro*-catalyst has a significant effect on the product outcome (Scheme 15).[86] No conversion of **67** happened, with catalysts equipped with poor nucleophilic groups at C-2, such as the hydroxy methylene function in **70**. The desired product **69** was furnished, when the replacement of the alcohol moiety by more Lewis basic group, such as an acid or amide function in **71**. A series of iodobenzamides with various substituents were screened at the nitrogen atom. However, fine-tuning the structure in the periphery of the *N*-substituents in catalysts **59**, provided dramatic changes in the reactivity and selectivity.



Entry	Catalyst	Time (h)	Ratio of **68**:**69**	Yield (%)
1	**70a/70b**	24	----	----
2	**71a/71b**	6	1:0	30/74
3	**59a/59b**	3	1:0	96/94
4	**72a/72b/72c**	3	3:1	89/92/85

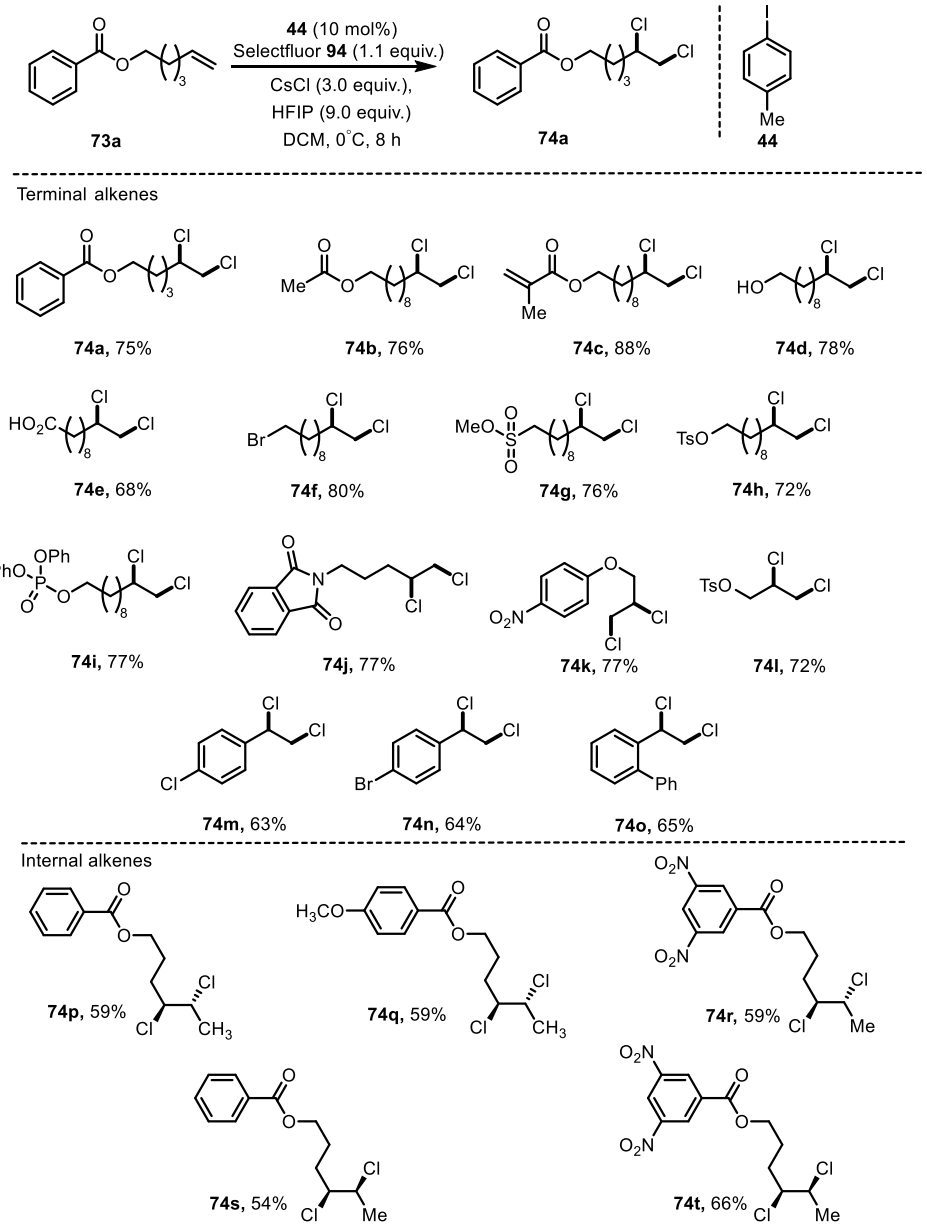
Scheme 15. Influence of the *o*-substituents in pre-catalysts on the bromination of amide **67**.

Replacing the carboxyl-containing side chain in **59** by a substituent exhibiting purely electron-donating properties, such as the alkyl, benzyl, or phenyl moiety in **72**, gave rise to oxoindole **68**, but also to a significant amount of dibrominated product **69** under the same

reaction conditions. In summary, fine-tuning the electronic properties of the *o*-substituents in iodobenzene *pre*-catalysts affected the reaction rate and the chemoselectivity. This catalyst-base reactivity clearly correlated with the nucleophilicity and thus with the strength of the *trans*-effect exhibited by the *o*-substituent in the iodane intermediates **59'**.

Recently, Gilmour et al[87] reported a hypervalent iodane-catalyzed vicinal dichlorination of unactivated alkenes, *in situ* generations of *p*-TolICl$_2$ **1c**, which was performed using Selectfluor **94** as oxidation and CsCl as chlorine source (Scheme 16).

Inspired by Gulder et al[88] recent study on haliranium-ion cyclization cascades, HFIP was added in this reaction as a co-solvent, which had a notable effect on reaction efficiency, **74a** was furnished in 88% yield, an array of functional groups substrates were employed in this system, e.g., ester **74b**, **74c** were obtained in synthetically useful yields, unprotected alcohols **74d** as well as free acids **754e** were performed well in 78% and 68% yield separately, The primary bromide (80%, **74f**) and the corresponding sulfate and tosylate were compatible with the general conditions (76%, **74g**; 72%, **74h**), **74i** was furnished in 77% yield, considering about the significance of phosphate groups in bioactive lipids.



Scheme 16 Catalytic vicinal dichlorination of unactivated alkenes using pre-catalyst **44**.

They found that this system was performed well in reduced spacer lengths substrates: the masked amine **74j** (77%), and protected **74k** (77%), **74l** (72%) could also be accessed. The corresponding products of styrene derivatives also could be obtained using this method separately (63%, **74m**; 64%, **74n**; 65%, **74o**). Internal alkenes were used in this reaction, and their corresponding products were obtained in moderate yields (54-66%), what they also found that this reaction system was highly stereospecific, for example, *anti*-configured products (**74p**-**74r**) were generated from the corresponding *E*-alkenes, and similarly *syn*-products (**74s**-**74t**) were derived from the starting *Z*-alkene (Scheme 16).

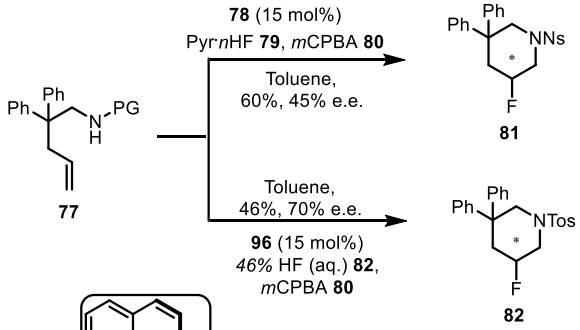
2.2.2. Catalytic fluorinations of alkenes

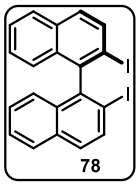
Kita and Shibata et al[89] reported a catalytic system using the *pre*-catalyst *p*-iodo toluene **44** in 2014, and *m*CPBA **80** as oxidant, as well as *pyr*·nHF **79** as fluorine source, piperidines derivatives **76** were furnished in the fluorocyclization of a various of terminal amino alkenes **75** (Scheme 17a). Kita and Shibata et al[89] further fine-tuned this system by conducting the first catalytic, enantioselective fluorination, Using catalytic loading of the axially chiral binaphthyl **78** afforded a moderate enantioselectivity of the fluorination of substrates **77**, providing the corresponding ß-fluoropiperidines **81** and **82** in moderate yields (46 %, 45% e.e. ; 60%, 70% e.e.) respectively (Scheme 17b).

The system of using hypervalent iodanes in catalytic fluorination reaction was further turned to difluorination processes. Kitamura et al[66] reported the geminal difluorination of styrene derivatives **28** using 20 mol% of *p*-iodotoluene **44** as pre-catalyst (Scheme 17c). The catalytic process led to gem-difluoro compounds **83** as the only products. The proposed mechanism proceeds were aryl iodonium intermediate/ 1, 2 aryl shift, which was commonly existed in hypervalent iodane chemistry. One year later, Gilmour et al.[67] described the first catalytic 1,2-difluorination of monosubstituted alkenes using the combination of selectfluor **94** together with the HF complexes of *pyr*·nHF **79** and NEt_3·3HF **93** to amine mixture of 4.5-5:1 (Scheme 17d). Jacobsen et al[68] reported a catalytic vicinal difluorination process, electron-deficient unsaturated amides **86** were converted into the fluorinated amides **88** in high yields (60-90%) in excellent diastereoselectivity(d.r.>95:5, Scheme 17e). The enantioselective 1,2-difluorination of cinnamide **89** using the C-2 symmetric pre-catalyst (*S, S*-**90**) was studied in this reaction, and difluorinated products **91** were obtained in 51% yield with an excellent enantiomeric excess of 93% (Scheme 17e).

a.

b.

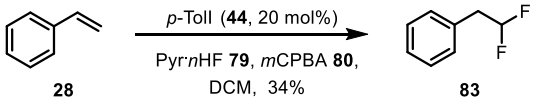




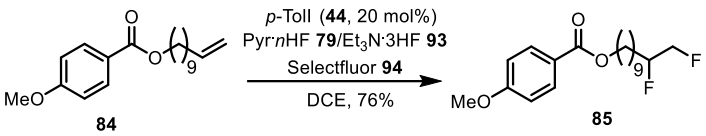
Ns = 2-nitrobenzenesulfonyl

Ts (Tos) = *p*-toluenesulfonyl

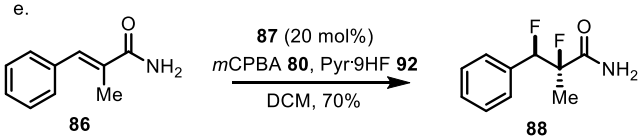
c.

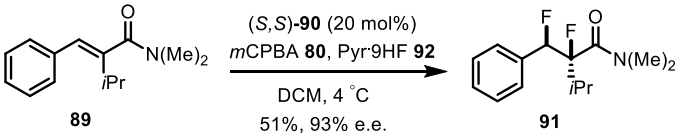


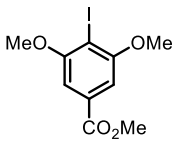
d.

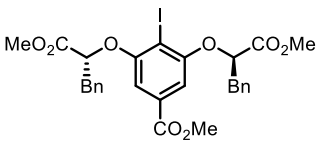


e.





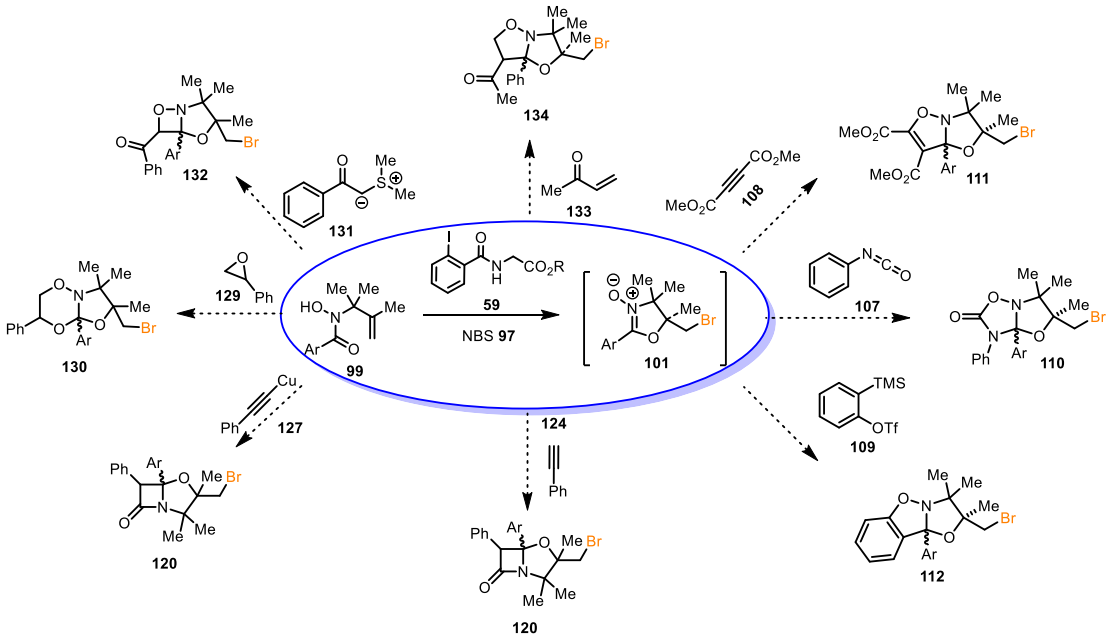




Scheme 17. Hypervalent iodane-catalyzed fluorinations of alkenes: a). catalytic amino fluorinations of amino alkenes **75**; b). catalytic, enantioselective amino fluorinations of **77**; c). catalytic, geminal difluorinations of styrenes **28**; d). catalytic, vicinal difluorinations of unactivated olefins **84**; e). diastereo- and enantioselective 1, 2-difluorinations of acrylamides derivatives (**86**, **89**).

3. Projects Goals

Hypervalent λ^3-iodane halogenation reagents have received massive attention over the last 30 years and showed themselves as valuable and reliable organic alternatives to common transition-metal compounds, due to their low toxicity and mild reactivity. Gulder et al. [84] in 2012 developed the first organocatalytic bromocarbocyclization system for the synthese of C-3 disubstituted oxoindoles **63** in excellent yields (Scheme 13a). Then hydroxy carboxyl amide **66** were obtained in good to excellent yields (67-98%) using the combination of *o*-iodobenzamide **59** as the pre-catalyst with *N*-bromosuccinimide (NBS) as the oxidant (Scheme 13),[85] as well as β-lactams and α-hydroxy-β-amino acids were accessed by λ^3-iodane-catalyzed rearrangement of imides.[90] Inspired by the research program of a series of excellent work in the Gulder group[32], [78], [84-86]dealing with the exploration of unusual reactivities and selectivities triggered by hypervalent λ^3-iodanes, we envision that the catalytic bromination system will be possible to furnish novel organic compounds, e.g., ketonitrones[160] **101**, and this reaction maybe go through the similar mechanism procedure with the previous rearrangement reaction in the Gulder group.[85] Kept these in mind, we wished to conduct the reaction between *N*-allylhydroxamic acids **99** as the starting material and NBS **97** as the bromine source. At first, *N*-allylhydroxamic acids **99** could be obtained by ene reactions of acylnitroso compounds with olefins.[91]



Scheme 18. The conception of pre-catalyst idoine **59** catalyzed bromocyclization.

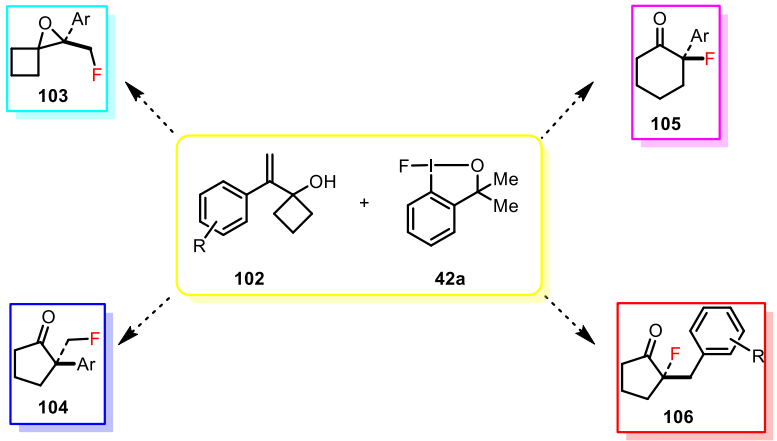
And then the ketonitrone[160] **101** was obtained by this catalytic system, which might be applied to try [3+2] cycloadditions with varies 1,3-dipolarophiles **98**, such as phenyl isocyanate **107,** dimethyl acetylenedicarboxylate (DMAD) **108**, 2-(trimethylsilyl) aryl triflate **109,** copper phenylacetylide **127,** sulfur ylide **131,** but-3-en-2-one **133,** oxiranes **129**, and phenylacetylene **124** to furnish novel heterocyclic compounds. We hoped to consider more selective and reactive improvement of this catalytic system, and transfer this concept to other substrate classes to find novel, yet unexplored synthetic compounds. For example, the whole system of the conversion of *N*-allylhydroxamic acids **99** into **101** will be realized in one-pot, general, and one-step reaction, on the condition that ketonitrones[160] **101** were *in situ* generated in the system (Scheme 18).

Based on the above hypothesis, the designed hypervalent λ^3-iodane-catalyzed bromocyclization was shown as follows:

- Synthese and using *N*-allylhydroxamic acids **99** as substrates;
- Optimization of the reaction parameters of *N*-allylhydroxamic acids **99** with a range of 1,3-dipolarophiles **98**;

- Conversion of *N*-allylhydroxamic acids **99** and *1*, *3*-dipolarophiles **98** into novel heterocyclic compounds **100** with the combination catalytic system of **59** as the *pre*-catalyst, and NBS in a one-pot reaction.

In 2016, the Gulder group[78] established a hypervalent λ^3-fluoro-iodane mediated cyclization using cyclic fluoro-iodane **42a** (Scheme 9). Benzoxazepine **50a** was afforded via an aryl iodonium/1, 2-aryl migrations reaction process, as well as benzoxazines **51a** was formed using other electrophilic F-sources, such as selectfluor **94**. In order to expand the application area of this system, cyclobutanols **102** and cyclic fluoro-iodane **42a** were employed as the modern template, as we envision that four possible corresponding products will be generated through the procedure, such as oxa-three member ring species **103**, a-Ar cyclopentanones **104**, a-fluoro cyclopentanones **106**, and cyclohexanones **105** (Scheme 19).



Scheme 19. λ^3-Iodane mediated fluorocyclization of cyclobutanols **102**.

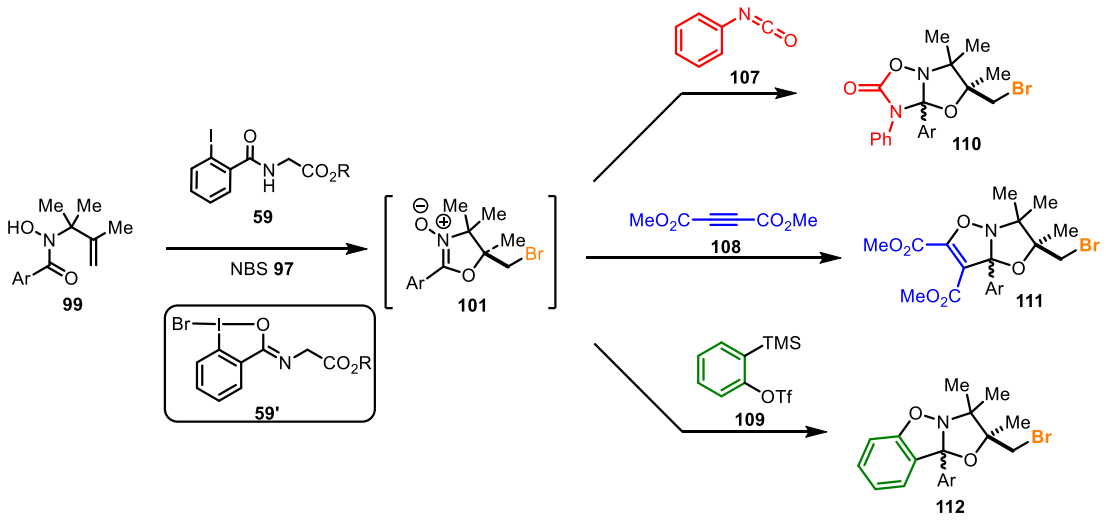
The outline is designed as follows:

- Synthese of cyclobutanols **102** and studying on the scope of substrates;
- Optimization of reaction conditions to realize the conversion of **102** into the corresponding products;
- Expanding the scope of this cascade reaction to asymmetric conversion, or even using the catalytic loading of hypervalent iodanes in this reaction.

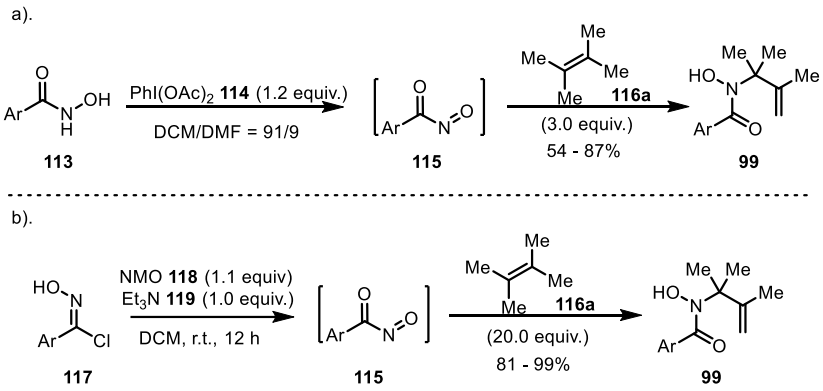
II. Results and Discussion

1. Hypervalent Iodane Catalyzed Cascade Reactions for the Generation of *N, O*-Heterocycle Compounds

On the basis of the excellent previous reports, [78], [84-86], [90] the application of the catalytic hypervalent iodane reagent / NBS (*N*-Bromosuccinimide) system in bromocyclization was further explored in my thesis. Herein, we developed the hypervalent λ^3-iodane catalyzed bromocyclization of *N*-allylhydroxamic acids **99** involving iodine (I) **59** / (III) **59'** species. *In situ* generated ketonitrones[160] **101**, were smoothly trapped by a variety of 1, 3-dipolarophiles, including electron-poor alkynes **108**, phenyl isocyanates **107**, and 2-(trimethylsilyl)aryl triflates **109**, affording the corresponding desired *N, O*-heterocycle compounds (**110** - **112)** respectively (Scheme 20).



Scheme 20. λ^3-iodane triggered the cascade cycloadditions.



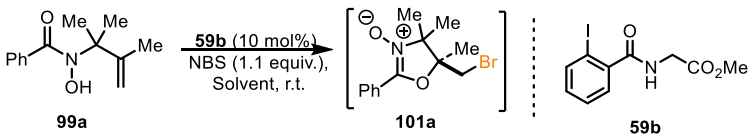
Scheme 21. Two typical synthetic methodologies of *N*-allylhydroxamic acids **99**.

The *N*-allylhydroxamic acids **99** were sysnthesized according to the following two procedures. The first methodology was that commercially available hydroxamic acids **113** were oxidized by iodosobenzene diacetate **114** to generate *N*-acylnitroso enophile intermediates **115**, and then trapped by tetramethylethylene **116** as ene substrates (54 - 87% yield, Scheme 21a).[91]

The second synthetic system was referred as the reactions started from hydroximoyl chloride **117** and NMO **118** in the presence of Et_3N, and *in situ* generated the nitrile oxides **115**, then nitrile oxides **115** was intercepted by tetramethylethylene **116** to afford *N*-allylhydroxamic acids **99** (81 - 99%, Scheme 21b).[157]

And then, according to the doctoral work of Dr. Anna Andries in our group, in the first step, I tried the hypervalent iodane catalyzed bromocyclization under the same reaction conditions with those used by her in the previous work, [158] namely iodobenzamide **59b** as the pre-catalyst, NBS as an oxidant in acetonitrile as a solvent, at room temperature (Table 1, entry 1), the corresponding ketonitrone **101a** [160] was afforded in high yield (> 95%).

Table 1. Optimization of the reaction conditions for the catalytic iodane **59b** mediated cyclization of the *N*-allylhydroxamic acid **99a**.



Entry	Solvent	Time (min.)	Yield[a] (%)
1	CH_3CN	10	> 95 (89)[b]
2	THF	5	> 95
3	$CHCl_3$	5	> 95
4	Toluene	5	> 95
5	HFIP	5	> 95
6[c]	CH_3CN	60	-----

[a]^{1}NMR yield; [b] Isolated yield; [c] No catalyst **59b**; HFIP = 1,1,1,3,3,3 -hexafluoro-2-propanol, THF = tetrahydrofuran.

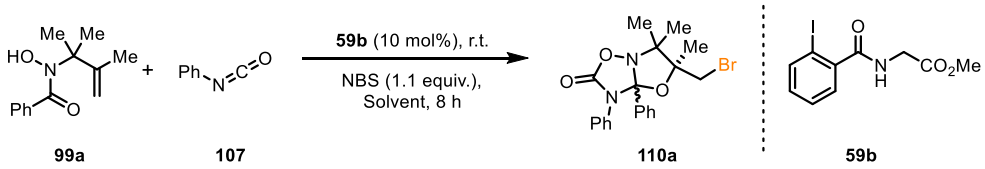
The research was commenced by using bromocyclization of *N*-allylhydroxamic acid **99a** with NBS in the presence of iodobenzamide catalyst **59b** as model templates (Table 1). Firstly, *N*-allylhydroxamic acid **99a** could be easily prepared by the ene reaction of acylnitroso compounds with olefins.[91] Ketonitrone **101a**[160] was obtained in good yield (> 95%) by using the standard conditions for halocarbocyclization and the conversion of **99a** was realized completely in a series of solvents separately (Table 1, entries 1-5). The ketonitrone **101a** could be solely isolated in 89% yield with high regioselectivity after 5 minutes, as the reaction finished via 5-exo-trig cyclization, and no six-member ring was formed. In the control experiment, **101a** was not detected without catalyst **59b** in the reaction (Table 1, entry 6).

And then the application of the novel ketonitrone **101a** in synthetic chemistry was studied, it was noteworthy that *in situ* generated bromine-containing ketonitrone **101a** could be intercepted by 1, 3-dipolarophiles in one-pot simultaneously, and realized the formation of the desired *N, O*-heterocycles (**110 - 112**).

As we know, the 1, 3-dipolar cycloaddition has been one of the most useful synthetic methodologies for the synthese of substituted cyclic structures,[92-96] then we set out to

investigate the cycloaddition of *N*-allylhydroxamic acid **99a** with phenyl isocyanate **107a** (Table 2).

Table 2. Optimization of the reaction conditions between *N*-allylhydroxamic acid **99a** and phenyl isocyanate **107**.



Entry	Solvent	d.r.[a]	Yield(%)[b]
1	HFIP	55:45	70
2	DCM	61:39	43
3	THF	65:35	10
4	Toluene	64:36	78
5	DMF	50:50	70
6	CH_3CN	45:55	95
7	Isopropanol	40:60	40
8	Hexane	60:40	75
9	$CHCl_3$	53:47	78

[a]Determined by ^{1}H NMR, [b]^{1}NMR yield.

We began our study by testing the reaction of *N*-allylhydroxamic acid **99a** with phenyl isocyanate **107** in the presence of iodobenzamide pre-catalyst **59b**. To our delight, in the presence of 10 mol % of catalyst **59b**, the reaction could proceed smoothly in HFIP at room temperature to give the desired product **110a** in 70% yield (Table 2, entry 1). The evaluation of solvents was subsequently carried out. As shown in Table 2, the corresponding product **110a** could be obtained in 43% yield in DCM (Table 1, entry 2). Other solvents, such as THF and isopropanol gave low yield separately (10%, 40%, Table 1, entries 3 and 7). When polar solvent CH_3CN was utilized, the desired product **110a** was obtained in poor diastereomercontrol (d.r. = 45:55) (Table 1, entry 6). Less polar solvent toluene was also invited in the reaction, and the product **110a** could be generated in a higher diastereoselectivity, yet a slightly lower yield (78%, d.r. = 64:36) (Table 1, entry 4). However,

evaluation of other less polar solvents, such as, hexane, which did not give any improved results (d.r. = 60:40) (Table 1, entry 8). Using chloroform as the solvent, a poor diastereomer control was generated (78%, d.r. = 53:47, entry 9).

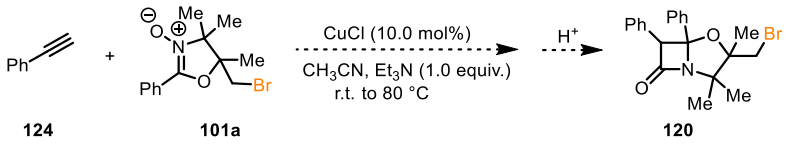
The impact of nitrogen-containing heterocycles on the well-being of mankind was demonstrated by the β-lactams **120**, which was a four-membered cyclic amide (azetidin-2-ones), with the discovery of the most popular drug, i.e., penicillin **121** in 1928,[101] the magic age of antibiotic discovery was created. Many semi-synthetic antibacterial medicines within the β-lactam family have been coined since Fleming's milestone discovery. ß-lactams **120** not only acted as useful building blocks in organic chemistry, e.g. paclitaxel **122** (Taxol),[102] but also played an important role in bioactive compounds. However, the construction of such four-membered heterocycles, has been a challenging task for a long time, and there will be still several major limitations to be conquered, e.g. complicated access to starting materials, non-practical reaction conditions, low structural variability, and multiple by-products in the progress of the reaction remain significant obstacles. To overcome the problems in ß-lactams **120** synthese, new pathways toward these highly rewarding structures are necessary to be further explored.

Kinugasa and Hashimoto explored the copper promoted reaction of nitrones with phenylacetylide gave β-lactams in 1972.[103] This reaction was highly useful for synthese of β-lactams, which were key structures for biologically important antibiotics and received large attention. This reaction involved a 1, 3-dipolar cycloaddition rearrangement cascade process, which was catalyzed by copper ions and treated with an organic base.

We have previously developed synthesis of lactam derivatives in excellent 60 - 95% yield,[85] namely the λ^3-iodane catalyzed rearrangement of imides **123**, using 10 mol% of *o*-iodobenzamide **59a** as the catalyst and *N*-bromosuccinimide (NBS) **97** as the oxidant in one pot, so we hoped to extend the catalytic method to the realization of novel β-lactams **120**.

we commenced a preliminary research on the synthese of β-lactam **120** via kinugasa reaction

of isolated ketonitrones **101a** with terminal alkynes **124**. Firstly, we started our research using phenylacetylene **124** and isolated ketonitrones **101a** as starting materials to test the standard kinugasa reaction conditions (Scheme 22), the methodology was that (triethyl)amine as the base to seize the proton of terminal alkyne, and a copper acetylide was formed which could be trapped by generated ketonitrones **101a** to afford β-Lactam **120**.



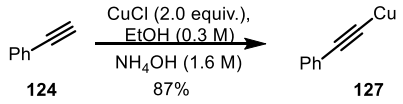
Scheme 22. Studies on the synthesis of ß-lactam **120** via the kinugasa reaction.

Copper (I) chloride in acetonitrile was added in phenylacetylene **124** and dry (triethyl)amine, which stirred at room temperature for two hours until a light yellow solid appeared in the mixture, to this solution was added ketonitrones **101a** in one port, the result was monitored by TLC. The corresponding β-lactam **120** could not be detected after ten hours (Scheme 22). None of products were detected with prolonging the reaction time to thirty hours, and only the starting material recovery. Elevating the reaction temperature to 80 ^{o}C, accompanied with longer time, which was compared with room temperature reaction conditions gave no conversion of the starting materials unfortunately.

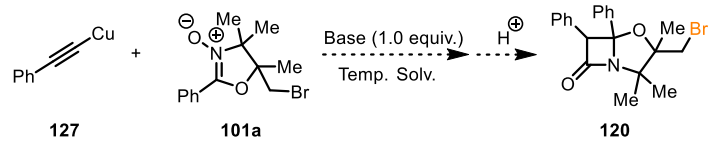
In order to further study the reaction, we synthesized the intermediate reactive species Cu (I) alkyne **125**, which was isolated, purified and used for the next step (Table 3). Herein, we tried the reaction as follows:

Table 3. a) Synthesis of copper phenylacetylide **127**; b) Studies on the formation of β-lactam **120** via the kinugasa reaction.

a).



b).



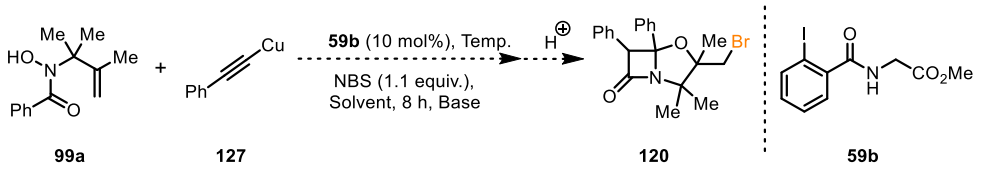
Entry	Base	Temperature (^{o}C)	Solvent	Results[b]
1	-----	r.t.	CH_3CN	n.d.
2	Et_3N	r.t.	CH_3CN	n.d.
3	Pyridine	0	CH_3CN	n.d.
4	DIPA[a]	40	CH_3CN	n.d.
5	Proton sponge	40	CH_3CN	n.d.
6	DIPA	40	DMF	n.d.

[a]DIPA = $(i\text{-Pr})_2$ NH, [b] the reaction was monitored by TLC combined with GC-MS, n.d.= not detected the corresponding product **120**.

We moved our research to the synthese of the β-lactam **120** in one-pot, using the synthetic method that was firstly discovered by Kinugasa and Hashimoto in 1972,[103] namely, the treatment of a copper acetylide **127** with a nitrone **101a** afforded β-lactams **120**. Copper phenylacetylide **127**[104] was synthesized and isolated previously via adding phenylacetylene **124** with copper (I) chloride **125** and ammonia in ethanol for 2 hours, then light yellow copper phenylacetylide **127** was obtained easily and then the reactions of copper (1) phenylacetylide **127** with nitrones **101a** were performed in dry acetonitrile under a nitrogen atmosphere at room temperature without the exogenous base (Table 3), the result came out that no β-lactam **120** was generated (entry 1), screening different bases were carried out subsequently, one equivalent (triethyl) amine was utilized as additive in the synthese of β-lactams **120** (entry 2), and pyridine was also screened as base separately (entry 3), both of them gave an identical result that no formation of the target β-lactam **120**. The invitation of diisopropylamine (DIPA) was based on previous reports, in which sterically obstructed

secondary amines were found to give superior yields of the desired β-lactam,[105] other bases were also examined (entries 4-6), yet the desired β-lactam **120** could not be obtained.

Table 4. Screening reaction conditions for Kinugasa reaction.

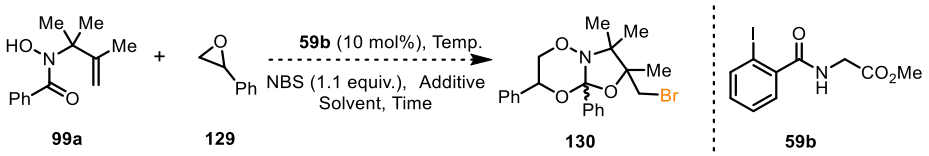


99a **127** **120** **59b**

Entry	Solvent	Temperature (^{o}C)	Base	Yield (%)
1	DCM	r.t.	Pyridine	0
2	CH_3CN	r.t.	Pyridine	0
3	CH_3CN	50	Pyridine	0
4	CH_3CN	80	Pyridine	0
5	DMF	100	Et_3N	0
6	$CHCl_3$	r.t.	Et_3N	0

To a solution of *N*-allylhydroxamic acid **99a** (0.20 mmol, 1.0 equiv.) in solvent (2.0 mL, 0.1 M) was added phenylethynylcopper **127** (0.22 mmol, 1.1 equiv.), **59b** (0.01 mmol, 0.1 equiv.) and NBS (1.1 equiv.) at room temperature.[58] The mixture was stirred at different temperature in the dark environment, which was monitored by TLC. We began Kinugasa Reaction by testing the reaction of **99a** and phenylethynylcopper **127** with the iodine catalyst **59b**. As we could see in Table 4, in the presence of 10 mol% loading of catalyst, the reaction could not proceed in DCM at room temperature, only the start material recovery (Table 4, entry 1). Evaluations of the solvent effect were subsequently carried out. As shown in Table 4, the desired product **120** could not be obtained in DCM (Table 4, entry 2). Other solvents, such as acetonitrile, DMF and chloroform also gave no product (Table 4, entries 3-6). Further screening of reaction temperature and base made no difference, such as 100 ^{o}C and pyridine or (triethyl)amine, which could not get the corresponding product ß-lactam **120**.

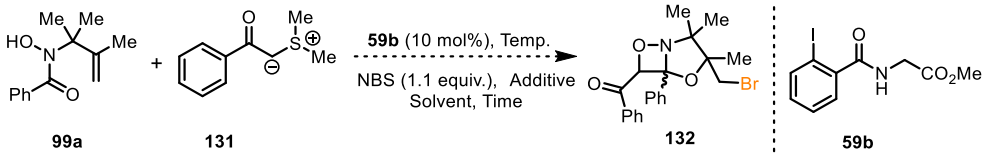
Table 5. Transformations of *N*-allylhydroxamic acid **99a** and oxiranes **129**.[61]



Entry	Solvent	Temperature (°C)	Time (h)	Additive (mol%)	Result
1	HFIP	40	20	$AlCl_3$(10)	0
2	DCM	40	4	$AlCl_3$(10)	0
3	DCM	r.t.	10	$AlCl_3$(10)	0
4	DCM	0	8	$AlCl_3$(10)	0
5	DCM	40	14	$Cu(OTf)_2$(10)	< 5%
6	DCM	40	14	$Zn(NTf)_2$(10)	< 5%
7	CH_3CN	50	4	$AlCl_3$(10)	0
8	Toluene	50	23	$BF_3{\cdot}OEt_2$	Complex

Herein, we tried a new catalytic method for the synthesis of 1,2,4-dioxazinanes **130** (with oxiranes **129**), At the outset of this study, our focus was directed toward finding an appropriate catalyst and suitable reaction conditions for the annulation of oxirane **129** with **99a**. Our initial experiments, using $AlCl_3$ (10 mol%) in HFIP, unfortunately, no product was formed even after a prolonged reaction time (Table 5, entry 1). When the temperature was increased to 50 ℃ in the presence of 10 mol % of $AlCl_3$, there was still no product after 23 h reaction time (Table 5, entries 7 and 8). Changing the additive from $AlCl_3$ to $Cu(OTf)_2$ and $Zn(NTf)_2$ (Table 5, entries 5 and 6), no product was detected, yet the recovery of oxiane **129**, and the use of BF_3 ·etherate led to a complex system (Table 5, entry 8).

Table 6. The reaction of *N*-allylhydroxamic acid **99a** and sulfur ylide **131**.

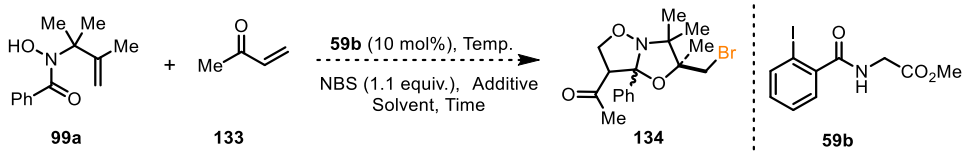


Entry	Solvent	Temperature (°C)	Time (h)	Additive	Result
1	HFIP	50	24	-----	r.s.m
2	DCM	40	24	K_2CO_3	r.s.m

3	CH_3CN	40	24	K_2CO_3	r.s.m
4	Toluene	90	13	-----	r.s.m
5	Toluene	80	23	$BF_3{\cdot}OEt_2$	r.s.m

After the sulfur ylide **131** was prepared according to the procedure in the previous literature,[62] we began our study by testing the reaction of the hydroxamate **99a** with the sulfur ylide **131** and iodine catalyst **59b**. In the presence of 10 mol % of iodine catalyst **59b**, the reaction could not proceed smoothly in HFIP at room temperature to give the desired product **132** (Table 6, entry 1). Evaluations of the solvent effect were subsequently carried out. As shown in Table 6, the desired product **132** could not be obtained in DCM (Table 6, entry 2). Both of acetonitrile and toluene gave no product (Table 6, entries 3 and 4), and not being the product **132** was formed even after a prolonged reaction time at an elevated temperature (Table 6, entry 5).

Table 7. The reaction of *N*-allylhydroxamic acid **99a** and the but-3-en-2-one **133**.

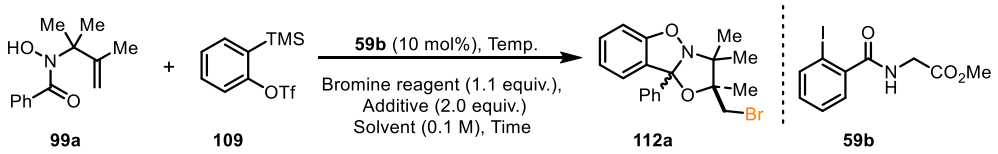


Entry	Solvent	Temperature (^oC)	Time (h)	Additive (mol %)	Result
1	Toluene	r.t.	8	$BF_3{\cdot}OEt_2$ (10)	n.d.
2	DCM	r.t.	8	$BF_3{\cdot}OEt_2$ (10)	n.d.
3	CH_3CN	r.t.	8	$BF_3{\cdot}OEt_2$ (10)	n.d.
4	CH_3CN	-20	15	$BF_3{\cdot}OEt_2$ (10)	n.d.
5	Toluene	-20	15	----	n.d.
6	DCM	-20	15	$BF_3{\cdot}OEt_2$ (10)	n.d.
7	Toluene	50	15	$BF_3{\cdot}OEt_2$ (10)	n.d.

We wished to exploit the but-3-en-2-ones **133** as the starting material in this catalytic system, according to this concept, reactions of screening various solvents were carried out initially at room temperature, which gave only unsatisfactory results, namely, the decomposition of **133**

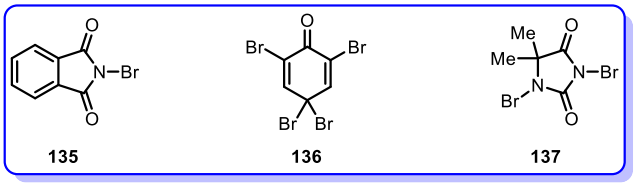
(Table 7, entries 1-3). Decreasing the temperature of the mixture (-20 °C, Table 7, entry 4) led no improvement of the reactivity, as well as the presence of boron trifluoride diethyl etherate or not (Table 7, entries 4-5). Elevating the temperature was screened, yet no formation of the desired product **134** (Table 7, entry 7).

Table 8. The reaction of *N*-allylhydroxamic acid **99a** and 2-(trimethylsilyl) aryl triflate **109**.



Entry	Bromine reagent	Temperature (°C)	Solvent	Additive	Time (h)	Yield[a]	d.r.[b]
1	NBS	r.t.	CH_3CN	C_SF	29	91%	50:50
2	**135**	r.t.	CH_3CN	C_SF	29	34%	50:50
3	**136**	r.t.	CH_3CN	C_SF	29	12%	50:50
4	**137**	r.t.	CH_3CN	C_SF	29	26%	50:50
5	NBS	r.t.	Toluene	C_SF	29	80%	50:50
6	NBS	r.t.	THF	C_SF	29	79%	50:50
7	NBS	r.t.	HFIP	C_SF	35	---	---
8	NBS	40	CH_3CN	C_SF	12	63	50:50
9	NBS	60	CH_3CN	C_SF	12	88	55:45
10	NBS	0	CH_3CN	C_SF	40	29[d]	50:50
11	NBS	-20	CH_3CN	C_SF	40	trace	n.d.
12	NBS	60	CH_3CN	TBAF	12	n.d.	n.d.
13	NBS	60	CH_3CN	KF	12	n.d.	n.d.
14	NBS	60	CH_3CN	KF/18-crown-6	12	22%	50:50

[a]yield determined by ^{1}H NMR spectroscopy (using 1,3,5-Trimethoxybenzene as the internal standard).[b]determined by the ^{1}H NMR spectrum of the crude mixture.

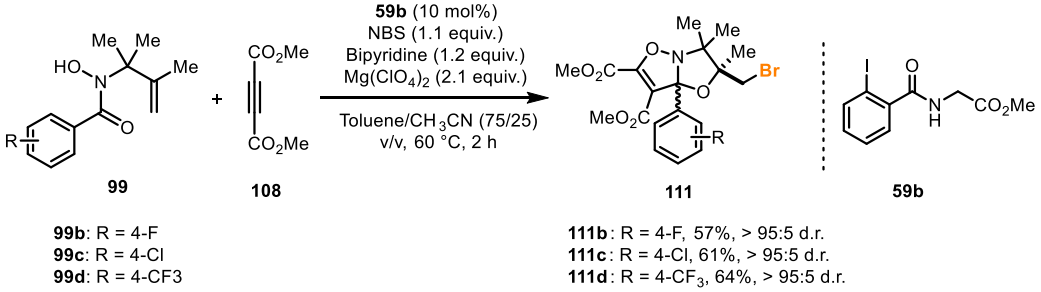


We commenced our studies by examining the effects of various reaction parameters on the yield of this iodine-catalyzed domino reaction using *N*-allylhydroxamic acid **99a** and 2-(trimethylsilyl)phenyl trifluoromethane sulfonate **109** (Table 8). To our delight, in the presence of 10 mol% of pre-catalyst **59b**, the reaction could proceed smoothly in acetonitrile at room temperature to give the desired product in 91% yield (Table 8, entry 1). As we can see from Table 8, further screening of bromine reagents were displayed that **112a** could be obtained in a sharply decreased yield with the same diastereoselectivity, when NBS was replaced by **135**, **136**, **137** separately (Table 8, entries 2-4). Evaluation of the solvent effect was carried out consequently.

As shown in Table 8, the desired product **112a** could be obtained in 80% yield in toluene and 79% in THF (Table 8, entries 5 and 6). HFIP was used as the solvent at room temperature, which yet gave only the starting material recovery (Table 8, entry 7). Evaluation of the temperature effect was also subsequently carried out, the desired product **112a** was generated in moderate yield with poor diastereomer controls, while the reaction temperature was increased to 40 even 60 ^{o}C subsequently (Table 8, entries 8-9). Further screening displayed that a lower reaction temperature could sharply decrease the reactivity, yet it had no effect on the selectivity of this system (Table 8, entries 10 - 12).

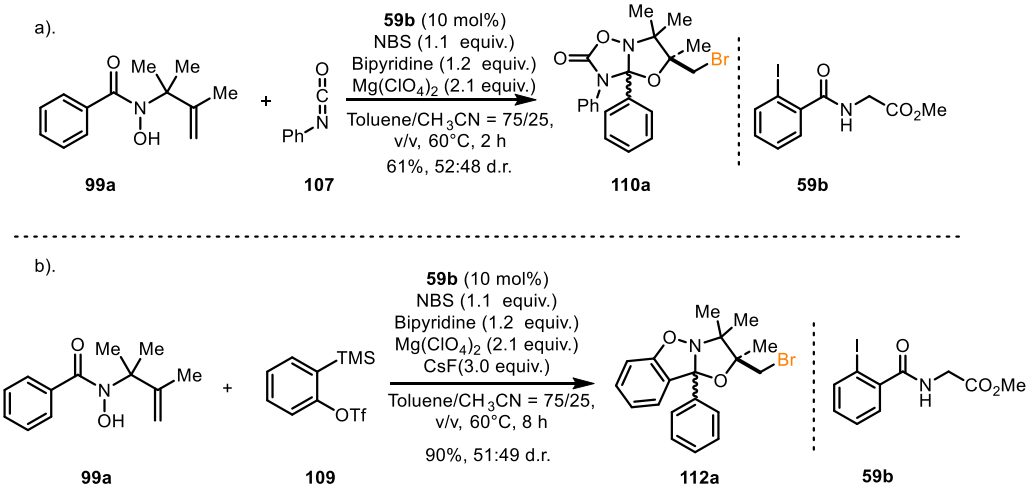
We moved on to screen different additives, namely TBAF, or KF as the fluoride reagent, under the similar reaction conditions. Unfortunately, both of TBAF and KF led to no conversion of the starting material **99a,** (Table 8, entries 12 - 13). However, the addition of phase transfer 18-crown-6 in the reaction gave the formation of a small amount of the desired product **112a,** mainly because that the phase transfer could increase the solubility of KF in acetonitrile, besides that the coordination between 18-crown-6 and potassium cation made the fluorine ion react with 2-(trimethylsilyl) aryl triflate **109** easily (Table 8, entry 14). Finally,

the desired product **112a** could be obtained in 88% yield at 60 °C.



Scheme 23. The reaction between *N*-allylhydroxamic acid **99a** and DMAD **108**.

At the same time, Dr. Ayan Dasgupta worked together with me on this project, and he screened different Lewis acids, solvents, and reaction temperatures of the reaction between *N*-allylhydroxamic acid **99a** and dimethyl acetylenedicarboxylate (DMAD) **108**,[161] Electro-withdrawing substitutes at phenyl group (**99b**, 4-F; **99c**, 4-Cl; **99d**, 4-CF_3) substrates gave corresponding products (**111b**, **111c**, **111d**) in highly diastereoselective way with moderate to good yields (57 - 64%, > 95:5 d.r.), using the reaction system of bipyridine and $Mg(ClO_4)_2$ at 60 °C.

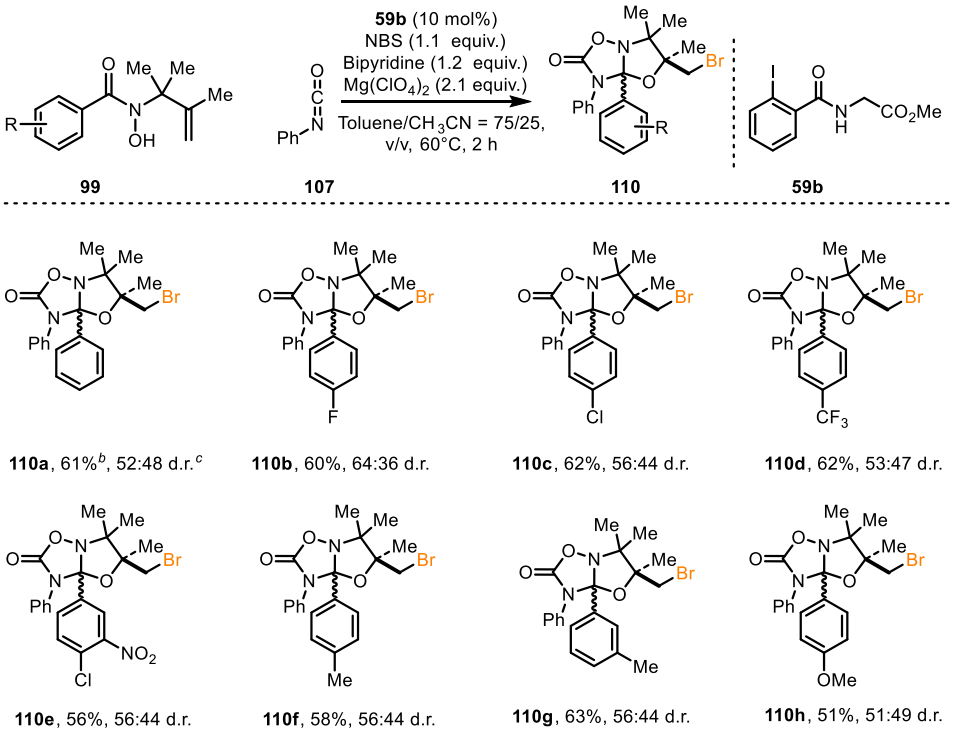


Scheme 24 Screening the reaction conditions of the *N*-allylhydroxamic acid **99a**, phenyl isocyanate **107**, and 2-(trimethylsilyl) aryl triflate **109** separately.

The identical optimization system for *N*-allylhydroxamic acids **99** and DMAD **108** was employed in reactions between the *N*-allylhydroxamic acid **99a** and phenyl isocyanates **107**

(Scheme 24a), as well as **99a** and 2-(trimethylsilyl) aryl triflate **109** respectively (Scheme 24b). Unfortunately, both of poor diastereoselectivities (52:48 d.r., 51:49 d.r.) were generated in moderate to high yield. The poor selectivity between *N*-allylhydroxamic acids **99** and phenyl isocyanates **107,** probably due to isocyanates were much more reactive than DMAD **108** in cycloadditions and thus do not allow the bromomethylene groups or aryl groups to sufficiently distinguish the *trans*- or *cis*- faced attack of phenyl isocyanates **107**.

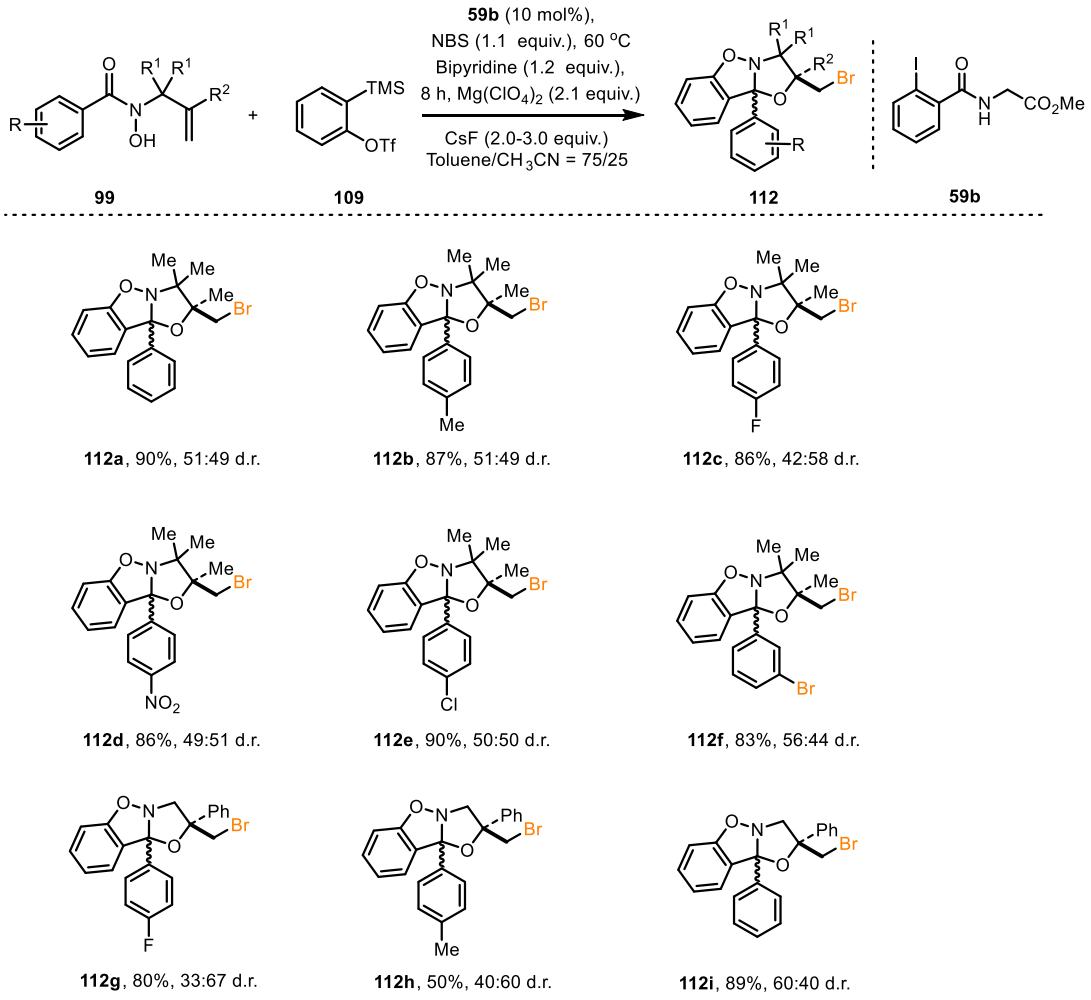
In summary, we made a lot of effort and screened reactions of *N*-allylhydroxamic acids **99** and several different 1,3-dipolarophiles, such as phenyl isocyanate **107,** dimethyl acetylenedicarboxylate (DMAD) **108**, 2-(trimethylsilyl) aryl triflate **109,** copper phenylacetylide **127,** sulfur ylide **131,** but-3-en-2-one **133,** oxiranes **129**, and phenylacetylene **124** under a variety of reaction conditions. Three novel desired compounds (**110**, **111**, **112**) were formed via the synthetic method i.e., the substrate *N*-allylhydroxamic acids **99,** with 10 mol% the glycine derived iodine reagent **59b** as the pre-catalyst in the solvent.



[b]isolated yield; [c]d.r. determined by NMR.

Scheme 25. The substrate scope of the reaction of *N*-allylhydroxamic acids **99** and phenyl isocyanate **107**.

We wished to extend the scope of the standard system in *N*-allylhydroxamic acids **99** with 1, 3-dipolarophile phenyl isocyanate **107** (Scheme 25). In this case, a series of substrates **99**, for example, substrates of *para*-position at phenyl groups, including electro-withdrawing, electro-donating substitutes, and these of *meta*-substituted phenyl groups gave similar poor diastereomer ratios and moderate yields (51-62%, 51:49 - 64:36 d.r.). Electro-withdrawing groups e.g., 4-F, 4-Cl, 4-CF_3 at the aromatic ring derivatives afforded moderate yields and similar diastereomer ratios (**110 b-d**), while almost no diastereoselectivity was obtained using 10**7a** as the substrate (**110a**), there was the same result with the electron-donating group (-OMe) at *para*-position in **107h** (**110h**). Substrates equipped by 3-Me, 4-Me, 4-Cl, 3-NO_2 were converted into the corresponding heterocycles with the identical poor diastereocontrol (**110e**, **110f**, **110g**, entries 5-7). Probably because that the phenyl isocyanate **107** is too much reactive in [3+2] cycloadditions and thus do not allow the bromomethylene groups or aryl groups to sufficiently distinguish the *trans*- or *cis*- faced attack of phenyl isocyanates **107**, and desired compounds **110** were unstable species, they were readily to decompose not only during the reactive procedure in the system, but also in the purification with silica gel column.



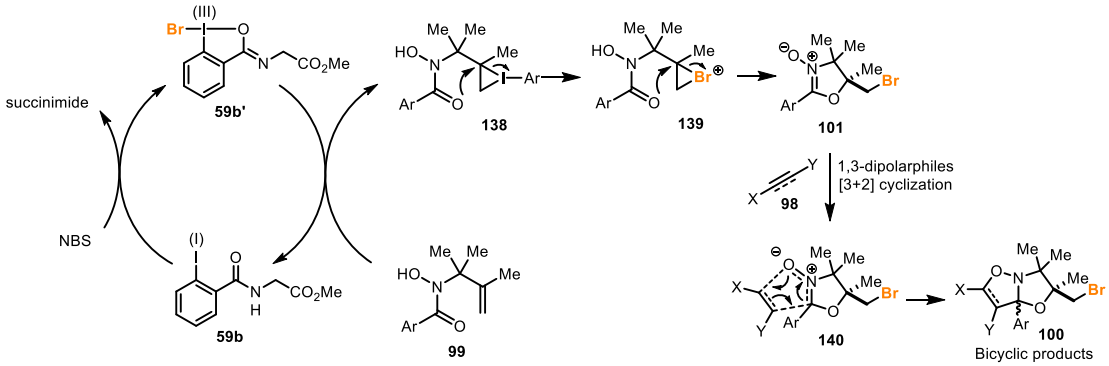
[b]yield referred to isolated yield; [c]d.r. was determined by NMR.

Scheme 26. The substrate scope of the reaction of**99** and 2-(trimethylsilyl) aryl triflate **109**.

We further explored the one-pot reaction between *N*-allylhydroxamic acid **99** and 2-(trimethylsilyl)aryl triflate **109**. The optimization reaction conditions were suitable for λ^3-iodane catalyzed cyclization of **99** in different structures**,** providing the corresponding *N*, *O*-heterocycles (Scheme 26) in moderate to high yield, yet poor to moderate selectivity. Substrates (R^1 = Me) with electro-withdrawing substitutes at *para*- , *meta*- position were screened (**99c**, R = 4-F; **99d**, R = 4-NO_2; **99e**, R = 4-Cl; **99f**, R = 3-Br), unfortunately, corresponding products were got in high yield, which gave poor diastereoselectivity (Scheme 26, **112c-f**). Another different kind of substrates were used in this system (R^1 = H, R^2 = Ph), the electro-withdrawing group substituted substrate gave a moderate diastereocontrol and a high yield (80%, 33:67 d.r., **112g**), while the rest of substrates offered corresponding

heterocycles in moderate yield with unsatisfactory selectivity (**112h-i**).

To account for the results of the present catalytic reaction, we proposed the mechanism as follows (Scheme 27).[85]



Scheme 27. Plausible catalytic cycles for the heterocyclic compounds.

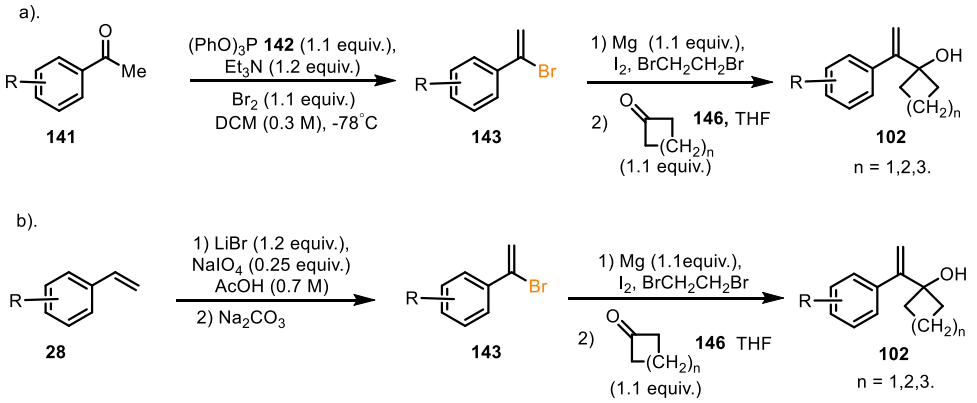
Firstly, the catalytic cycles was triggered by the intramolecular cyclization of **99** with a generated, actual, more reactive bromo-iodane reagent **59b'**, which was prepared through the oxidation of **59b** by NBS, to form oxazoline *N*-oxide **101**. In this process, the bromonium species **139** was afforded by the replacement of iodine with bromine. Herein, the regiospecific 5-exo-tet rearrangement was obtained via intramolecular nucleophilic attack, to afford the intermediate **101,** which in turn then underwent the known [3+2] cycloaddition with the corresponding 1, 3-dipolarophiles **98** furnishing the bicyclic reaction products **100** in a single pot reaction sequence.

2. Hypervalent Fluoro-Iodane Triggered Semipinacol Rearrangements

In 2005, Tu et al [110] reported a synthetic method of β-F aldehyde triggered by a combination of stoichiometric quinine/selectfluor **94** via semipinacol rearrangement of allylic alcohols, the corresponding β-fluoro aldehydes could be obtained with moderate enantioselectivity and reactivity. And then the catalytic cinchona-alkaloid derivatives/NFSI as the fluoro reagent induced fluorination/ semipinacol rearrangement was discovered by the same group in 2012, through which β-fluoroketones could be prepared straightforwardly.[111e] One year later, Alexakis and co-workers[112], [113] also developed an organocatalytic fluorination-induced semipinacol rearrangement of allylic alcohols via the combination of binol-derived phosphoric acids/selectfluor **94**. Consequently, a variety of ß-fluoro spiro-ketones were generated from the corresponding strained allylic alcohols in good yield. However, β-fluoro synthons were mostly offered through those reactions.

Cyclic ketones containing α-quaternary centres were attractive synthetic targets, as they were intriguing utilized intermediates for natural product syntheses. [114-118] Namely, the optically active 2-methyl-2-arylcyclopentanone derivatives were employed as key intermediates in the total synthese of (−)-aphanorphine,[119], [120] (−)-isoeupamne,[121] and tochiunyl acetate.[122] Among the methods to synthesize α-quaternary centres compounds, the construction of quaternary C−F stereogenic centres was the most synthetically challenging and also the least developed area of research. Inspired by our previous results and our long-standing interest in hypervalent iodane-mediated novel reactions,[78], [123] we have recently discovered an efficient tandem system to the synthesis of a-fluoro ketones via a hypervalent λ^3-fluoro iodane /$AgBF_4$ combination mediated unusual semipinacol rearrangement of allylic alcohols (Scheme 29). This tandem reaction, as far as we know, was firstly discovered to prepare the a-fluoro carbonyl compounds which have been important syntons in organic chemistry.[124] Herein, we presented our investigational results in detail.

Firstly, cyclobutanols **102** as starting materials were synthesized as follows (Scheme 28):



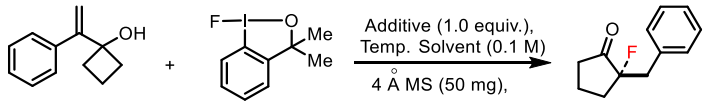
Scheme 28. a). Using triphenyl phosphite **142** and bromine to synthesize bromostyrenes **143** and cyclobutanols **102**; b). The synthesis of (1-bromovinyl)benzenes **143** and cyclobutanols **102**.

The first procedure was referred as the conformation of vinyl halides from ketones via a $(PhO)_3P^+BrBr^-$ $(TPPBr_2)^-$ **144**[125], [126] promoted dihalodeoxobisubstitution (Scheme 28a). Then the vinyl bromides **143** could be used for the next step without any further purification, Grignard reagents were *in situ* obtained from **169**, and then the nucleophilic attack between the cyclic ketones **146** and *in situ* Grignard reagents gave cyclobutanols **102**.

The second method was that styrene **28** in acetic acid was added the lithium bromide and the $NaIO_4$ successively.[43], [127], [128] The oxidation of metal bromide by $NaIO_4$ gave *in situ* generated elemental bromine, which further rapidly dibrominated styrene **28a,** and then the dibrominated species reacted with added potassium carbonates to offer the **143**, the nucleophilic attack between the cyclic ketones **146** and *in situ* generated Grignard reagent offered cyclobutanols **102**.

With substrates **102** in hand, we began our investigation with cyclobutanol **102a** and used reaction conditions similar to those used [123] in the master thesis of Michael Röhrl in our group, namely hypervalent λ^3-fluoro iodane **42a,** molecular sieves,[85],[134] $AgBF_4$ [111a-d]as the Lewis acid, and a solvent, at room temperature (Table 9).

Table 9. Investigation of reaction conditions.



102a **42a** **106a**

Entry	Solvent	Time (h)	Additive	Temp.[a]	Yield (%)[b]
1	Toluene	8	$AgBF_4$	r.t.	n.d.[c]
2	CH_3CN	8	$AgBF_4$	r.t.	n.d.
3	DMF	8	$AgBF_4$	r.t.	13
4	$CHCl_3$	8	$AgBF_4$	r.t.	22
5	MeOH	8	$AgBF_4$	r.t.	n.d.
6	THF	8	$AgBF_4$	r.t.	n.d.
7	DCM	8	$AgBF_4$	r.t.	50
8	DCM	8	-----	r.t.	n.d.

[a] r.t. = room temperature. [b]NMR yield was determined by internal standard 1,3,5- tri methoxybenzene, [c] n.d. = not detected desired product.

Initially, cyclobutanol **102a** was chosen as the model substrate for the optimization of reaction conditions. Using hypervalent fluoro λ^3-iodane **42a** with one equivalent $AgBF_4$ as the additive was evaluated. Gratifyingly, the desired product cyclopentanone **106a** was obtained in a very promising isolated 50% yield (Table 9, entry 7). *N*, *N*-dimethylformamide (DMF), i.e., aprotic polar solvents as the reaction medium afforded the target compound **106a** in 18% yield (Table 9, entry 3); While the reaction gave no product **106a** in THF and acetonitrile (Table 9, entries 2 and 6), it was also the same case with that in protic polar solvents, i.e., MeOH, there no target compound **106a** was detected (Table 9, entry 5). On the contrary, non-polar solvent e.g. toluene as the reaction medium could not afford the target product **106a** either (Table 9, entry 1). However, chloroform as the solvent led to 22% yield. It was notable that no reaction occurred in the absence of Lewis acid under otherwise identical reaction condition, which was as a control experiment, and the Lewis acid was necessary for this reaction, as Lewis acid could activate the hypervalent fluoro λ^3-iodane **42a**[111a-d], [114] (Table 9, entry 8).

Table 10. Optimization of additives of the reaction.

102a **42a** **106a**

Entry	Additive	Time (h)	Temp.	Yield (%)[a]
1	$AgNO_3$	8	r.t.	n.d.[d]
2	AgOAc	8	r.t.	n.d.
3	$[Cu(CH_3CN)_4]BF_4$	8	r.t.	34
4	$BF_3{\cdot}OEt_2$	8	r.t.	n.d.
5	$Pd(BF_4)_2(CH_3CN)_4$	8	r.t.	22
6	$AgBF_4$	8	r.t.	50
7	$TiCl_4$	8	r.t.	n.d.

[a]NMR yield was determined by internal standard 1,3,5-trimethoxybenzene.

With the optimized solvent in hand, we then investigated the effect of varies Lewis acids as additives (Table 10). Other additives were first examined and compared to $AgBF_4$. Silver salts were screened as the first choice. When $AgNO_3$ was used as the additive instead of $AgBF_4$, the target compound **106a** could not be obtained, yet only the recovery of starting material cyclobutanol **102a** and also the hypervalent fluoro λ^3-iodane **42a** (Table 10, entry 1). AgOAc was also utilized as the additive in this system, however, no conversion of the cyclobutanol **102a** occurred either, only the starting material was recovered (Table 10, entry 2). $AgBF_4$ as the additive in this system might not just act as Lewis acid activing the hypervalent fluoro λ^3-iodane **42a**. With that idea in mind, we screened copper and palladium (BF_4^-) salts as additives. $[Cu(CH_3CN)_4]BF_4$ was utilized in the system, the cyclopentanone with the C-F quaternary stereogenic center compound **106a** was obtained in 34% yield at room temperature after 8 h less than that of $AgBF_4$ as the additive (Table 10, entry 3), while $Pd(BF_4)_2(CH_3CN)_4$ as the additive gave even a lower yield (22% , Table 10, entry 5). These two examples might also further prove our hypothesis that the BF_4 ion was a critical factor to realize this system. The screening of Lewis acids were carried out in the following reactions, $BF_3{\cdot}OEt_2$ as an additive gave not only the decomposition of the cyclobutanol **102a**, but also the decomposition of fluoroiodane reagent **42a**, a messy system was obtained (Table 10, entry 4). When titanium salt was used as additive, no conversion of the starting material and no decomposition occurred in this system (Table 10, entry **7**).

Table 11. Optimization of the temperature of the reaction.

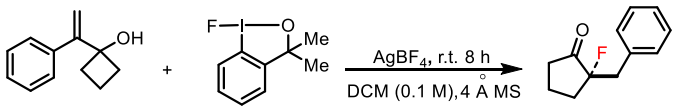
102a **42a** **106a**

Entry	Temperature (℃)	Time (h)	Yield (%)[a]
1	-20	48	n.d.
2	0	12	61
3	r.t.	8	50
4[c]	40	8	20

[a]NMR yield was determined by internal standard 1,3,5-trimethoxybenzene.

Evaluation of the reaction temperature was subsequently carried out. As shown in table 11, Furthermore, the reaction at room temperature was a desirable condition for this cyclization reaction process, while the reaction at a lower temperature, i.e. 0 ^{o}C slightly increased the yield but at prolonged reaction times. However, no target compound **106a** was detected at -20 ^{o}C (Table 11**,** entry 1). The reaction of cyclobutanol **102a** was still furnished in acceptable 61% yield, although a longer reaction time was required (Table 11, entry 2). It was important that the yield was dramatically decreased under elevated temperatures, and a poor conversion happened to **106a** at 40 ^{0}C, as decomposition occurred simultaneously (Table 11, entry 4).

Table 12. Optimization of reaction conditions of the ratio of $AgBF_4$ and hypervalent λ^3-iodane **42a**.



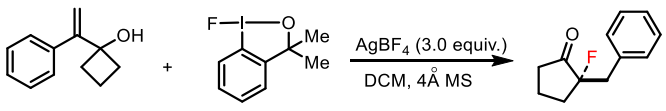
102a **42a** **106a**

Entry	The ratio of $AgBF_4$ /**42a** (equiv./equiv.)	r.s.m	Yield (%)[a]
1	1.0 / 1.0	0%	50
2	3.0 / 2.0	0%	63
3	3.0 / 1.5	0%	59
4	3.0 / 1.0	40%	43
6	2.0 / 3.0	70%	< 5
7	1.0 / 3.0	70%	< 5
8	3.0 / 3.0	< 5%	90

[a]NMR yield was determined by internal standard 1,3,5-trimethoxybenzene.

Subsequently, we continued our study on the ratio between $AgBF_4$ and hypervalent fluoro λ^3-iodane **42a,** because the target compound **106a** was only obtained in moderate yield. The results were shown in Table 12. The corresponding product **106a** was generated in 50% yield under 1.0 equiv. $AgBF_4$ and 1.0 equiv. **42a**, and the loading of $AgBF_4$ was based on that of the substrate cyclobutanol **102a**. At the same time, there was no recovery of starting material **102a** (Table 12, entry 1). Using three equivalent $AgBF_4$ combined with two equivalent hypervalent fluoro λ^3-iodane **42a** led to 63% yield (Table 12, entry 2), a slightly increasing yield compared with that of the first entry. While the target product **106a** in 59% yield was obtained using the methodology of three equivalent $AgBF_4$ combined with two equivalent hypervalent fluoro λ^3-iodane **42a** (Table 12, entry 3). When the load of hypervalent fluoro λ^3-iodane **42a** was decreased to one equivalent with still three equivalent $AgBF_4$, the unreacted starting material cyclobutanol **102a** gave signals in ^{1}H NMR, while the reaction provided low yield (Table 12, entry 4). Subsequently, several loadings of $AgBF_4$ were screened with three equivalent hypervalent fluoro λ^3-iodane **42a**, 90% yield of the target compound **106a** was obtained with 7% the recovery of starting material with 3 equivalent of $AgBF_4$ (Table 12, entry 8), and then added $AgBF_4$ was decreased to two equivalent, and even one equivalent separately, while the loading of **42a** was still three equivalent in both two system, the astonishing results came out that almost only trace amount of target compounds were generated (Table 12, entries 6 and 7). In conclusion, $AgBF_4$ was the key factor for this system, it was used as Lewis acid not only activating the fluoroiodane **42a**, but also probably providing fluorine ion for the target product **106a**.

Table 13. Investigation of the concentration of the reaction.

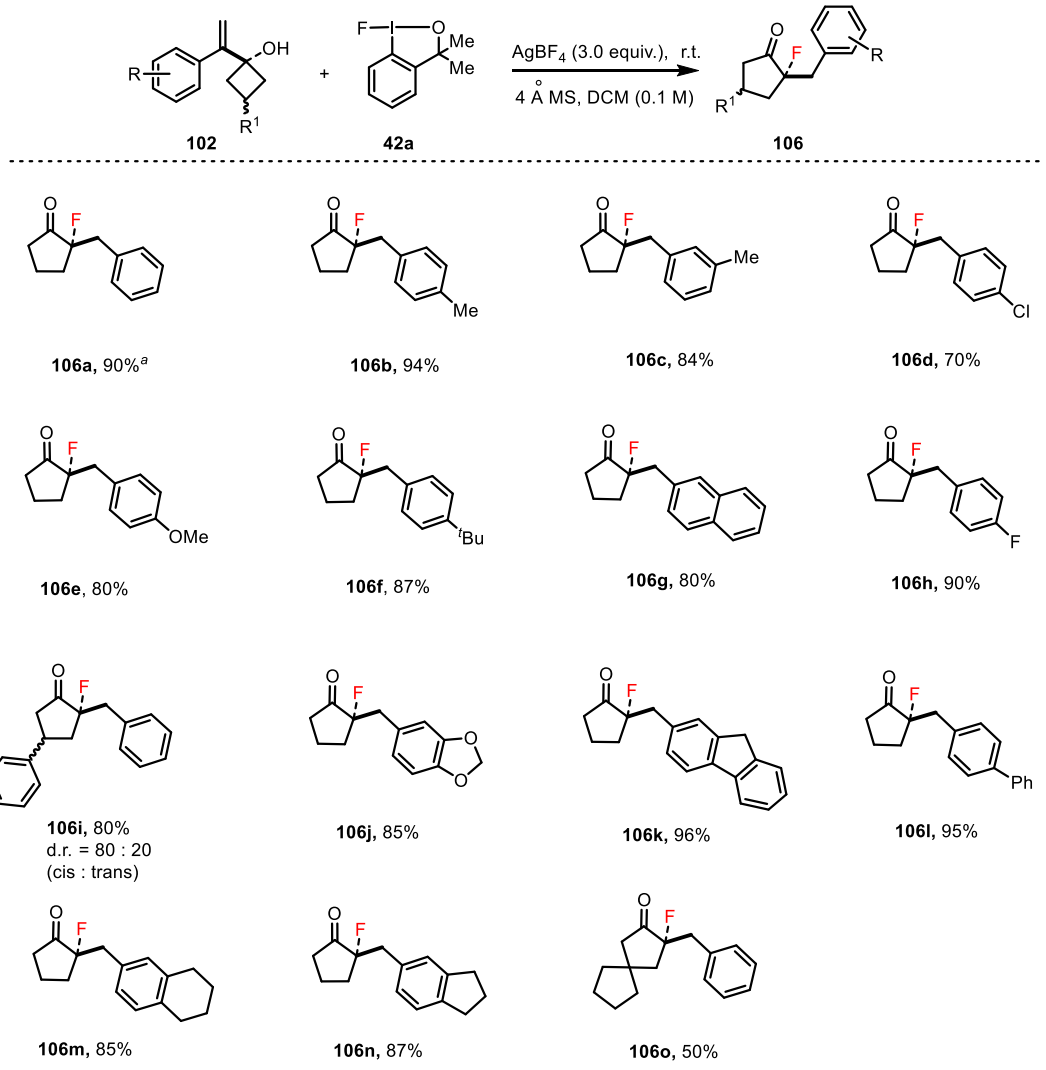


102a **42a** **106a**

Entry	Concentration	Yield[a]
1	0.05 M	83%
2	0.1 M	90%
3	0.2 M	45%

[a]NMR yield was determined by internal standard 1,3,5-trimethoxybenzene.

The further screening of the concentrations was carried out, and the results were showed in Table 13. The standard reaction concentration for screening other parameters was 0.1 mmol/mL, the target compound **106a** could be obtained in 90% yield under this reaction conditions (Table 13, entry 2). While diluting the reaction changed the concentration from 0.1 M to 0.05M, the yield of the target product **106a** was only 7% less than that of 0.1 M concentration (Table 13, entry 1). However, changing the concentration of the reaction to 0.2 M led to 45% yield, which was expected for an intramolecular process (Table 13, entry 3).

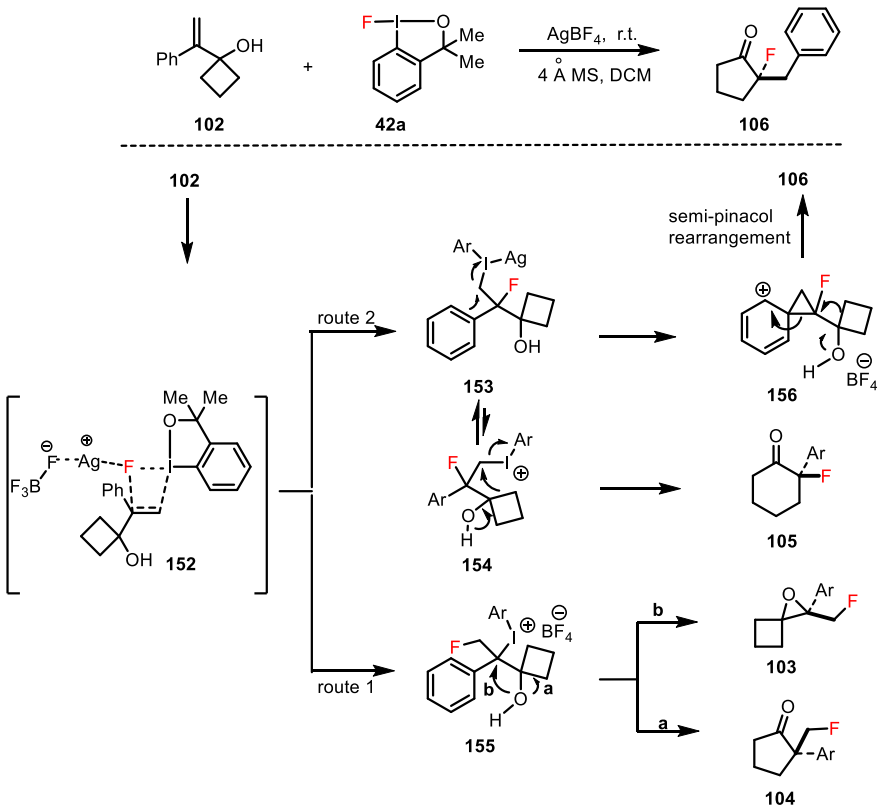


[a]isolated yield.

Scheme 29. The scope of target compounds **106**.

I and Peng-Yuan Zhao then set out to explore the scope of this reaction, and the results were

summarized in Scheme 29. It was found that a wide range of cyclopentanones **106** containing α-F quaternary centers with different substitute groups could be constructed smoothly in good to excellent yields (70-96%). Initially, using phenyl group substituted cyclobutanol **102a** gave the corresponding product **106a** in 90% yield. The *para*-tolyl product **106b** was obtained in high yield (94%), while a slightly low yield of **106c** was observed with a *meta*-Me group (84%). The 4-Cl substituted phenyl cyclobutanol **106d** was also suitable for the system, which afforded **106d** in 70% yield. Electrone-donoating groups substituted substrates, such as **106e**, and **106k** gave the almost same moderate yield, respectively (80%, 85%). ^{t}Bu at *para*-position compound also was generated in high yield (87%, **106f**). Electro-withdraw group product **106h** could be offered in 90% yield, bulky groups substituted substrates, for example **102k**, **102m**, **102n**, and **102g** gave the corresponding products in moderate to high yields (96%, **106k**; 85%, **106m**; 87%, **106n**; 80%, **106g**). The substituted groups at cyclobutyl substrates were also studied, and the corresponding products, e.g., **106i** were generated in moderate yields (80%). **106o** could also be offered in 50% yield.

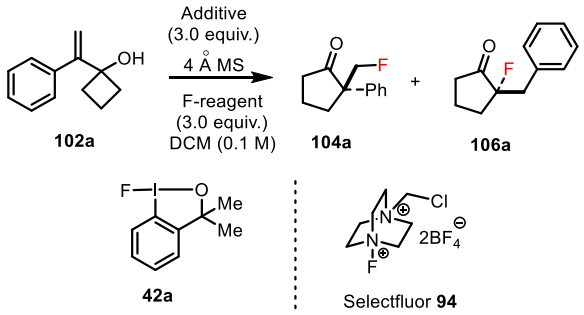


Scheme 30. Typical mechanism of the formation of **106** triggered by hypervalent λ^3-iodane **42a**.

The proposed mechanism was shown as followed (Scheme 30). Initially, an activation of the F-iodane **42a** proceeded via the coordination of the Lewis acids $AgBF_4$ to the fluorine rather than to the oxygen atom.[111a-d] then the double bond of cyclobutanols **102** had the nucleophilic attack of the activated iodane to form metathesis transition state **152**, [114] followed by two further transformation steps. The intermediate **155** was obtained through route 1, which could afford two products, namely **103** via the route **b**, while the route a provided cyclopentanones **104**.

Noteworthy, aryl migrations were generally widespread in hypervalent iodane chemistry, [62], [129-132] and the unusual rearrangement could also happen to the conversion of **153** into **156** through the route 2. The nucleophilic attacking to iodine by ß-phenyl group in **153** generated the stereospecific phenonium ion **156**, and the spiral three-member ring in the **156** released the ring strength through semi-pinacol rearrangement to form α-F substituted cyclopentanones **106** (Scheme 30).

Table 14. Screening different additives and fluoro-reagents.

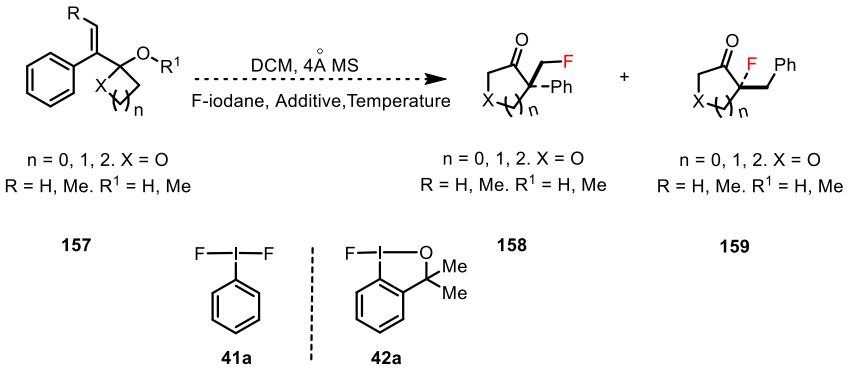


Entry[a]	Additive	F-reagent	Result
1	----	**42a**	n.d.
2	$Et_3N{\cdot}3HF$	**42a**	n.d.
3	$Et_3N{\cdot}5HF$	**42a**	n.d.
4[c]	$AgBF_4$	**94**	**104a** (90%)[b]
5	----	**94**	**104a** (90%)[b]

[a]NMR yield was determined by internal standard 1,3,5-trimethoxybenzene.

Using different fluoro-reagents and additives were carried out subsequently (Table 14). Firstly,

the exclusion of additive resulted in no formation of the desired product **106a** (Table 14, entry 1), which indicated that $AgBF_4$ was crucial to trigger the conversion of **102a**. Interestingly, the treatment of **102a** with the cyclic hypervalent iodane fluoro reagent **42a** and the addition of $NEt_3 \cdot 5HF$ resulted in no formation of cyclopentanone **106a** (Table 14, entry 3). No conversion of **102a** was observed, as $NEt_3 \cdot 3HF$ was used as the additive (Table 14, entry 2). A variety of different F-sources were tested, such as N-F reagent, i.e., selectfluor **94**, surprisingly, **104a** was obtained in quantitative as the corresponding product, without the 1, 2-phenyl group migration (90%, Table 14, entry 4). This chemical divergent phenomenon was previously reported by the Gulder group.[78] The **104a** was also offered in high yield with no additive (Table 14, entry 5).



Scheme 31. Screening other structure substrates as the starting materials.

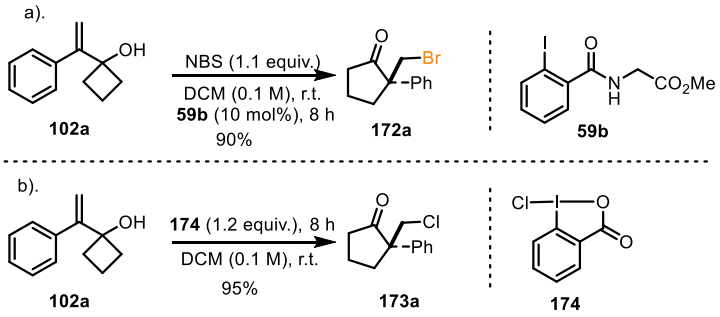
In order to expand the scope of substrate, firstly, the reaction of cyclopropanol **157a** (n = 0, X = O, R = H, R^1 = H) with iodane reagent **41a and 42a** separately was explored. The optimum conditions namely $AgBF_4$ (3.0 equiv.), **42a** (3.0 equiv.), in DCM at room temperature was studied. However, no conversion of **157a** was observed, and only the observation of the hydrolysis of **157a.** Reducing the loading of $AgBF_4$ and hypervalent iodane **42a** to (1.0 equiv. or 1.1 equiv.) separately still gave the decomposition of **157a**. And then **157b** (n = 2, R = H, R^1 = H) was subjected to the hypervalent iodane triggered unusual cyclization. Firstly, cyclopentanol **157b** was subjected to the optimal conditions namely 3.0 equivlent $AgBF_4$, 3.0 equivlent **42a**, in DCM at room temperature, no conversion of **157b** was detected, yet the recovery of the starting material **157b**, Elevating the reaction temperature to 40 ^oC led to the

total consumptions of **157b**. However, neither of **158b** or **159b** was observed. In the meantime, other silver salts were screened, such as AgOAc,[133] bearing a moderately basic charged ligand acetate might facilitate deprotonation of hydroxyl in **157b** to generate the oxygen anion, yet no conversion of **157b** was observed even with three equiv. AgOAc and three equiv. **42a**. Replacement of **42a** with **41a** (difluoroiodotoluene), which was more active than **42a**, led to no formation of the desired product **158b** and **159b.**

Except for the terminal alkenes, three different groups-substituted alkenes were preliminary studied in this reaction. At first, the cyclobutanol **157c** (n = 1, R = Me, R^1 = H) was subjected to the reaction system, namely **42a** as fluoro-reagent, with $AgBF_4$ in DCM at room temperature. Unfortunately, no corresponding products **158b** and **159b** were detected, except for the recovery of the starting material **157c**.

Oxa-cyclobutanol [134] **157d** (n = 1, X = O, R = H, R^1 = H) was also used in this system, firstly, neither of the corresponding products, such as **158b** and **159b** was detected, only the recovery of the starting material **157d**. Investigations of the reaction temperatures were studied subsequently. Elevating the temperature to 40 ^oC had no effect on the reactivity. In order to carry the reaction at high temperature, DCE was used as the solvent, yet still no conversion of **157d** was detected under 80 ^oC. We moved on to using the more reactive difluoro-iodane agent **41a**, in order to furnish the product **158b** and **159b**. However, only the decomposition of **157d** and **41a** were obtained, no desired signal appeared on ^{19}F NMR and GS-MS. Using less loading of $AgBF_4$ and **41a** (difluoroiodotoluene), and also no corresponding compounds **158b** and **159b** were detected.

Then both of the bromination and chlorination of cyclobutanol **170a** were studied separately (Scheme 32). Using the combination of **59b** as pre-catalyst and NBS as the bromine source, the bromination product **172a** was afforded in isolated 90% yield (Scheme 32, a). When 1.1 equivalent **174** was used as the chlorine source, the total conversion of **102a** happened, which afforded a yield of 95% of **173a** (Scheme 32, b).

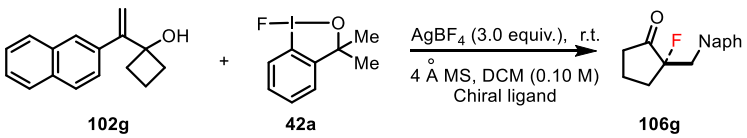


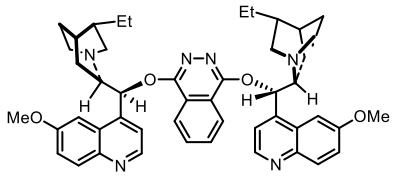
Scheme 32. Investigations of the bromination and chlorination of **102a**.

With the prevalence of fluorinated pharmaceuticals and pesticides, the asymmetric incorporation of fluorine into organic compounds has attracted considerable attention. For the reason that the C−F quaternary stereogenic centers in these molecules convey rather versatile effects, which influence the reactivity of the neighboring functional groups and lipophilicity of the biomolecules. Although the development of asymmetric fluorination methodology has made significant progress in recent years,[136, 137] the asymmetric construction of a quaternary stereogenic center containing fluorine is quite still synthetically challenging.

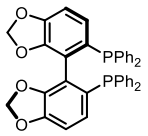
Next, we turned our attention to a preliminary study on enantioselectivity of the construction of carbon−fluorine quaternary stereogenic centers compounds **106** using hypervalent fluoro λ^3-iodane reagent **42a** (Table 15).

Table 15. Evaluation of different chiral ligands.

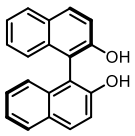




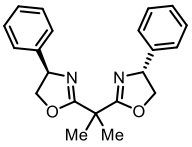
175, $(DHQD)_2PHAL$



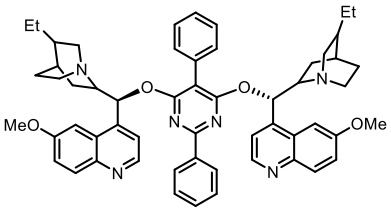
176, (*R*)-SEGPHOS



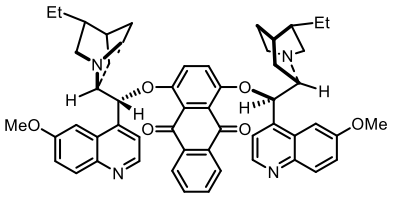
177, (*R*)-BINOL



178, (*R,R*)-2,2'-Isopropylidenebis (4-phenyl-2-oxazoline



179, $(DHQD)_2Pyr$



180, $(DHQ)_2AQN$

Entry[a]	Chiral ligand (mol%)	Temp. (^oC)	e.e. (%)[a]	Yield (%)[b]
1	$(DHQD)_2$ PHAL **175** (10)	0	0	r.s.m.
2	$(DHQ)_2$ PHAL **175** (10)	r.t.	0	90
3	$(DHQ)_2$ PHAL **175** (300)	r.t.	0	r.s.m[c]
4	(*R*)-SEGPHOS **176** (10)	r.t.	0	80
5	(*R*)-BINOL **177** (10)	r.t.	0	85
6	(*R,R*)-2,2'-Isopropylidenebis (4-phenyl-2-oxazoline **178** (10)	r.t.	0	85
7	$(DHQD)_2Pyr$ **179** (10)	r.t.	--	r.s.m.
8	$(DHQD)_2AQN$ **180** (10)	r.t.	--	r.s.m.

[a]Determined by HPLC analysis using a chiral stationary phase (chiral IA column). [b] Isolated yield. [c]r.s.m = recovery of the starting material.

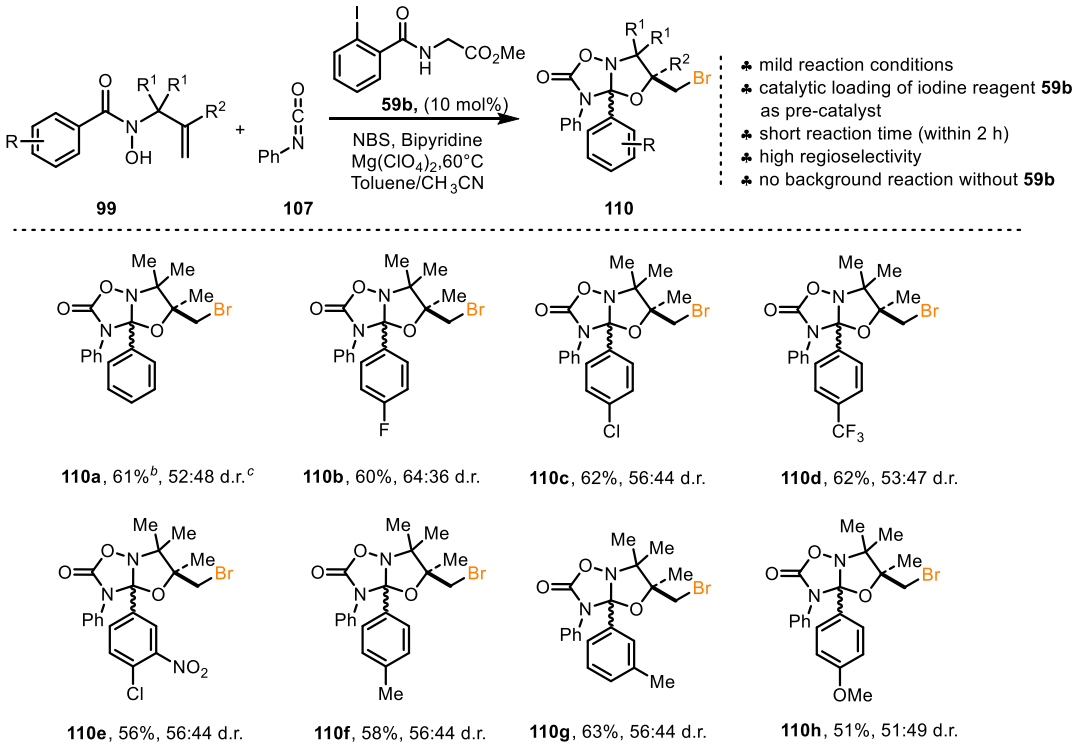
Asymmetric halogenation cascade reactions have been proven to be highly efficient methodologies to form chiral quaternary carbon centers. Some groups have reported highly enantioselective construction of quaternary carbon centers ketones through bromination, chlorination, and fluorination-induced semipinacol rearrangement.[141-145] Enlighted by these elegant works, Peng-yuan and I would like to use chiral ligands in this reaction, to realize the formation of chiral quaternary C-F centers-containing small molecular (Table 15). We began our study by testing the reaction of cyclobutanol **102g** with **42a** and $AgBF_4$ in DCM. In the

presence of 10 mol% $(DHQD)_2$ PHAL **175** at 0 ^oC in DCM (Table 15, entry 1), unfortunately, the target product **106g** could not be formed under this condition. Elevating the temperature to room temperature led to surprising variations in the yield, **106g** could be formed in 90% yield with 0% e.e. (Table 15, entry 2). However, adding three equivalent loading of $(DHQ)_2$PHAL **175** led to the recovery of starting material **102g**, without any desired product (Table 15, entry 3). Screening various chiral ligands was carried out subsequently, in the presence of 10 mol % of (R)-SEGPHOS **176** or (R)-BINOL **177**, the reaction could proceed smoothly in DCM at room temperature to give the desired products in high yield, but they were racemic mixtures (Table 15, entries 4-6). No conversion of the starting material **102g** happened in the presence of 10 mol% $(DHQD)_2$Pyr **179**, which was the same result with 10 mol% $(DHQD)_2$AQN **180** (Table 15, entries 7 and 8).

3. Summary

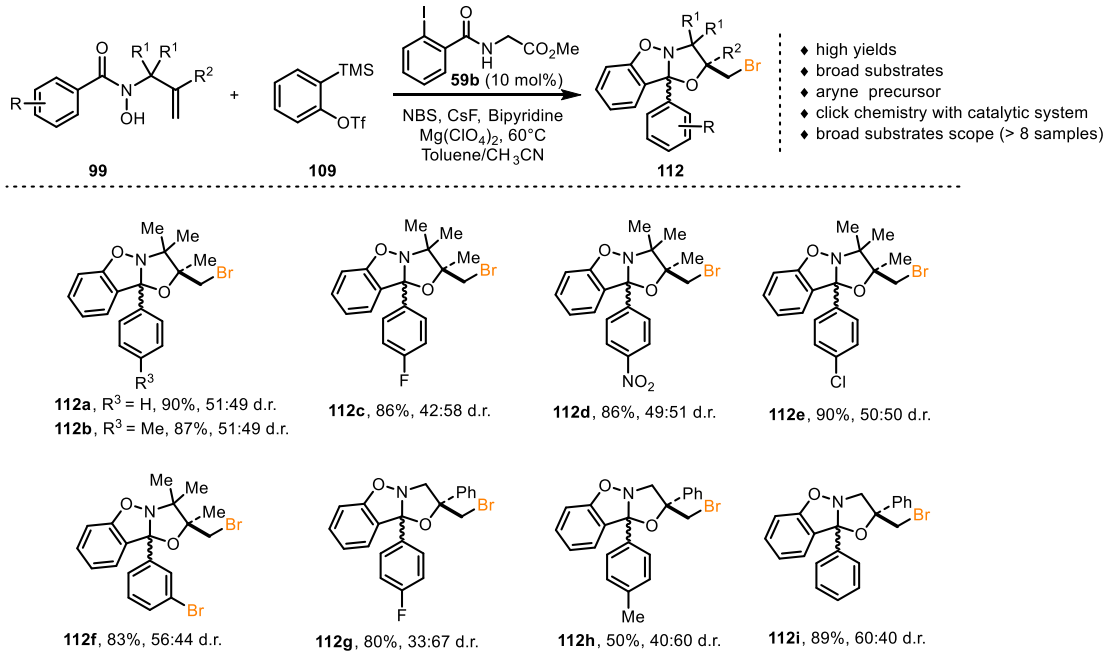
Iodanes compounds possess reactivity similar to those of transition metals, however, have the advantage of environmental sustainability and efficient utilization of natural resources. The contents in this thesis expanded the application of hypervalent iodane reagents in novel, chemo-, and regioselective, yet unavailable synthetic area, especially, to develop innovative hypervalent iodane triggered methodologies, which furnished access to new halogenated structural motifs with yet unknown biological and physicochemical characteristics. The outcomes were shown in a sequence as bellows.

The development of a novel *o*-iodobenzamide **59b** catalyzed system with *N*-bromosuccinimide NBS as the oxidation was realized, a series of *N*, *O*-heterocycles **100** from *N*-allylhydroxamic acids **99** and a variety of 1, 3-dipolarophiles, namely, phenyl isocyanate **107,** dimethyl acetylenedicarboxylate (DMAD) **108**, 2-(trimethylsilyl) aryl triflate **109,** copper phenylacetylide **127,** sulfur ylide **131,** but-3-en-2-one **133,** oxiranes **129**, and phenylacetylene **124** were carried out, and it turned out that three [161] categories of novel corresponding heterocycles **110**, **111**, and **112** were formed in moderate to high regio-, chemoselectivity via the reaction separately. As shown in Scheme 33, the R^1 and R^2 groups could be methyl, A broad range of R groups were tolerated, including electron-withdrawing substitutes (**110b−e**) or electro-donating substitutes (**110f** and **110h**) at phenyl groups. Under the optimal reaction conditions, a series of *N*-allylhydroxamic acids **99** were screened (Scheme 34). The R^1 groups might be methyl or H, R^2 groups could be a phenyl group except for methyl (**112g-i**), a series of synthetically functional groups showed comparable reactivity, including electronwithdrawing (**112c-g**) and electron-donating groups **112b** were tolerated.



[b]isolated yield; [c]d.r. determined by NMR.

Scheme 34. The substrate scope of the reaction of *N*-allylhydroxamic acids **99** and phenyl isocyanate **107**.

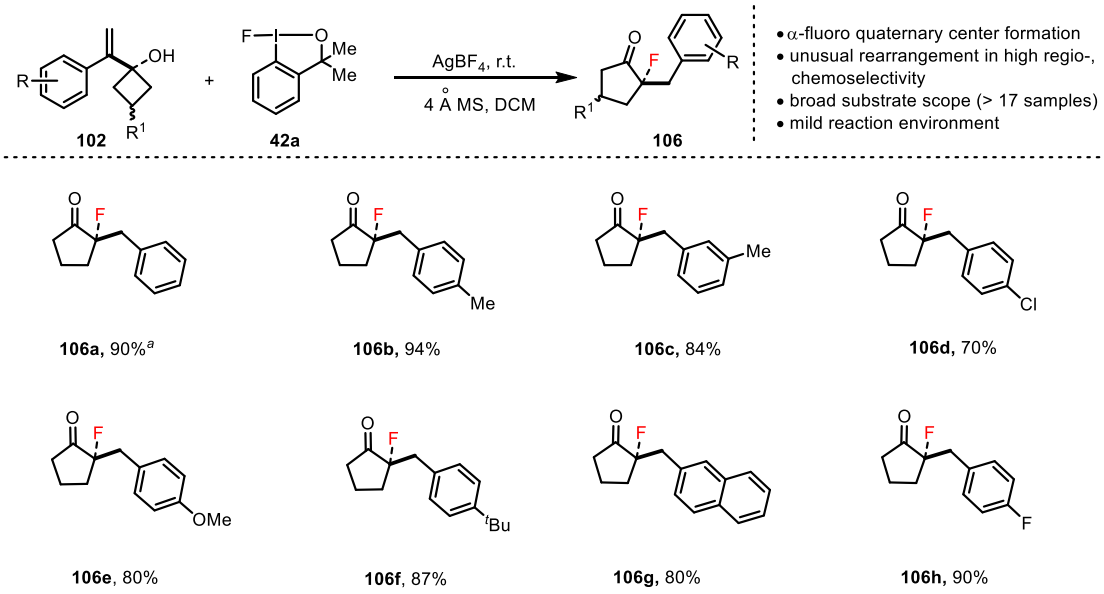


[a]Yield referred to isolated yield; [b]d.r. was determined by NMR.

Scheme 35. Substrate Scope of the formation of *N*,*O*-heterocycles **112**.

Having furnished this one-pot *o*-iodobenzamide **59b** catalyzed [3+2] cyclization of *N*-allylhydroxamic acids **99**, we wondered what would get from the reaction of *N*-allylhydroxamic acids **99** with other sorts of 1, 3-dipolarophiles, including copper phenylacetylide **127**, sulfur ylide **131**, but-3-en-2-one **133**, oxiranes **129**, and phenylacetylene **124**. Unfortunately, no anticaipated *N*, *O*-heteocycles furnished at all.

In the next step, moisture- and air-stable cyclic hypervalent *F*-iodane reagent **42a** mediated high regio-, stereoselective fluorinations of cyclobutanols **102** were realized with $AgBF_4$ as an exogenous Lewis acid (Scheme 36). A variety of functional synthons bearing *a*-fluoro quaternary units were developed in good reactivity. A broad of substrate scope (> 17 examples) and sole five-member ring products **106** were realized. A series of functional groups were tolerated, the R^1 could be aliphatic groups (**106i**, **106o**). A broad range of R groups also were tolerated, including naphthyl substituent (**106g**), phenyl groups substituted with electron-withdrawing or electron-donating groups, including halogen (**106d**, **106h**), ether (**106e**, **106j**). A proposal four-step mechanism involving a metathesis /fluorination/1, 2-aryl shift /semi-pinacol reaction was hypothesized.



[a]Yield was isolated yield.

Scheme 36. The scope of target compounds **106**.

In summary, on the basis of screening reactions, oxa-cyclobutanol, cyclopentanol, and cyclopropanol were not suitable substrates for the methodology of hypervalent iodane triggered unusual rearrangement, while most cyclobutanols **102** were smoothly converted into the desired products **106** very well. Among of them, various functional groups, including electro-rich, -poor, ether, bicyclic phenyl group and halogens were tolerated. Substituents on

the cyclobutyl framework impacted mainly on the reactivity (**106i**, **106o)**. Sterically hindered substituents on the phenyl groups did not impact hugely on the reaction yield.

III. Experimental Section

1. General Information

Schlenk flasks were dried at 250 ^{o}C by heating gun under high vacuum. Air or moisture sensitive reactions were carried out in dry, high vacuum Schlenk flasks. The chemicals utilized were commercially obtained from abcr, Acros, Carbolution, Merck, Sigma Aldrich and TCI without purification, except for NBS, which needed to be recrystallized from water. Anhydrous THF and DCM were obtained from *MBraun* MB-SPS 800 solvent purification system. DCM was kept in dried Schlenk flask with previously activated 3Å molecular sieves.

1.1. Solvent

The solvents dichloromethane, diethyl ether and tetrahydrofuran (THF) were purified and dried for use under dry conditions through a solvent cleaning system (SPS-800) from M. Braun GmbH via the following phases:

Tetrahydrofuran:	2 × MB-KOL-A (alumina)
Diethyl ether:	1 × MB-KOL-A (alumina), 1 × MB-KOL-M Type (molecular sieve 3 Å)
Dichloromethane:	2 × MB-KOL-M Type 2 (molecular sieve 3Å)

The solvents *N, N*-dimethylformamide (DMF), ethanol (EtOH), hexafluoroisopropanol (HFIP), methanol (MeOH), toluene and acetonitrile (CH_3CN) were dried according to a protocol over activated molecular sieves and stored under argon.[158] Solvents for using in thin layer chromatography (TLC), as well as for using in moisture and air insensitive reactions, were purified by simple distillation, except for EtOAc, which available from Fisher in analytical grade , Solvent mixtures were reported as volume / volume (v/v).

1.2. Analytical methods

Chromatography

Thin-layer chromatography (TLC) for monitoring reaction was carried out with aluminum precast plates from Merck or Macherey Nagel (0.25 mm Kieselgel 60, F254). Substances were visualized by fluorescence detection under UV light with the wavelengths λ = 254 nm and λ = 366 nm, or stained by derivatization depending on the functional groups present with dipping solutions:

Potassium permanganate solution ($KMnO_4$):	4.00 g $KMnO_4$ and 2.00 g $NaHCO_3$ in 200 mL distilled H_2O
Phospomolybdic acid (PMA):	10.00 g phospomolybdic acid in 100 mL distilled H_2O

High-pressure liquid chromatography (HPLC)

High-pressure liquid chromatography (HPLC) for analytical separation was carried out on a CHROMASTER system from Hitachi consisting of autosampler 5210 (injection volume 10-25 µL), pumping system 5110, diode array detector 5430 and column oven 5310. System control and evaluation of the measurements were carried out with the software EZCHROM ELITE. The mobile phase acetonitrile, water, isopropanol and n-hexane were used in HPLC grade with acidic additive (0.01% trifluoroacetic acid).

Nuclear magnetic resonance (NMR)

NMR was recorded on *Bruker* AV300, *Bruker* AV 400, *Bruker* AV500 spectrometers. The chemical shifts δ were given in ppm and were reported in the ^1H spectrum relative to the residual proton signals of the deuterated solvents used: $CDCl_3$, δ = 7.26 ppm, C_6D_6, δ = 7.16 ppm, DMSO-*d6*, δ = 2.50 ppm. For the ^{13}C spectra, chemical shift information referred to the deuterium-coupled multiplet of the solvent was used. $CDCl_3$, δ = 77.16 ppm, C_6D_6, δ = 128.06 ppm, DMSO-*d6*, δ = 39.52 ppm. Multiplicities of the signals were given with the following abbreviations and their combinations: Multiplicities of the signals were given with the following abbreviations and their combinations: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, p = pentet, sex = sextet, hept = heptet, m = multiplet, br = wide signal.

The reported coupling constants *J* correspond to the mean values of the experimentally found values in Hertz (Hz).

Mass spectra (MS)

MS was conducted on a Finnigan MAT SSQ 7000 (MS-EI, 70 EV) or a Thermo Scientific LTQ-FT ultra and Thermo Fischer Scientific LTQ Orbitrap XL spectrometer (ESI HRMS).

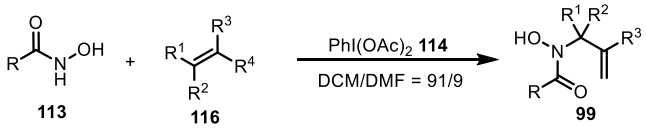
Infrared spectra (**IR**)

IR was recorded on a *JASCO* FT/IR-Spectrometer by ATR technique and was reported in terms of frequency of absorption (cm^{-1}).

2. General Synthese Procedures

2.1. General synthesis instructions

AAV 1 Synthesis of *N*-allylhydroxamic acids **99** from hydroxamic acid **113**.



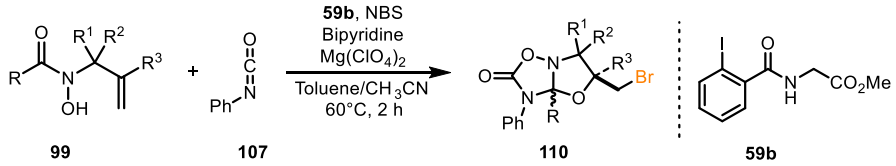
113 116 99

Hydroxamic acid **113** (1.3 mmol, 1.0 equiv.) was dissolved in DCM/DMF (91/9, 25 mL) and the mixture was added slowly (around over 8 h) to a solution of the olefin **116** (4.0 mmol, 3.0 equiv.) and iodosobenzene diacetate **114** (1.5 mmol, 1.2 equiv.) in DCM (25 mL) at 0 ℃. The reaction mixture was stirred for another 16 h, sat. sodium thiosulfate solution (25 mL) was added smoothly to quench the mixture, the organic phase dried over $MgSO_4$ and the solvent was removed (20 ^{o}C, 7.5 Torr). The products **99** were purified by column chromatography (Petroleum ether/Et_2O = 89/11). [91]

AAV 2 Synthesis of *N*-allylhydroxamic acids **99** from hydroximoyl halides **117**.[157]

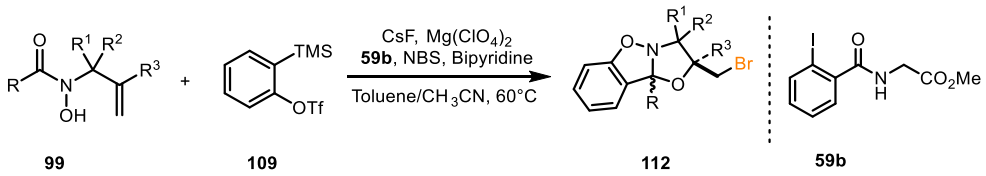
Adding a DCM (25 mL) solution of hydroximoyl halides **117** (1.30 mmol, 1.0 equiv.) to a stirred solution of the *N*-Methylmorpholine **118** (NMO, 1.43 mmol, 1.1 equiv.), Et_3N (1.0 equiv.) and excess olefins **116** (26.00 mmol, 20.0 equiv.) in DCM at 0 ℃, The reaction mixture was stirred for another 8 h at r.t., HCl (1.0 M) solution (10 mL) was added smoothly to quench the mixture, the organic phase dried over $MgSO_4$ and the solvent was removed (20 ^oC, 7.5 Torr). The products **99** were purified by column chromatography (Petroleum ether/Et_2O = 89/11).[157]

AAV 3 The reaction of *N*-allylhydroxamic acid **99** and phenyl isocyanate **107**.



To a solution of *N*-allylhydroxamic acid **99** (0.20 mmol, 1.0 equiv.), NBS (0.22 mmol, 1.1 equiv.), and hypervalent iodane **59b** (10 mol%) in toluene (2 mL) stirred at room temperature for 5 min, was added $Mg(ClO_4)_2$ (0.42 mmol, 2.1 equiv.), and the mixture was stirred at 60 ^oC for 1 h, then phenyl isocyanate **107** (0.24 mmol, 1.2 equiv.) and bipyridine (0.24 mmol, 1.2 equiv.) in toluene (3 mL) was added, stirred for 2 h, the reaction mixture was quenched with saturate Na_2SO_3 solution (5 mL), extracted with ethyl acetate (10 mL x 3), saturated NH_4Cl (aq.) solution, brine solution, $MgSO_4$ dried it. After the removal of solvent, using a rotary evaporator, the residue was purified by MPLC (medium pressure liquid chromatography) using acetonitrile and water mixture (v/v) as eluent in very short duration of time.

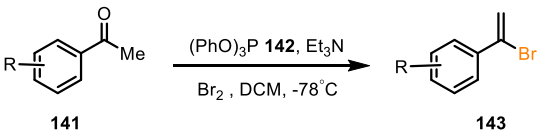
AAV 4 The reaction of *N*-allylhydroxamic acid **99** and 2-(trimethylsilyl)aryl triflate **109**.



99 **109** **112** **59b**

To a stir solution of *N*-allylhydroxamic acid **99** (0.20 mmol, 1.0 equiv.) in dry toluene (2 mL), recrystallized *N*-Bromosuccinimide (NBS) (39 mg, 0.22 mmol, 1.1 equiv.) was added followed by the addition of the iodine catalyst **59b** (3.19 mg, 0.01 mmol, 0.1 equiv.) under argon atmosphere. After stirring at room temperature for one hour, $MgClO_4$ (46.8 mg, 0.21 mmol, 2.1 equiv.) in acetonitrile (0.5 mL) was added to the reaction flask and stirred the reaction mixture at 60 ^oC for an hour. 2-(trimethylsilyl)aryl triflate **109** (0.120 mmol, 1.2 equiv.) in toluene (0.5 mL) was added to the same reaction flask, followed by the addition of bipyridine (0.120 mmol, 1.2 equiv.) and continued the reaction at 60 ^oC under argon atmosphere for additional 8 hours (monitored by TLC). Reaction mixture was quenched with saturated bicarbonate solution (5 mL) and compounds were extracted with ethyl acetated (10 mL x 3). Combined organic layers was washed with saturated NH_4Cl (aq.) solution and finally with brine solution. Combined organic layers were dried over $MgSO_4$ and solvent evaporated under reduced pressure (bath temperature should be below 40 ^oC). Crude product was purified directly by column chromatography on silica gel (Hexanes/Ether = 95/5) to afford the desired products **112**.

AAV 5 Synthesis of (1-bromovinyl) benzene **143** from ketones **141**.

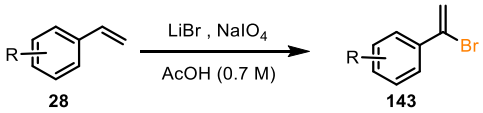


141 **143**

$(PhO)_3P$ **142** (5.76 mL, 22 mmol, 1.1 equiv.) was dissolved in dry DCM (60 mL), and the mixture was slowly added Br_2 (1.23 mL, 24 mmol, 1.2 equiv.) at -78 ^oC under argon atmosphere, then Et_3N (3.61 mL, 26 mmol, 1.3 equiv.) was added, acetophenones **141** (20 mmol, 1.1 equiv.) was added after 10 minutes,, the reaction mixture was stirred at room temperature for overnight, the reaction was then placed in an oil bath subsequently and heated at reflux for 2 hours, and then it was cooled to room temperature, followed by adding 20 mL saturated sodium sulfite to quench the reaction. The mixture was extracted with DCM (3 ×30

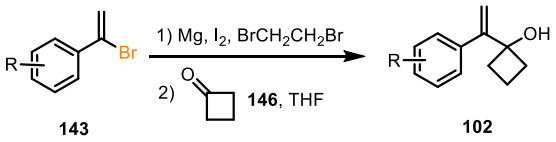
mL), and the combined organic phase was washed with brine and dried over Na_2SO_4, filtered and concentrated, and then purification of the residue by chromatography. The resulting (1-bromovinyl) benzene **143** was obtained as colorless sensitive oil and could be used directly for the subsequent reactions.[125]

AAV 6 Synthesis of (1-bromovinyl) benzene **143** from styrene derivatives **28**.



To a solution of styrene **28** (1.0 equiv.) in AcOH (0.7 M) was added LiBr (2.2 equiv.) and $NaIO_4$ (0.5 equiv.) successively. The reaction mixture was stirred overnight at r.t. After completion of the reaction as shown by TLC, the volatiles were evaporated under reduced pressure. The resulting residue was partitioned between diethyl ether and water and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water, sat. Na_2CO_3 and brine dried over Na_2SO_4 and evaporated under reduced pressure. [127] And then (1, 2-dibromoethyl) benzene was added to a solution of potassium carbonate (2.0 equiv.) in MeOH/THF (50/50, v/v). After the reaction finished, which was quenched by water, evaporated most of the solvent, then extracted by diethyl ether and washed with brine, dried over Na_2SO_4 and evaporated. The corresponding **143** was obtained as light sensitive colorless oil and used directly for the subsequent reactions without further purification.

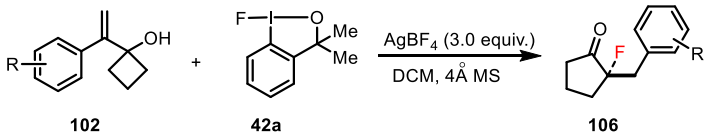
AAV 7 Synthese of cyclobutanols **102**.



A crystal of iodine under N_2 atmosphere was added to a solution of Mg (288 mg, 12 mmol, 3.0 equiv.) in THF (20 mL), and also a solution of 1, 2-dibromoethane (300 mg, 0.1 equiv.) in THF (2 mL) was added together. The mixture was stirred until small bubbles were observed, and then a solution of α-bromostyrene **143** (728 mg, 4 mmol, 1.0 equiv.) in THF (3 mL) was then added. When the mixed solution was stirred for 1.5 h at 60 ^{o}C, a solution of cyclobutanone **146** (392 mg, 5.6 mmol, 1.4 equiv.) in THF (3 mL) was added at room

temperature. After stirring at 60 °C for overnight, saturated NH_4Cl (aq.) (10 mL) was added. The organic layer was extracted with ethyl acetate and washed with brine, separated, dried over Na_2SO_4, filtered and then concentrated. The residue was purified by silica gel column chromatography (Ethyl acetate/Petroleum ether = 1/20, v/v) to afford the product **102**.

AAV 8 Synthese of cyclopentanones **106**.

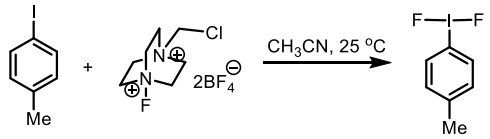


102 + 42a → 106

Cyclobutanol **102** (0.20 mmol, 1.0 equiv.), **42a** (0.60 mmol, 3.0 equiv.), 4Å MS (100 mg), $AgBF_4$ (0.60 mmol, 3.0 equiv.) and DCM (2.0 mL, 0.1 M) were added in one-pot in a dry 15 mL Schlenk flask, then the reaction was stirred under totally dark for overnight. After the reaction was completed (monitored by TLC), the reaction was quenched by the addition of saturated Na_2SO_3 aqueous solution (5 mL). After the separation, the liquid layer was extracted with ethyl acetate three times and the organic phase was combined, and then washed with brine, dried over Na_2SO_4, filtered and then concentrated. The residue was purified by flash column chromatography on silica gel (Petroleum ether/Ethyl acetate = 95/5) to afford the target product **106**.

2.2. General synthesis procedures for iodine (I) and iodane (III) reagents

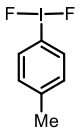
Difluoro(*p*-tolyl)-λ^3-iodane (41a).



44 + Selectfluor **94** → **41a**

Selectfluor **94** (0.92 g, 2.6 mmol, 2.6 equiv.) was added in the mixture of

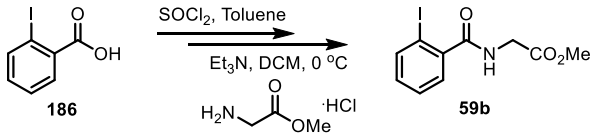
iodo-4-methylbenzene (0.22 g, 1.0 mmol, 1.0 equiv.) at room temperature stirring for 4 h, and then 2 drop of $Et_3N{\cdot}3HF$ was added and the mixture was stirred for 1 min, the solvent was removed under reduced pressure and then the residue was extracted by (hexane/chloroform = 70/30, v/v) for 3 times, the product was obtained as a white solid by removing the solvent under reduced pressure.



41a

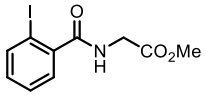
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.2 Hz, 2H, C_{Ar}-H), 6.93 (d, *J* = 7.9 Hz, 2H, C_{Ar}-H), 2.29 (s, 3H, CH_3) ppm;
^{19}F NMR (376 MHz, $CDCl_3$): δ -176.86 ppm.
The physical and spectroscopic data is in accordance with these reported in the literature.[150]

Methyl (2-iodobenzoyl) glycinate (59b).



186 **187** **59b**

Thionyl chloride (2.88 g, 1.8 mL, 24.2 mmol, 2.0 equiv.) was added to a solution of 2-iodobenzoic acid **186** (3 g, 12.1 mmol, 1.0 equiv.) at 0 ℃ in dry toluene (24.8 mL, 0.5 M). The mixture was stirred under reflux for 4 h and the solvent was removed *in vacuum*, dissolved the mixture in 10 mL DCM, and then at 0 ℃, it was added to a solution of NEt_3 (2.45 g, 3.40 mL, 24.2 mmol, 2.0 equiv.) and also glycine methyl ester hydrochloride **187** (1.67 g, 13.3 mmol, 1.1 equiv.) in DCM (65.0 mL, 0.2 M). After stirred for 1 h, water was added to quench the reaction, and the organic layer was washed with 10% aqueous HCl and 5% aqueous NaOH, and then the organic layer was dried by $MgSO_4$, DCM was evaporated by rotary machine under vacuum. And then the combined organic layer was concentrated to dryness to afford methyl (2-iodobenzoyl) glycinate **59b** (2.62 g, 8.20 mmol, 70% yield) as a white solid.



59b

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (t, *J* = 5.8 Hz, 1H, NH), 7.87 (d, *J* = 7.8 Hz, 1H, C_{Ar}-H), 7.44 (t, *J* = 7.3 Hz, 1H, C_{Ar}-H), 7.35 (dd, *J* = 7.4, 1.2 Hz, 1H, C_{Ar}-H), 7.22-7.12 (m, 1H, C_{Ar}-H), 3.89 (d, J = 5.9 Hz, 2H, CH_2), 3.63 (s, CH_3) ppm;

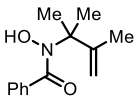
^{13}C NMR (101 MHz, DMSO-d_6) δ 171.6 (C=O), 170.1(C=O), 142.3(C_{Ar}-H), 140.0 (C_{Ar}-H), 131.9 (C_{Ar}-H), 128.9 (C_{Ar}-H), 128.7 (C_{Ar}-H), 93.59 (C_{Ar}-H), 41.63 (CH) ppm;

The physical and spectroscopic data is in accordance to these reported in the literature.[84]

2.3. Synthesis procedures for *N*-allylhydroxamic acids 99

_N_-(2, 3-dimethylbut-3-en-2-yl)-_N_-hydroxybenzamide (99a)

N-hydroxybenzamide **118a** (1.3 mmol, 1.0 equiv.), 2, 3-dimethylbut-2-ene **116a** (4.0 mmol, 3.0 equiv.) and iodosobenzene diacetate **114** (1.5 mmol, 1.2 equiv.) were put together in the reaction, the process was according to AAV 1. N-allyhydroxamic acid **99a** was obtained as a white solid (1.2 mmol, 90% yield).



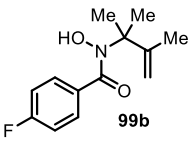
99a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.42 (m, 2H, C_{Ar}-H), 7.38 (q, *J* = 8.1, 6.8 Hz, 3H, C_{Ar}-H), 4.86 (s, 1H, CH), 4.83 (s, 1H, CH), 1.81 (s, 3H, CH_3), 1.42 (s, 6H, CH_3) ppm.

The physical and spectroscopic data is in accordance to these reported in the literature.[91]

_N_-(2, 3-dimethylbut-3-en-2-yl)-4-fluoro-_N_-hydroxybenzamide (99b)

The process was according to AAV 1.

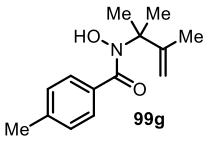


99b

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 8.7, 5.5 Hz, 2H, C_{Ar}-H), 6.95 (t, *J* = 8.7 Hz, 2H, C_{Ar}-H), 4.86 (s, 1H, CH), 4.76 (s, 1H, CH), 1.78 (s, 3H, CH_3), 1.50 (br s, 7H, CH_3, OH) ppm. The physical and spectroscopic data is in accordance to these reported in the literature.[91]

_N_-(2, 3-dimethylbut-3-en-2-yl)-_N_-hydroxy-4-methylbenzamide (99g)

The process was according to AAV 1.

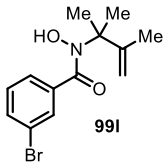


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.1 Hz, 2H, C_{Ar}-H), 7.16 (d, *J* = 7.9 Hz, 2H, C_{Ar}-H), 4.86 (s, 1H, CH), 4.82 (s, 1H, CH), 2.37 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.41 (br s, 7H, CH_3, OH) ppm.

The physical and spectroscopic data is in accordance to these reported in the literature. [91]

3-bromo-_N_-(2,3-dimethylbut-3-en-2-yl)-_N_-hydroxybenzamide (99l)

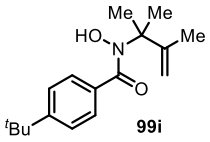
The process was according to AAV 1.



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H, C_{Ar}-H), 7.55 (d, *J* = 8.0 Hz, 1H, C_{Ar}-H), 7.40 (d, *J* = 7.7 Hz, 1H, C_{Ar}-H), 7.24 (d, *J* = 7.8 Hz, 1H, C_{Ar}-H), 4.87 (s, 1H, CH), 4.85 (s, 1H, CH), 1.81 (s, 3H, CH_3), 1.47 (s, 6H, CH_3) ppm. The physical and spectroscopic data is in accordance to these reported in the literature.[91]

4-(tert-butyl)-_N_-(2,3-dimethylbut-3-en-2-yl)-_N_-hydroxybenzamide (99i)

The process was according to AAV 1.

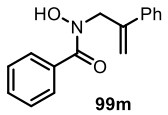


99i

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.7 Hz, 2H, C_{Ar}-H), 7.48 (d, *J* = 8.7 Hz, 2H, C_{Ar}-H), 4.86 (s, 1H, CH), 4.82 (s, 1H, CH), 1.81 (s, 3H, CH_3), 1.43 (s, 6H, CH_3), 1.32 (s, 9H, CH_3) ppm;

***N*-hydroxy-*N*-(2-phenylallyl)benzamide (99m)**

The process was according to AAV 2.



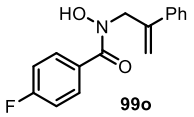
99m

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H, CH), 7.89 (s, 1H, C_{Ar}-H), 7.55 - 7.44 (m, 4H, C_{Ar}-H), 7.40 (t, *J* = 7.4 Hz, 2H, C_{Ar}-H), 7.36 - 7.28 (m, 3H, C_{Ar}-H), 5.57 (s, 1H, CH), 5.44 (s, 1H, CH), 4.67 (s, 2H, CH_2) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.33 (C=O), 142.05 (C_{Ar}-H), 138.26 (C=C), 134.32 (C_{Ar}-H), 132.79 (C_{Ar}-H), 131.25 (C_{Ar}-H), 130.11 (C_{Ar}-H), 128.86 (C_{Ar}-H), 128.76 (C_{Ar}-H), 128.56 (C_{Ar}-H), 128.53 (C_{Ar}-H), 128.24 (C_{Ar}-H), 127.75 (C=C), 63.7 (CH) ppm.

4-fluoro-*N*-hydroxy-*N*-(2-phenylallyl)benzamide (99o)

The process was according to AAV 2.

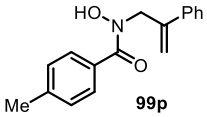


99o

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (m, 2H, C_{Ar}-H), 7.35-7.27 (m, 4H, C_{Ar}-H), 7.24 (m, 1H), 7.08 (m, 2H), 5.57 (s, 1H, CH), 5.43 (s, 1H, CH), 4.66 (s, 2H, CH) ppm;

***N*-hydroxy-4-methyl-*N*-(2-phenylallyl)benzamide (99p)**

The process was according to AAV 2.



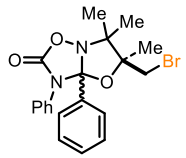
99p

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.1 Hz, 2H, C_{Ar}-H), 7.34-7.27 (m, 5H, C_{Ar}-H), 7.20 (d, *J* = 7.9 Hz, 2H, C_{Ar}-H), 5.56 (s, 1H, CH), 5.44 (s, 1H, CH), 4.67 (s, 2H, CH), 2.39 (s, 3H, CH_3) ppm.

The physical and spectroscopic data is in accordance to these reported in the literature.[156]

2.4. Synthesis for *N,O*-heterocyclic compounds 110 and 112

5-(bromomethyl)-5,6,6-trimethyl-3,3a-diphenyltetrahydro-2H-oxazolo[3,2-b][1,2,4]oxadiazol-2-one (110a)



110a

Colorless liquid;

Yield = 61%;

d.r. = 52:48;

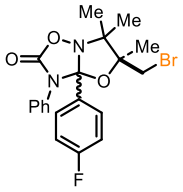
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.56 (m, 4H, C_{Ar}-H), 7.39-7.37 (major diastereomer, m, 2H, C_{Ar}-H), 7.30-7.22 (m, 12H, C_{Ar}-H) , 7.20-7.15 (major diastereomer, m, 2H, C_{Ar}-H), 4.02 (d, *J* = 8 Hz, 1 H, CH), 3.67 (major diastereomer, d, *J* = 12 Hz, 1 H, CH), 3.58 (minor diastereomer, d, *J* = 8 Hz, 1 H, CH), 3.49 (major diastereomer, d, *J* = 8 Hz, 1 H, CH) , 1.80 (minor diastereomer, s, 3H, CH_3), 1.62 (major diastereomer, s, 3H, CH_3), 1.59 (major diastereomer, s, 3H, CH_3), 1.53 (minor diastereomer, s, 3H, CH_3), 1.06 (major diastereomer, s, 3H, CH_3), 1.03 (major diastereomer, s, 3H, CH_3) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1 (C=O), 152.8 (C=O), 137.9 (C_{Ar}-H), 137.8 (C_{Ar}-H), 133.55 (C_{Ar}-H), 133.50 (C_{Ar}-H), 129.5 (C_q), 129.4 (C_q), 128.8 (C_{Ar}-H), 128.2 (C_{Ar}-H), 127.7 (C_{Ar}-H), 127.3 (C_{Ar}-H), 127.1 (C_{Ar}-H), 126.7 (C_{Ar}-H), 126.5 (C_{Ar}-H), 111.4 (C_{Ar}-H), 111.0 (C_{Ar}-H), 87.48 (C_q), 87.16 (C_q), 71.38 (C_q), 71.17 (C_q), 39.30 (CH_2), 37.21 (CH_2), 26.03 (CH_3), 23.74 (CH_3), 22.80 (CH_3), 21.47 (CH_3), 20.94 (CH_3), 19.16 (CH_3) ppm;

IR (film) $\tilde{\nu}_{max}$ = 3069, 3005, 2986, 2945, 1764, 1594, 1499, 1454, 1369, 1260, 1211, 1168, 1119, 1062, 1002, 960, 907, 843, 752, 734, 702 cm^{-1};

HRMS (ESI; m/z) calculated for $C_{20}H_{22}BrN_2O_3$ $[M+H]^+$ 417.0808 found 417.0810.

5-(bromomethyl)-3a-(4-fluorophenyl)-5,6,6-trimethyl-3-phenyltetrahydro-2H-oxazolo[3, 2-b][1,2,4]oxadiazol-2-one (110b)



110b

Colorless liquid;

Yield = 60%;

d.r. = 64:36;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.51 (major diastereomer, m, 3H, C_{Ar}-H), 7.34 (major diastereomer, d, 1H, J = 4 Hz, C_{Ar}-H), 7.25-7.23 (minor diastereomer, m, 2H, C_{Ar}-H), 7.20-7.17 (major diastereomer, m, 3H, C_{Ar}-H), 6.96-6.91 (minor diastereomer, m, 3H, C_{Ar}-H), 3.97 (major diastereomer, d, 1H, *J* = 12 Hz, CH), 3.63 (minor diastereomer, d, 1H, *J* = 12 Hz, CH), 3.55 (major diastereomer, d, 1H, *J* = 12 Hz, CH), 3.44 (minor diastereomer, d, 1H, *J* = 12 Hz, CH), 1.76 (major diastereomer, s, 3H, CH_3), 1.60 (minor diastereomer, s, 3H, CH_3), 1.55 (major diastereomer, s, 3H, CH_3). 1.51 (minor diastereomer, s, 3H, CH_3), 1.04 (major diastereomer, s, 3H, CH_3), 1.01 (minor diastereomer, s, 3H, CH_3) ppm;

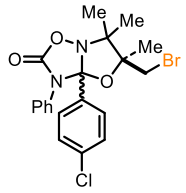
^{13}C NMR (101 MHz, $CDCl_3$): δ 164.4 (C_{Ar}-H), 161.9 (C_{Ar}-H), 152.9 (C=O), 152.6 (C=O), 134.0 (C_{Ar}-H), 133.9 (C_{Ar}-H), 133.4 (C_{Ar}-H), 129.4 (C_{Ar}-H), 129.2 (C_q), 129.0 (C_q), 127.9 (C_{Ar}-H), 127.8 (C_{Ar}-H), 126.7 (C_{Ar}-H), 126.6 (C_{Ar}-H), 123.7 (C_{Ar}-H), 115.4 (C_{Ar}-H), 115.3 (C_{Ar}-H), 115.1 (C_{Ar}-H), 111.0 (C_{Ar}-H), 110.6 (C_{Ar}-H), 87.69 (C_q), 87.36 (C_q), 71.46 (C_q), 71.26 (C_q), 39.12 (CH_2), 37.10 (CH_2), 26.05 (CH_3), 23.78 (CH_3), 22.72 (CH_3), 21.46 (CH_3), 20.88 (CH_3), 19.13 (CH_3) ppm;

^{19}F NMR (313 MHz, $CDCl_3$): δ -111.5, -111.6 ppm;

IR (film) $\tilde{\nu}_{max}$ = 3073, 3009, 2988, 2945, 1764, 1602, 1499, 1454, 1407, 1292, 1273, 1256, 1221, 1158, 111, 1098, 1058, 1005, 970, 903, 854, 826, 752, 730 cm^{-1};

HRMS (ESI; m/z) calculated for $C_{20}H_{21}BrFN_2O_3$ $[M+H]^+$ 435.0714 found 435.0716.

5-(bromomethyl)-3a-(4-chlorophenyl)-5,6,6-trimethyl-3-phenyltetrahydro-2H-oxazolo[3, 2-b][1,2,4]oxadiazol-2-one (110c)



110c

Colorless liquid;

Yield = 62%;

d.r. = 56:44;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.49 (major diastereomer, m, 3 H, C_{Ar}-H), 7.38 (minor diastereomer, d, 2H , *J* = 8 Hz, C_{Ar}-H), 7.28-7.19 (major diastereomer, m, 10 H, C_{Ar}-H), 3.98 (major diastereomer, d, 1H, *J* = 12 Hz, C_{Ar}-H), 3.64 (minor diastereomer, d, 1H, *J* = 12 Hz, CH), 3.56 (major diastereomer, d, 1H, *J* = 8 Hz, CH), 3.45 (minor diastereomer, d, 1H, *J* = 12 Hz, CH), 1.78 (major diastereomer, s, 3H, CH_3), 1.61 (minor diastereomer, s, 3H, CH_3), 1.56 (major diastereomer, s, 3H, CH_3), 1.52 (minor diastereomer, s, 3H, CH_3), 1.05 (major diastereomer, s, 3H, CH_3), 1.02 (minor diastereomer, s, 3H, CH_3) ppm;

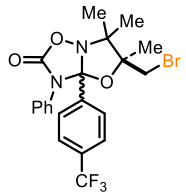
^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9 (C=O), 152.6 (C=O), 136.6 (C_{Ar}-H), 136.5 (C_{Ar}-H), 135.6 (C_{Ar}-H), 135.5 (C_{Ar}-H), 133.3 (C_{Ar}-H), 133.2 (C_{Ar}-H), 129.1 (C_q), 129.0 (C_q), 128.7 (C_{Ar}-H), 128.6 (C_{Ar}-H), 128.5 (C_{Ar}-H), 127.9 (C_{Ar}-H), 126.7 (C_{Ar}-H), 126.5 (C_{Ar}-H), 110.9 (C_{Ar}-H), 110.5 (C_{Ar}-H), 87.75 (C_q), 87.40 (C_q), 71.46 (C_q), 71.26 (C_q), 39.05 (CH_2), 37.04

(CH_2), 26.04 (CH_3), 23.77 (CH_3), 22.68 (CH_3), 21.43 (CH_3), 20.83 (CH_3), 19.07 (CH_3) ppm;

IR (film) $\tilde{\nu}_{max}$ = 3069, 3009, 2991, 2945, 1764, 1598, 1499, 1457, 1369, 1284, 1260, 1207, 1164, 1090, 1058, 1016, 996, 970, 903, 854, 815 cm^{-1};

HRMS (ESI; m/z) calculated for $C_{20}H_{21}BrClN_2O_3$ $[M+H]^+$ 451.0419 found 451.0420.

5-(bromomethyl)-5,6,6-trimethyl-3-phenyl-3a-(4-(trifluoromethyl)phenyl)tetrahydro-2H-oxazolo[3,2-b][1,2,4]oxadiazol-2-one (110d)



110d

Colorless liquid;

Yield = 62%;

d.r. = 53:47;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74-7.68 (major diastereomer, m, 4H, C_{Ar}-H), 7.56-7.53 (minor diastereomer, m, 4H, C_{Ar}-H), 7.39-7.36 (major diastereomer, m, 2H, C_{Ar}-H), 7.30-7.19 (minor diastereomer, m, 8H, C_{Ar}-H), 4.00 (major diastereomer, d, 1H, *J* = 12 Hz, CH), 3.66 (minor diastereomer, d, 1 H, *J* = 8 Hz, CH), 3.57 (major diastereomer, d, 1 H, *J* = 12 Hz, CH), 3.45 (minor diastereomer, d, 1 H, *J* = 12 Hz, CH), 1.80 (major diastereomer, s, 3H, CH_3), 1.63 (minor diastereomer, s, 3H, CH_3), 1.58(major diastereomer, s, 3H, CH_3), 1.54 (minor diastereomer, s, 3H, CH_3), 1.04 (major diastereomer, s, 3H, CH_3), 1.01 (minor diastereomer, s, 3H, CH_3) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9 (C=O), 152.5 (C=O), 141.8 (C_{Ar}-H), 133.1 (C_{Ar}-H), 131.8 (C_{Ar}-H), 131.7 (C_{Ar}-H), 131.4 (C_{Ar}-H), 129.2 (C_q), 128.1 (C_{Ar}-H), 127.8 (C_{Ar}-H), 127.6 (C_{Ar}-H), 126.8 (C_{Ar}-H), 126.6 (C_{Ar}-H), 125.4 (C_{Ar}-H), 125.3 (C_{Ar}-H), 125.2 (CF_3), 125.1 (CF_3), 122.4 (C_{Ar}-H), 110.7 (C_{Ar}-H), 110.2 (C_{Ar}-H), 87.96 (C_q), 87.59 (C_q), 71.54 (C_q), 71.36 (C_q),

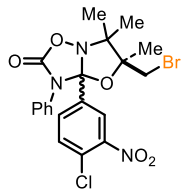
38.94 (CH_2), 36.93 (CH_2), 26.06 (CH_3), 23.80 (CH_3), 22.68 (CH_3), 21.45 (CH_3), 20.80 (CH_3), 19.05 (CH_3) ppm;

^{19}F NMR (313 MHz, $CDCl_3$): δ -62.8 ppm;

IR (film) $\tilde{\nu}_{max}$ = 3073, 3012, 1288, 2945, 1771, 1619, 1594, 1499, 1407, 1369, 1273, 1211, 1168, 1126, 1069, 1002, 907, 868, 830, 752, 730 cm^{-1};

HRMS (ESI; m/z) calculated for $C_{21}H_{21}BrF_3N_2O_3$ $[M+H]^+$ 485.0682 found 485.0683.

5-(bromomethyl)-3a-(4-chloro-3-nitrophenyl)-5,6,6-trimethyl-3-phenyltetrahydro-2H-oxazolo[3,2-b][1,2,4]oxadiazol-2-one (110e)



110e

Colorless liquid;

Yield = 56%;

d.r. = 56:44;

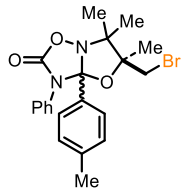
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (minor diastereomer, d, 1H, *J* = 4 Hz, C_{Ar}-H), 8.07 (major diastereomer, d, 1H, *J* = 4 Hz, C_{Ar}-H), 7.74-7.69 (minor diastereomer, m, 2H, C_{Ar}-H), 7.49-7.46 (major diastereomer, m, 2 H, C_{Ar}-H), 7.42-7.39 (minor diastereomer, m, 3H, C_{Ar}-H), 7.34-7.23 (major diastereomer, m, 8 H, C_{Ar}-H), 3.96 (minor diastereomer, d, 1H, *J* = 12 Hz, CH), 3.65 (major diastereomer, d, 1H, *J* = 8Hz, CH), 3.56 (minor diastereomer, d, 1H, *J* = 12 Hz, CH), 3.45 (major diastereomer, d, 1H, *J* = 12 Hz, CH), 1.80 (minor diastereomer, s, 3H, CH_3), 1.63 (major diastereomer, s, 3H, CH_3), 1.58 (minor diastereomer, s, 3H, CH_3), 1.54 (major diastereomer, s, 3H, CH_3), 1.07 (minor diastereomer, s, 3H, CH_3), 1.04 (minor diastereomer, s, 3H, CH_3) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6 (C=O), 152.2 (C=O), 147.5 (C_{Ar}-H), 147.5 (C_{Ar}-H), 138.6 (C_{Ar}-H), 132.6 (C_{Ar}-H), 132.1 (C_{Ar}-H), 132.0 (C_{Ar}-H), 131.7 (C_{Ar}-H), 131.5 (C_{Ar}-H), 129.5 (C_q), 129.4 (C_q), 128.5 (C_{Ar}-H), 128.4 (C_{Ar}-H), 126.6 (C_{Ar}-H), 126.5 (C_{Ar}-H), 124.5 (C_{Ar}-H), 124.3 (C_{Ar}-H), 109.8 (C_{Ar}-H), 109.3 (C_{Ar}-H), 88.52 (C_q), 88.11 (C_q), 71.69 (C_q), 71.56 (C_q), 38.56 (CH_2), 36.60 (CH_2), 26.15 (CH_3), 23.83 (CH_3), 22.51 (CH_3), 21.40 (CH_3), 20.69 (CH_3), 18.92 (CH_3) ppm;

IR (film) $\tilde{\nu}_{max}$ = 3069, 3012, 2988, 2949, 1767, 1598, 1535, 1503, 1479, 1457, 1373, 1294, 1281, 1242, 1207, 1171, 1122, 1069, 1048, 1020, 970, 911, 868, 826, 749, 734 cm^{-1};

HRMS (ESI; m/z) calculated for $C_{20}H_{20}BrClN_3O_5$ 496.0269 found 496.0271.

5-(bromomethyl)-5,6,6-trimethyl-3-phenyl-3a-(p-tolyl)tetrahydro-2H-oxazolo[3,2-b][1,2,4]oxadiazol-2-one (110f)



110f

Colorless liquid;

Yield = 58%;

d.r. = 56:44;

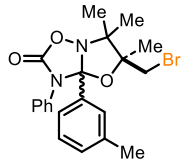
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.40 (major diastereomer, m, 6H, C_{Ar}-H), 7.30-7.18 (minor diastereomer, m, 8H, C_{Ar}-H), 7.11-7.08 (major diastereomer, m, 4H, C_{Ar}-H), 4.02 (minor diastereomer, d, 1H, *J* = 12 Hz, CH), 3.69 (major diastereomer, d, 1H, *J* = 8 Hz, CH), 3.59 (minor diastereomer, d, 1H, *J* = 12 Hz, CH), 3.50 (major diastereomer, d, 1H, *J* = 12 Hz, CH), 2.31 (minor diastereomer, s, 3H, CH_3), 2.30 (s, 3H, CH_3), 1.80 (minor diastereomer, s, 3H, CH_3), 1.64 (major diastereomer, s, 3H, CH_3), 1.60 (minor diastereomer, s, 3H, CH_3), 1.54 (major diastereomer, s, 3H, CH_3), 1.09 (minor diastereomer, s, 3H, CH_3), 1.05 (minor diastereomer, s, 3H, CH_3) ppm;

^{13}C NMR (401 MHz, $CDCl_3$): δ 153.1 (C=O), 152.8 (C=O), 139.47 (C_{Ar}-H), 139.41 (C_{Ar}-H), 135.0 (C_{Ar}-H), 133.7 (C_{Ar}-H), 128.9 (C_q), 128.8 (C_q), 127.5 (C_{Ar}-H), 127.2 (C_{Ar}-H), 126.6 (C_{Ar}-H), 126.4 (C_{Ar}-H), 111.6 (C_{Ar}-H), 111.2 (C_{Ar}-H), 87.38 (C_q), 87.06 (C_q), 71.37 (C_q), 71.15 (C_q), 39.33 (CH_2), 37.27 (CH_2), 26.08 (CH_3), 23.80 (CH_3), 22.81 (CH_3), 21.49 (CH_3), 21.27 (CH_3), 20.98 (CH_3), 19.21 (CH_3) ppm;

IR (film) $\tilde{\nu}_{max}$ = 3041, 3041, 3016, 2988, 2945, 2924, 1760, 1602, 1496, 145, 1366, 1292, 1273, 1260, 1211, 1179, 1164, 1143, 1115, 1062, 1024, 998, 970, 911, 847, 808, 752 cm^{-1};

HRMS (ESI; m/z) calculated for $C_{21}H_{24}BrN_2O_3$ $[M+H]^+$ 431.0965 found 431.0967.

5-(bromomethyl)-5,6,6-trimethyl-3-phenyl-3a-(m-tolyl)tetrahydro-2H-oxazolo[3,2-b][1,2,4]oxadiazol-2-one (110g)



110g

Colorless liquid;

Yield = 63%;

d.r. = 56:44;

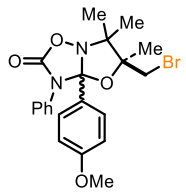
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.38 (major diastereomer, m, 5H, C_{Ar}-H), 7.31-7.16 (minor diastereomer, m, 9H, C_{Ar}-H), 7.12-7.08 (major diastereomer, m, 2H, C_{Ar}-H), 4.03 (minor diastereomer, d, 1H, *J* = 12 Hz, CH), 3.70 (major diastereomer, d, 1H, *J* = 8 Hz, CH), 3.61 (minor diastereomer, d, 1H, *J* = 12 Hz, CH), 3.52 (major diastereomer, d, 1H, *J* = 12 Hz, CH), 2.34 (minor diastereomer, s, 3H, CH_3), 2.33 (major diastereomer, s, 3H, CH_3), 1.82 (minor diastereomer, s, 3H, CH_3), 1.65 (major diastereomer, s, 3H, CH_3), 1.62 (minor diastereomer, s, 3H, CH_3), 1.56 (major diastereomer, s, 3H, CH_3), 1.11 (minor diastereomer, s, 3H, CH_3), 1.07 (major diastereomer, s, 3H, CH_3) ppm;

^{13}C NMR (401 MHz, $CDCl_3$): δ 153.3 (C=O), 152.8 (C=O), 138.0 (C_{Ar}-H), 137.9 (C_{Ar}-H), 137.8 (C_{Ar}-H), 133.6 (C_{Ar}-H), 128.9 (C_q), 128.0 (C_q), 127.9 (C_{Ar}-H), 127.7 (C_{Ar}-H), 127.6 (C_{Ar}-H), 126.7 (C_{Ar}-H), 126.5 (C_{Ar}-H), 124.5 (C_{Ar}-H), 124.3 (C_{Ar}-H), 111.5 (C_{Ar}-H), 111.1 (C_{Ar}-H), 87.42 (C_q), 87.09 (C_q), 71.39 (C_q), 71.18 (C_q), 39.31 (CH_2), 37.27 (CH_2), 26.10 (CH_3), 23.81 (CH_3), 22.80 (CH_3), 21.55 (CH_3), 21.52 (CH_3), 20.96 (CH_3), 19.19 (CH_3) ppm;

IR (film) $\tilde{\nu}_{max}$ = 3062, 3037, 3012, 2988, 2938, 1760, 1598, 1538, 1457, 1369, 1267, 1213, 1164, 1150, 1119, 1024, 996, 907, 847, 822, 783, 749, 734, 709 cm^{-1};

HRMS (ESI; m/z) calculated for $C_{21}H_{24}BrN_2O_3$ $[M+H]^+$ 431.0965 found 431.0967.

5-(bromomethyl)-3a-(4-methoxyphenyl)-5,6,6-trimethyl-3-phenyltetrahydro-2H-oxazolo [3,2-b][1,2,4]oxadiazol-2-one (110h)



110h

Colorless liquid;

Yield = 51%;

d.r. = 51:50;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.47 (major diastereomer, m, 4H, C_{Ar}-H), 7.40-7.38 (minor diastereomer, m, 2H, C_{Ar}-H), 7.29-7.18 (major diastereomer, m, 9H, C_{Ar}-H), 6.80-6.76 (minor diastereomer, m, 4H, C_{Ar}-H), 4.00 (major diastereomer, d, 1H, *J* = 8 Hz, CH), 3.77 (minor diastereomer, s, 3H, CH_3), 3.76 (major diastereomer, s, 3H, CH_3), 3.66 (minor diastereomer, d, 1H, *J* = 8 Hz, CH), 3.57 (major diastereomer, d, 1H, *J* = 8 Hz, CH), 3.48 (minor diastereomer, d, 1H, *J* = 8 Hz, CH), 1.78 (minor diastereomer, s, 3H, CH_3), 1.61 (major diastereomer, s, 3H, CH_3), 1.58 (minor diastereomer, s, 3H, CH_3), 1.52 (major diastereomer, s, 3H, CH_3), 1.07 (minor diastereomer, s, 3H, CH_3), 1.04 (major diastereomer, s,

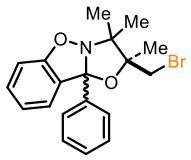
3H, CH_3) ppm;

^{13}C NMR (401 MHz, $CDCl_3$): δ 160.2 (C=O), 153.1 (C=O), 152.8 (C_{Ar}-H), 133.6 (C_{Ar}-H), 130.0 (C_{Ar}-H), 129.9 (C_{Ar}-H), 128.9 (C_q), 128.8 (C_q), 128.6 (C_{Ar}-H), 127.6 (C_{Ar}-H), 126.7 (C_{Ar}-H), 126.4 (C_{Ar}-H), 113.5 (C_{Ar}-H), 113.4 (C_{Ar}-H), 111.5 (C_{Ar}-H), 111.1 (C_{Ar}-H), 87.41 (C_q), 87.10 (C_q), 71.36 (C_q), 71.14 (C_q), 55.32 (CH_3), 55.30 (CH_3), 39.38 (CH_2), 37.28 (CH_2), 26.09 (CH_3), 23.80 (CH_3), 22.85 (CH_3), 21.51 (CH_3), 21.03 (CH_3), 19.25 (CH_3) ppm;

IR (film) $\tilde{\nu}_{max}$ = 3069, 3012, 2984, 2839, 1760, 1609, 1509, 1496, 1457, 1439, 1379, 1313, 1252, 1211, 1175, 1115, 1062, 1016, 996, 907, 847, 826, 755, 730, 699 cm^{-1};

HRMS (ESI; m/z) calculated for $C_{21}H_{24}BrN_2O_4$ $[M+H]^+$ 447.0914, found 447.0915.

2-(bromomethyl)-2,3,3-trimethyl-9b-phenyl-2,3-dihydro-9bH-benzo[d]oxazolo[3,2-b]isoxazole (112a)



112a

Colorless liquid;

Yield = 90%;

d.r. = 67:33;

***R*$_f$** = 0.7 (silica gel, Hexanes/Ethyl acetate = 95/5);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.63 (major diastereomer, m, 4H, C_{Ar}-H), 7.38 – 7.30 (major diastereomer, m, 2H, C_{Ar}-H), 7.27 – 7.25 (minor diastereomer, m, 3H, C_{Ar}-H), 3.64 – 3.61 (major diastereomer, d, *J* = 3.61 Hz, 1H, CH), 3.59-3.57 (major diastereomer, d, *J* = 3.57 Hz, 1H, CH), 3.46-3.44 (minor diastereomer, d, *J* = 3.45 Hz, 1H, CH), 3.36 – 3.33 (minor diastereomer, d, *J* = 3.33 Hz, 1H, CH), 1.67 (major diastereomer, s, 3H, CH_3), 1.58 (minor diastereomer, s, 3H, CH_3), 1.57 (major diastereomer, s, 3H, CH_3), 1.48 (major diastereomer, s,

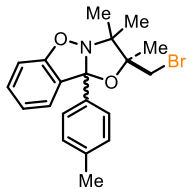
3H, CH_3), 1.39 (minor diastereomer, s, 3H, CH_3), 1.08 (major diastereomer, s, 3H, CH_3), 1.06 (minor diastereomer, s, 3H, CH_3) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.7 (C_{Ar}-H), 154.5 (C_{Ar}-H), 142.6 (C_{Ar}-H), 142.5 (C_{Ar}-H), 130.8 (C_{Ar}-H), 130.3 (C_{Ar}-H), 130.3 (C_{Ar}-H), 130.1 (C_{Ar}-H), 128.0 (C_{Ar}-H), 127.9 (C_{Ar}-H), 127.8 (C_{Ar}-H), 127.7 (C_{Ar}-H), 126.3 (C_{Ar}-H), 126.1 (C_{Ar}-H), 125.0 (C_{Ar}-H), 124.4 (C_{Ar}-H), 121.9 (C_{Ar}-H), 121.5 (C_{Ar}-H), 107.4 (C_q), 104.9 (C_{Ar}-H), 104.6 (C_{Ar}-H), 85.8 (C_q), 72.4 (C_q), 72.09 (C_q), 39.30 (CH_2), 38.18 (CH_2), 31.59 (CH_3), 26.15 (CH_3), 24.04 (CH_3), 22.66 (CH_3), 22.07 (CH_3), 21.84 (CH_3), 21.56 (CH_3), 19.87 (CH_3), 14.12 (CH_3) ppm;

IR (film) $\tilde{\nu}_{max}$ = 3037, 2984, 2935, 2371, 2324, 1630, 1477, 1463, 1234, 970, 899, 833, 747, 700 cm^{-1};

HRMS (ESI) calcd. for $C_{19}H_{20}BrNO_2^+$ $[M+H]^+$ 374.0677, found 374.0748.

2-(bromomethyl)-2,3,3-trimethyl-9b-(p-tolyl)-2,3-dihydro-9bH-benzo[d]oxazolo[3,2-b]isoxazole (112b)



112b

Colorless liquid;

Yield = 91%;

d.r. = 50:50;

$\boldsymbol{R_f}$ = 0.7 (silica gel, Hexanes/Ethyl acetate = 95/5);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.51 (major diastereomer, t, *J* = 7.53 Hz, 4H, C_{Ar}-H), 7.30-7.24 (minor diastereomer, m, 2H, C_{Ar}-H), 7.18-7.16 (major diastereomer, d, *J* = 7.17 Hz, 4H, C_{Ar}-H), 7.02-7.00 (minor diastereomer, d, *J* = 7.00 Hz, 1H, C_{Ar}-H), 6.93-6.86 (major diastereomer, m, 5H, C_{Ar}-H) 3.64-3.61 (minor diastereomer, d, *J* = 3.61 Hz, 1H, CH),

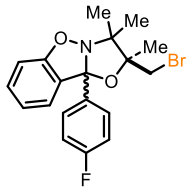
3.60-3.57 (major diastereomer, d, *J* = 3.57 Hz, 1H, CH), 3.47-3.44 (minor diastereomer, d, *J* = 3.44 Hz, 1H, CH), 3.36-3.33 (major diastereomer, d, *J* = 3.36 Hz, 1H, CH), 2.37 (minor diastereomer, s, 6H, CH_3), 1.67 (major diastereomer, s, 3H, CH_3), 1.58 (minor diastereomer, s, 3H, CH_3), 1.48 (minor diastereomer, s, 3H, CH_3), 1.39 (major diastereomer, s, 3H, CH_3), 1.10 (minor diastereomer, s, 3H, CH_3), 1.07 (major diastereomer, s, 3H, CH_3) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.78 (C_{Ar}-H), 154.57 (C_{Ar}-H), 139.82 (C_{Ar}-H), 139.68 (C_{Ar}-H), 137.54 (C_{Ar}-H), 137.49 (C_{Ar}-H), 131.04 (C_{Ar}-H), 130.56 (C_{Ar}-H), 130.23 (C_{Ar}-H), 130.10 (C_{Ar}-H), 128.73 (C_{Ar}-H), 128.65 (C_{Ar}-H), 126.30 (C_{Ar}-H), 126.13 (C_{Ar}-H), 125.03 (C_{Ar}-H), 124.44 (C_{Ar}-H), 121.90 (C_{Ar}-H), 121.50 (C_{Ar}-H), 107.46 (C_q), 105.03 (C_{Ar}-H), 104.68 (C_{Ar}-H), 85.78 (C_q), 72.39 (C_q), 72.09 (C_q), 39.37 (CH_2), 38.24 (CH_2), 26.20 (CH_3), 24.09 (CH_3), 22.11 (CH_3), 21.91 (CH_3), 21.59 (CH_3), 21.13 (CH_3), 19.92 (CH_3) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2985, 2927, 1602, 1477, 1462, 1375, 1235, 1178, 1065, 966, 899, 839, 746, 716, 685 cm^{-1};

HRMS (ESI) calcd. for $C_{20}H_{22}BrNO_2^+$ $[M+H]^+$ 388.0834, found 388.0905.

2-(bromomethyl)-9b-(4-fluorophenyl)-2,3,3-trimethyl-2,3-dihydro-9bH-benzo[d]oxazolo[3,2-b]isoxazole (112c)



112c

Colorless liquid;

Yield = 96%;

d.r. =50:50;

$\boldsymbol{R_f}$ = 0.7 (silica gel, Hexanes/Ethyl acetate = 95/5);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.61 (major diastereomer, m, 4H, C_{Ar}-H), 7.31-7.26

(minor diastereomer, m, 3H, C_{Ar}-H), 7.07-6.99 (major diastereomer, m, 4H, C_{Ar}-H), 6.95 -6.85 (minor diastereomer, m, 5H, C_{Ar}-H), 3.62-3.59 (major diastereomer, d, *J* = 1.00 Hz, 1H, CH), 3.58-3.55 (minor diastereomer, d, *J* = 2.32 Hz, 1H, CH), 3.44-3.42 (major diastereomer, d, *J* = 1.37 Hz, 1H, CH), 3.34-3.31 (minor diastereomer, d, *J* = 0.93 Hz, 1H, CH), 1.67 (major diastereomer, s, 3H, CH_3), 1.57 (minor diastereomer, s, 3H, CH_3), 1.47 (major diastereomer, s, 3H, CH_3), 1.38 (minor diastereomer, s, 3H, CH_3), 1.08 (major diastereomer, s, 3H, CH_3), 1.05 (minor diastereomer, s, 3H, CH_3) ppm;

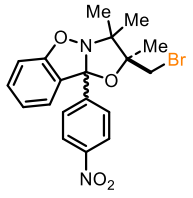
^{13}C NMR (101 MHz, $CDCl_3$): δ 163.65 (C_{Ar}-H), 161.18 (C_{Ar}-H), 154.80 (C_{Ar}-H), 138.68 (C_{Ar}-H), 138.65 (C_{Ar}-H), 138.59 (C_{Ar}-H), 138.56 (C_{Ar}-H), 130.53 (C_{Ar}-H), 130.46 (C_{Ar}-H), 130.32 (C_{Ar}-H), 130.05 (C_{Ar}-H), 128.22 (C_{Ar}-H), 128.14 (C_{Ar}-H), 128.03 (C_{Ar}-H), 127.95 (C_{Ar}-H), 124.94 (C_{Ar}-H), 124.36 (C_{Ar}-H), 122.01 (C_{Ar}-H), 121.61 (C_q), 115.01 (C_{Ar}-H), 114.92 (C_{Ar}-H), 114.80 (C_{Ar}-H), 114.71 (C_{Ar}-H), 104.67 (C_{Ar}-H), 104.30 (C_{Ar}-H), 98.51 (C_q), 86.04 (C_q), 72.43 (C_q), 72.13 (C_q), 39.15 (CH_2), 38.08 (CH_2), 26.15 (CH_3), 24.04 (CH_3), 21.98 (CH_3), 21.79 (CH_3), 21.54 (CH_3), 19.83 (CH_3) ppm;

^{19}F NMR (313 MHz, $CDCl_3$): δ -114.72 (s), -114.79 (s) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2985, 2927, 1604, 1506, 1462, 1375, 1284, 1234, 1190, 1154, 1091, 1066, 1013, 972, 928, 900, 845, 811, 747 cm^{-1};

HRMS (ESI) calcd for $C_{19}H_{19}BrFNO_2^+$ $[M+H]^+$ 392.0583, found 392.0654 .

2-(bromomethyl)-2,3,3-trimethyl-9b-(4-nitrophenyl)-2,3-dihydro-9bH-benzo[d]oxazolo[3,2-b]isoxazole (112d)



112d

Colorless liquid;

Yield = 90%;

d.r. = 50:50;

$\boldsymbol{R_f}$ = 0.30 (silica gel, hexanes/ethyl acetate = 95/5);

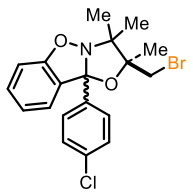
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24-8.22 (major diastereomer, m, 4H, C_{Ar}-H), 7.89-7.84 (minor diastereomer, t, *J* = 7.87 Hz, 4H, C_{Ar}-H), 7.35-7.28 (major diastereomer, m, 2H, C_{Ar}-H), 6.99-6.88 (minor diastereomer, m, 6H, C_{Ar}-H), 3.60-3.57 (major diastereomer, d, *J* = 3.60 Hz, 1H, CH), 3.57-3.54 (minor diastereomer, d, *J* = 3.54 Hz, 1H, CH), 3.42-3.39 (major diastereomer, d, *J* = 3.40 Hz, 1H, CH), 3.33-3.30 (minor diastereomer, d, *J* = 3.33 Hz, 1H, CH), 1.66 (major diastereomer, s, 3H, CH_3), 1.58 (minor diastereomer, s, 3H, CH_3), 1.47 (major diastereomer,s, 3H, CH_3), 1.37 (minor diastereomer, s, 3H, CH_3), 1.05 (major diastereomer, s, 3H, CH_3), 1.02 (minor diastereomer, s, 3H, CH_3) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.95 (C_{Ar}-H), 154.69 (C_{Ar}-H), 149.63 (C_{Ar}-H), 149.55 (C_{Ar}-H), 147.61 (C_{Ar}-H), 130.83 (C_{Ar}-H), 129.30 (C_{Ar}-H), 128.81 (C_{Ar}-H), 127.31 (C_{Ar}-H), 127.15 (C_{Ar}-H), 124.82 (C_{Ar}-H), 124.26 (C_{Ar}-H), 123.42 (C_{Ar}-H), 123.35 (C_{Ar}-H), 122.26 (C_{Ar}-H), 121.89 (C_{Ar}-H), 107.81 (C_{Ar}-H), 104.30 (C_{Ar}-H), 103.93 (C_q), 86.41 (C_q), 72.52 (C_q), 72.24 (C_q), 38.73 (CH_2), 37.73 (CH_2), 26.10 (CH_3), 23.98 (CH_3), 21.75 (CH_3), 21.43 (CH_3), 19.51 (CH_3) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2985, 2926, 2861, 1599, 1522, 1477, 143, 1348, 1234, 1191, 851, 747, 699 cm^{-1};

HRMS (ESI) calcd. for $C_{19}H_{19}BrN_2O_4^+$ $[M+H]^+$ 419.0528, found 419.0599.

2-(bromomethyl)-9b-(4-chlorophenyl)-2,3,3-trimethyl-2,3-dihydro-9bH-benzo[d]oxazolo [3,2-b]isoxazole (112e)



112e

Colorless liquid;

Yield = 93%;

d.r. =50:50;

$\boldsymbol{R_f}$ = 0.6 (silica gel, Hexanes/Ethyl acetate = 95/5);

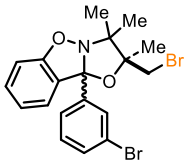
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 – 7.58 (major diastereomer, m, 4H, C_{Ar}-H), 7.35-7.26 (minor diastereomer, m, 6H, C_{Ar}-H), 7.00-6.85 (major diastereomer, m, 6H, C_{Ar}-H), 3.61-3.59 (minor diastereomer, d, *J* = 3.59, 1H, CH), 3.57-3.55 (major diastereomer, d, *J* = 3.55, 1H, CH), 1.66 (minor diastereomer, s, 3H, CH_3), 1.57 (major diastereomer, s, 3H, CH_3), 1.47 (minor diastereomer, s, 3H, CH_3), 1.37 (major diastereomer, s, 3H, CH_3), 1.08 (minor diastereomer, s, 3H, CH_3), 1.05 (major diastereomer, s, 3H, CH_3) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.74 (C_{Ar}-H), 154.82 (C_{Ar}-H), 154.60 (C_{Ar}-H), 141.39 (C_{Ar}-H), 141.29 (C_{Ar}-H), 133.88 (C_{Ar}-H), 133.83 (C_{Ar}-H), 130.54 (C_{Ar}-H), 130.40 (C_{Ar}-H), 130.29 (C_{Ar}-H), 129.81 (C_{Ar}-H), 128.25 (C_{Ar}-H), 128.17 (C_{Ar}-H), 127.81 (C_{Ar}-H), 127.63 (C_{Ar}-H), 124.93 (C_{Ar}-H), 124.36 (C_{Ar}-H), 122.05 (C_{Ar}-H), 121.65 (C_q), 107.60 (C_{Ar}-H), 104.57 (C_{Ar}-H), 104.21 (C_{Ar}-H), 86.07 (C_q), 72.45 (C_q), 72.15 (C_q), 39.10 (CH_2), 38.02 (CH_2), 26.16 (CH_3), 24.05 (CH_3), 21.95 (CH_3), 21.73 (CH_3), 21.52 (CH_3), 19.77 (CH_3) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2984, 2940, 1726, 1596, 1476, 1462, 1234, 1090, 971, 842, 746, 684 cm^{-1};

HRMS (ESI) calcd for $C_{19}H_{19}BrClNO_2^+$ $[M+H]^+$ 408.0288, found 408.0299.

2-(bromomethyl)-9b-(3-bromophenyl)-2,3,3-trimethyl-2,3-dihydro-9bH-benzo[d]oxazolo [3,2-b]isoxazole (112f)



112f

Colorless liquid,

Yield = 99%;

d.r. = 50:50;

$\boldsymbol{R_f}$ = 0.6 (silica gel, Hexanes/Ethyl acetate = 95/5);

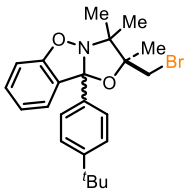
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (major diastereomer, dd, *J* = 7.85, 7.86 Hz, 1H, C_{Ar}-H), 7.82 (minor diastereomer, dd, *J* = 7.82 Hz, 1H, C_{Ar}-H), 7.61-7.57 (major diastereomer, m, 2H, C_{Ar}-H), 7.46-7.43 (minor diastereomer, m, 2H, C_{Ar}-H), 7.32-7.21 (major diastereomer, m, 5H, C_{Ar}-H), 7.01 (minor diastereomer, d, *J* = 7.03 Hz, 1H, C_{Ar}-H), 6.96-6.86 (major diastereomer, m, 6H, C_{Ar}-H), 3.56 (minor diastereomer, d, *J* = 3.55 Hz, 1H, CH), 3.43 (major diastereomer, d, *J* = 3.43 Hz, 1H, CH), 3.32 (minor diastereomer, d, *J* = 3.31 Hz, 1H, CH), 1.67 (major diastereomer, s, 3H, CH_3), 1.57 (minor diastereomer, s, 3H, CH_3), 1.47 (major diastereomer, s, 3H, CH_3), 1.37 (minor diastereomer, s, 3H, CH_3), 1.09 (major diastereomer, s, 3H, CH_3), 1.06 (minor diastereomer, s, 3H, CH_3) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.83 (C_{Ar}-H), 154.59 (C_{Ar}-H), 145.05 (C_{Ar}-H), 144.97 (C_{Ar}-H), 131.00 (C_{Ar}-H), 130.98 (C_{Ar}-H), 130.60 (C_{Ar}-H), 130.46 (C_{Ar}-H), 130.10 (C_{Ar}-H), 129.68 (C_{Ar}-H), 129.61 (C_{Ar}-H), 129.27 (C_{Ar}-H), 129.18 (C_{Ar}-H), 125.10 (C_{Ar}-H), 124.99 (C_{Ar}-H), 124.88 (C_{Ar}-H), 124.41 (C_{Ar}-H), 122.32 (C_{Ar}-H), 122.26 (C_q), 122.08 (C_{Ar}-H), 121.69 (C_{Ar}-H), 107.62 (C_{Ar}-H), 104.28 (C_{Ar}-H), 103.90 (C_{Ar}-H), 86.11 (C_q), 72.45 (C_q), 72.15 (C_q), 39.03 (CH_2), 37.98 (CH_2), 26.19 (CH_3), 24.05 (CH_3), 21.90 (CH_3), 21.67 (CH_3), 21.51 (CH_3), 19.70 (CH_3) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2986, 2984, 1602, 1568, 1476, 1462, 1376, 1259, 1232, 1189, 1066, 973, 900, 833, 747, 693 cm^{-1};

HRMS (ESI) calcd for $C_{19}H_{19}Br_2NO_2^+$ $[M+H]^+$ 451.9783, found 451.9854.

2-(bromomethyl)-9b-(4-(tert-butyl)phenyl)-2,3,3-trimethyl-2,3-dihydro-9bH-benzo[d]oxazolo[3,2-b]isoxazole (112g)



112g

Colorless liquid,

Yield = 82%;

d.r. = 50:50;

$\boldsymbol{R_f}$ = 0.5 (silica gel, Hexanes/Ethyl acetate = 95/5);

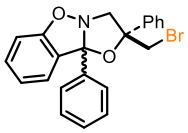
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 – 7.53 (m, 4H), 7.37 – 7.34 (m, 6H), 7.30 – 7.24 (dd, *J*= 7.05, 0.43 Hz, 1H), 7.05 -6.84 (m, 5H), 3.57-3.55 (d, *J* = 3.55 Hz, 1H), 1.68 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.07 (s, 3H, CH_3) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.83 (C_{Ar}-H), 157.16 (C_{Ar}-H), 154.77 (C_{Ar}-H), 154.59 (C_{Ar}-H), 153.58 (C_{Ar}-H), 150.67 (C_{Ar}-H), 150.60 (C_{Ar}-H), 139.56 (C_{Ar}-H), 139.41 (C_{Ar}-H), 136.26 (C_{Ar}-H), 131.24 (C_{Ar}-H), 131.00 (C_{Ar}-H), 130.50 (C_{Ar}-H), 130.20 (C_{Ar}-H), 130.07 (C_{Ar}-H), 129.68 (C_{Ar}-H), 127.81 (C_{Ar}-H), 127.47 (C_{Ar}-H), 126.11 (C_q), 125.91 (C_{Ar}-H), 125.77 (C_{Ar}-H), 125.14 (C_{Ar}-H), 124.90 (C_{Ar}-H), 124.82 (C_{Ar}-H), 123.75 (C_{Ar}-H), 122.33 (C_{Ar}-H), 121.83 (C_{Ar}-H), 121.45 (C_{Ar}-H), 110.16 (C_{Ar}-H), 107.43 (C_{Ar}-H), 105.01 (C_{Ar}-H), 104.67 (C_{Ar}-H), 85.69 (C_q), 72.39 (C_q), 72.10 (C_q), 39.37 (CH_2), 38.27 (CH_2), 34.52 (CH_3), 31.36 (CH_3), 31.26 (CH_3), 26.25 (CH_3), 24.16 (CH_3), 22.11 (CH_3), 21.93 (CH_3), 21.61 (CH_3), 19.93 (CH_3) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2963, 2904, 2869, 1732, 1610, 1477, 1462, 1375, 1267, 1237, 1213, 1013, 969, 898, 843, 748 cm^{-1};

HRMS (ESI) calcd. for $C_{23}H_{28}BrNO_2^+$ $[M+H]^+$ 430.1303, found 430.1376.

2-(bromomethyl)-2,9b-diphenyl-2,3-dihydro-9bH-benzo[d]oxazolo[3,2-b]isoxazole (112h)



112h

Colorless liquid,

Yield = 99%;

d.r. = 60:40;

$\boldsymbol{R_f}$ = 0.6 (silica gel, Hexanes/Ethyl acetate = 95/5);

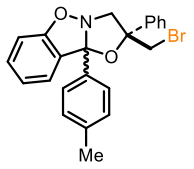
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.68 (d, *J* = 7.70 Hz, 2H), 7.46-7.44 (m, 4H), 7.39-7.37 (m, 4H), 6.36-6..33 (d, *J* = 6.34 Hz, 2H), 4.76-4.74 (d, *J* = 4.74 Hz, 1H), 4.51-4.46 (d, *J* = 4.51 Hz, 2H), 3.88-3.83 (d, *J* = 3.84 Hz, 2H), 3.77-3.73 (d, *J* = 3.77 Hz, 2H), 3.73-3.72 (d, *J* = 3.72 Hz, 1H), 3.66-3.63 (d, *J* = 3.64 Hz, 2H), 2.42 (s, 3H), 2.33 (s, 1H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.15 (C_{Ar}-H), 164.08 (C_{Ar}-H), 161.69 (C_{Ar}-H), 161.62 (C_{Ar}-H), 155.83 (C_{Ar}-H), 155.45 (C_{Ar}-H), 141.75 (C_{Ar}-H), 140.95 (C_{Ar}-H), 135.04 (C_{Ar}-H), 134.49 (C_{Ar}-H), 130.82 (C_{Ar}-H), 130.33 (C_{Ar}-H), 129.93 (C_{Ar}-H), 129.24 (C_{Ar}-H), 129.16 (C_{Ar}-H), 129.03 (C_{Ar}-H), 128.87 (C_{Ar}-H), 128.19 (C_{Ar}-H), 127.94 (C_{Ar}-H), 127.72 (C_{Ar}-H), 127.46 (C_{Ar}-H), 126.08 (C_{Ar}-H), 125.11 (C_{Ar}-H), 124.55 (C_{Ar}-H), 123.97 (C_{Ar}-H), 122.10 (C_{Ar}-H), 121.38 (C_q), 115.14 (C_{Ar}-H), 115.08 (C_{Ar}-H), 114.93 (C_{Ar}-H), 114.87 (C_{Ar}-H), 109.82 (C_{Ar}-H), 108.82 (C_{Ar}-H), 108.06 (C_{Ar}-H), 107.05 (C_{Ar}-H), 87.57 (C_{Ar}-H), 86.40 (C_q), 63.14 (CH_2), 61.71 (CH_2), 40.62 (CH_2), 39.50 (CH_2) ppm;

IR (film) $\tilde{\nu}_{max}$ = 3030, 1603, 1283, 1047, 1001, 859, 1123, 672 cm^{-1};

HRMS (ESI) calcd. for $C_{22}H_{18}BrNO_2^+$ $[M+ H]^+$ 408.0521, found 408.0594.

2-(bromomethyl)-2-phenyl-9b-(*p*-tolyl)-2,3-dihydro-9bH-benzo[d]oxazolo[3,2-b]isoxazole (112i)



112i

Colorless liquid,

Yield = 50%;

d.r. = 40:60;

R_f = 0.5 (silica gel, Hexanes/Ethyl acetate = 95/5);

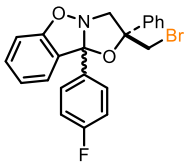
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.68 (d, *J* = 7.70 Hz, 2H), 7.46-7.44 (m, 4H), 7.39-7.37 (m, 4H), 6.36-6.35 (d, *J* = 6.34 Hz, 2H), 4.76 – 4.74 (d, *J* = 4.74 Hz, 1H), 4.51-4.46 (d, *J* = 4.51 Hz, 2H), 3.88-3.83 (d, *J* = 3.84 Hz, 2H), 3.77-3.73 (d, *J* = 3.77 Hz, 2H), 3.73-3.72 (d, *J* = 3..64 Hz, 2H), 3.66-3.63 (d, *J* = 3.64 Hz, 2H), 2.42 (s, 3H), 2.33 (s, 3H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.87 (C_{Ar}-H), 155.49 (C_{Ar}-H), 141.96 (C_{Ar}-H), 141.30 (C_{Ar}-H), 138.32 (C_{Ar}-H), 136.19 (C_{Ar}-H), 135.58 (C_{Ar}-H), 130.55 (C_{Ar}-H), 130.15 (C_{Ar}-H), 128.82 (C_{Ar}-H), 128.05 (C_{Ar}-H), 127.63 (C_{Ar}-H), 127.14 (C_{Ar}-H), 127.07 (C_{Ar}-H), 124.63 (C_{Ar}-H), 124.03 (C_{Ar}-H), 121.23 (C_q), 110.23 (C_{Ar}-H), 109.29 (C_{Ar}-H), 107.93 (C_{Ar}-H), 107.01 (C_{Ar}-H), 87.32 (C_q), 86.15 (C_q), 63.37 (CH_2), 61.69 (CH_2), 53.40 (CH_2), 40.79 (CH_2), 21.14 (CH_3), 21.13 (CH_3) ppm;

IR (film) $\tilde{\nu}_{max}$ = 3061, 3024, 2922, 2851, 2363, 2323, 1603, 1476, 1462, 1447, 1429, 1247, 749, 702 cm^{-1};

HRMS (ESI) calcd. for $C_{23}H_{20}BrNO_2^+$ $[M+H]^+$ 422.0670, found 422.0673.

2-(bromomethyl)-9b-(4-fluorophenyl)-2-phenyl-2,3-dihydro-9bH-benzo[d]oxazolo[3,2-b]isoxazole (112j)



112j

Colorless liquid,

Yield = 80%;

d.r. = 33:67;

$\boldsymbol{R_f}$ = 0.4 (silica gel, Hexanes/Ethyl acetate = 95/5);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.79 (m, 2H), 7.56-7.54 (m, 1H), 7.47-7.34 (m, 4H), 7.16 – 7.09 (m, 9H), 7.04-7.02 (d, *J* = 7.03 Hz, 1H), 7.00-6.96 (m, 2H), 6.96-6.88 (t, *J* = 6.92 Hz, 1H), 6.34 – 6.32 (d, *J* = 6.34 Hz, 1H), 4.78 – 4.74 (d, *J* = 4.78 Hz, 1H), 4.50 – 4.46 (d, *J* = 4.50 Hz, 2H), 3.89 – 3.86 (d, *J* = 3.86 Hz, 1H), 3.79 – 3.76 (d, *J* = 3.76 Hz, 1H), 3.71 – 3.67 (d, *J* = 3.69 Hz, 1H), 3.65 – 3.62 (d, *J* = 3.62 Hz, 1H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.15 (C_{Ar}-H), 164.08 (C_{Ar}-H), 161.69 (C_{Ar}-H), 161.62 (C_{Ar}-H), 155.83 (C_{Ar}-H), 155.45 (C_{Ar}-H), 141.75 (C_{Ar}-H), 140.95 (C_{Ar}-H), 135.04 (C_{Ar}-H), 134.49 (C_{Ar}-H), 130.82 (C_{Ar}-H), 130.33 (C_{Ar}-H), 129.93 (C_{Ar}-H), 129.24 (C_{Ar}-H), 129.16 (C_{Ar}-H), 129.12 (C_{Ar}-H), 129.03 (C_{Ar}-H), 128.87 (C_{Ar}-H), 128.19 (C_{Ar}-H), 127.94 (C_{Ar}-H), 127.72 (C_{Ar}-H), 127.46 (C_{Ar}-H), 126.08 (C_{Ar}-H), 125.11 (C_{Ar}-H), 124.55 (C_{Ar}-H), 123.97 (C_{Ar}-H), 122.10 (C_{Ar}-H), 121.38 (C_q), 115.14 (C_{Ar}-H), 115.08 (C_{Ar}-H), 114.93 (C_{Ar}-H), 114.87 (C_{Ar}-H), 109.82 (C_{Ar}-H), 108.82 (C_{Ar}-H), 108.06 (C_{Ar}-H), 107.05 (C_{Ar}-H), 87.57 (C_q), 86.40 (C_q), 63.14 (CH_2), 61.71 (CH_2), 40.62 (CH_2), 39.50 (CH_2) ppm;

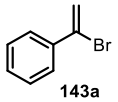
^{19}F NMR (313 MHz, $CDCl_3$): δ -113.68 (s), -113.86 (s) ppm;

IR (film) $\tilde{\nu}_{max}$ = 3065, 3029, 2957, 2926, 2368, 2314, 1723, 1603, 1507, 1462, 1226, 748, 702 cm^{-1};

HRMS (ESI) calcd. for $C_{22}H_{17}BrFNO_2^+$ $[M+H]^+$ 426.0427, found 426.0499.

2.5. Synthesis for *α*-bromo styrene derivatives 143

(1-bromovinyl)benzene (143a)



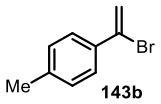
143a

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 - 7.59 (m, 2H, C_{Ar}-H), 7.40 - 7.32 (m, 3H, C_{Ar}-H), 6.13 (d, *J* = 2.0 Hz, 1H, CH), 5.80 (d, *J* = 2.0 Hz, 1H, CH) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.58 (C_{Ar}-H), 131.03 (C_{Ar}-H), 129.11 (C_{Ar}-H), 128.31 (C_{Ar}-H), 127.34 (C=C), 117.70 (C=C) ppm.

The physical and spectroscopic data is in accordance to these reported in the literature.[125]

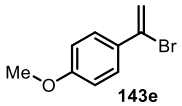
1-(1-bromovinyl)-4-methylbenzene (143b)



143b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.2 Hz, 2H, C_{Ar}-H), 7.19 (d, *J* = 9.2 Hz, 2H, C_{Ar}-H), 6.12 (d, *J* = 2.0 Hz, 1H, CH), 5.77 (d, *J* = 2.0 Hz, 1H, CH), 2.41 (s, 3H, CH_3) ppm. The physical and spectroscopic data is in accordance to these reported in the literature. [125]

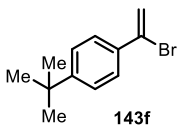
1-(1-bromovinyl)-4-methoxybenzene (143e)



143e

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, *J* = 9.0 Hz, 2H, C_{Ar}-H), 6.89 (d, *J* = 9.0 Hz, 2H, C_{Ar}-H), 6.04 (d, *J* = 2.0 Hz, 1H, CH), 5.71 (d, *J* = 2.0 Hz, 1H, CH), 3.85 (s, 3H, CH_3) ppm. The physical and spectroscopic data is in accordance to these reported in the literature. [125]

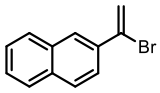
1-(1-bromovinyl)-4-(*tert*-butyl)benzene (143f)



143f

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.7 Hz, 2H, C_{Ar}-H), 7.41 (d, *J* = 8.8 Hz, 2H, C_{Ar}-H), 6.13 (d, *J* = 2.0 Hz, 1H, CH), 5.78 (d, *J* = 2.0 Hz, 1H, CH), 1.37 (s, 9H, CH_3) ppm.

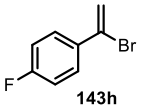
2-(1-bromovinyl)naphthalene (143g)



143g

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (s, 1H, C_{Ar}-H), 7.94-7.86 (m, 2H, C_{Ar}-H), 7.83 (d, *J* = 9.0 Hz, 1H, C_{Ar}-H), 7.72 (dd, *J* = 8.7, 1.9 Hz, 1H, C_{Ar}-H), 7.55 (dt, *J* = 5.7, 3.5 Hz, 2H, C_{Ar}-H), 6.30 (d, *J* = 2.1 Hz, 1H, CH), 5.92 (d, *J* = 2.1 Hz, 1H, CH) ppm.

1-(1-bromovinyl)-4-fluorobenzene (143h)

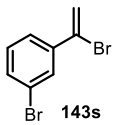


143h

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (dd, *J* = 8.9, 5.3 Hz, 2H, C_{Ar}-H), 7.03 (t, *J* = 8.7 Hz, 2H, C_{Ar}-H), 6.05 (d, *J* = 2.1 Hz, 1H, CH), 5.76 (d, *J* = 2.1 Hz, 1H, CH) ppm.

The physical and spectroscopic data is in accordance to these reported in the literature. [125]

1-bromo-3-(1-bromovinyl)benzene (143s)



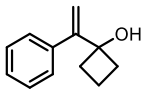
143s

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H, C_{Ar}-H), 7.46 (d, *J* = 8.0 Hz, 1H, C_{Ar}-H), 7.22 (t, *J* = 7.9 Hz, 1H, C_{Ar}-H), 6.13 (s, 1H, CH), 5.82 (s, 1H, CH) ppm. The physical and spectroscopic data is in accordance to these reported in the literature. [125]

2.6. Synthesis procedures for cyclobutanols 102

1-(1-phenylvinyl) cyclobutan-1-ol (102a)

(according to AAV 7)



102a

Colorless liquid;

Yield = 50%;

***R*$_f$** = 0.7 (silica gel, Petroleum ether/EtOAc = 90/10);

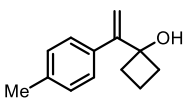
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.1 Hz, 2H, C_{Ar}-H), 7.32 (dt, *J* = 13.9, 7.0 Hz, 3H, C_{Ar}-H), 5.38 (s, 1H, CH), 5.36 (s, 1H, CH), 2.53-2.45 (m, 2H, CH), 2.30-2.21 (m, 2H, CH), 1.99 (ddq, *J* = 15.0, 9.5, 5.7 Hz, 2H, CH, OH), 1.69-1.59 (m, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.4 (C_{Ar}-H), 138.1 (C_{Ar}-H), 127.1 (C_{Ar}-H), 126.6 (C_{Ar}-H), 126.5 (C=C), 111.8 (C=C), 77.07(C_q), 34.68 (CH_2), 12.33 (CH_2) ppm;

The physical and spectroscopic data is in accordance to these reported in the literature. [134]

1-(1-(*p*-Tolyl) vinyl) cyclobutanol (102b)

(according to AAV 7)



102b

Colorless liquid;

Yield = 87%;

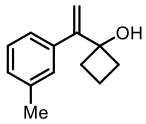
R_f = 0.6 (silica gel, Petroleum ether/EtOAc = 90/10);

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53-1.65 (m, 1H, CH), 1.89-2.02 (m, 1H, CH), 2.11 (br, 1H, CH, OH), 2.18-2.27 (m, 2H, CH), 2.33 (s, 3H, CH), 2.41-2.50 (m, 2H, CH), 5.31 (s, 2H, CH_2), 7.12 (d, *J* = 8.1 Hz, 2H, C_{Ar}-H), 7.36 (d, *J* = 8.1 Hz, 2H, C_{Ar}-H) ppm;

^{13}C NMR (101MHz, $CDCl_3$): δ 152.2 (C_{Ar}-H), 137.2 (C_{Ar}-H), 136.1 (C_{Ar}-H), 128.8 (C_{Ar}-H), 127.5 (C=C), 112.1 (C=C), 78.10 (C_q), 35.70 (CH_2), 21.10 (CH_2), 13.30 (CH_3) ppm;
The physical and spectroscopic data is in accordance to these reported in the literature. [134]

1-(1-(m-tolyl)vinyl)cyclobutan-1-ol (102c)

(according to AAV 7)



102c

Colorless liquid;

Yield = 85%;

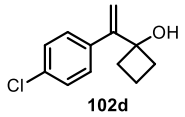
R_f = 0.6 (silica gel, Petroleum ether/EtOAc = 90/10);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.22 (m, 3H, C_{Ar}-H), 7.14 (d, J = 7.2 Hz, 1H, C_{Ar}-H), 5.39 (s, 1H, CH), 5.36 (s, 1H, CH), 2.51 (ddd, J = 12.4, 8.8, 5.7 Hz, 2H, CH), 2.39 (s, 2H, CH), 2.34 – 2.23 (m, 2H, CH), 2.09 – 1.98 (m, 2H, CH, OH), 1.75 – 1.59 (m, 1H, CH) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 152.6 (C_{Ar}-H), 139.2 (C_{Ar}-H), 137.8 (C_{Ar}-H), 128.4 (C_{Ar}-H), 128.3 (C_{Ar}-H), 128.1 (C_{Ar}-H), 124.7 (C=C), 112.6 (C=C), 78.11 (C_q), 35.74 (CH_2), 21.56 (CH_2), 13.39 (CH_3) ppm;
The physical and spectroscopic data is in accordance to these reported in the literature. [134]

1-(1-(4-chlorophenyl)vinyl)cyclobutan-1-ol (102d)

(according to AAV 7)



102d

Colorless oil;

Yield = 70%;

$\boldsymbol{R_f}$ = 0.7 (silica gel, Petroleum ether/EtOAc = 90/10);

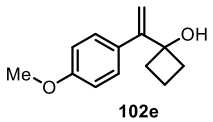
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.41 (m, 2H, C_{Ar}-H), 7.31-7.26 (m, 2H, C_{Ar}-H), 5.38 (s, 1H, CH), 5.35 (s, 1H), 2.44 (dddd, *J* = 12.2, 8.7, 5.6, 2.8 Hz, 2H), 2.22 (tdd, *J* = 9.3, 6.7, 2.8 Hz, 2H, CH), 2.04-1.92 (m, 2H, OH, CH), 1.62 (dtt, *J* = 11.1, 8.9, 6.8 Hz, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.4 (C_{Ar}-H), 137.5 (C_{Ar}-H), 133.4 (C_{Ar}-H), 132.9 (C_{Ar}-H), 128.9 (C_{Ar}-H), 128.3 (C=C), 113.3 (C=C), 78.01 (C_q), 38.59 (CH_2), 35.62 (CH_2), 13.33 (CH_2) ppm;

The physical and spectroscopic data is in accordance to these reported in the literature. [134]

1-(1-(4-methoxyphenyl) vinyl)cyclobutan-1-ol (102e)

(according to AAV 7)



102e

Colorless liquid;

Yield = 90%;

$\boldsymbol{R_f}$ = 0.4 (silica gel, Petroleum ether/EtOAc = 90/10);

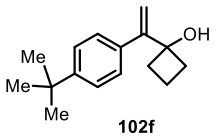
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 4 Hz, 1H, C_{Ar}-H), 7.45 (d, *J* = 4 Hz, 1H, C_{Ar}-H), 6.90 (d, *J* = 4 Hz, 1H, C_{Ar}-H), 6.88 (d, *J* = 4 Hz, 1H, C_{Ar}-H), 5.33 (s, 1H, CH), 5.32 (s, 1H, CH), 3.84 (s, 3H, CH_2), 2.54 – 2.45 (m, 2H, CH_2), 2.32 – 2.22 (m, 2H, CH, OH), 2.07 – 1.93 (m, 2H, CH), 1.72 – 1.58 (m, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.1 (C_{Ar}-H), 151.6 (C_{Ar}-H), 131.3 (C_{Ar}-H), 128.7 (C_{Ar}-H), 113.5 (C=C), 111.5 (C=C), 78.21 (C_q), 55.26 (CH_3), 35.72 (CH_2), 13.39 (CH_2) ppm;

The physical and spectroscopic data is in accordance to these reported in the literature. [134]

1-(1-(4-(tert-butyl) phenyl)vinyl)cyclobutan-1-ol (102f)

(according to AAV 7)



102f

Colorless liquid;

Yield = 89%;

$\boldsymbol{R_f}$ = 0.5 (silica gel, Petroleum ether/EtOAc = 90/10);

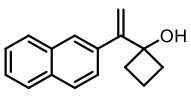
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.5 Hz, 2H, C_{Ar}-H), 7.36 (d, *J* = 8.5 Hz, 2H, C_{Ar}-H), 5.37 (d, *J* = 0.9 Hz, 1H, CH), 5.35 (d, *J* = 0.9 Hz, 1H, CH), 2.55 – 2.46 (m, 2H, CH), 2.28 (m, 2H, OH, CH), 1.99 (dddd, *J* = 11.0, 9.3, 7.2, 4.7 Hz, 2H, CH), 1.65 (dddd, *J* = 12.8, 8.8, 6.4, 4.4 Hz, 1H, CH), 1.33 (s, 9H, CH_3) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.9 (C_{Ar}-H), 150.5 (C_{Ar}-H), 135.9 (C_{Ar}-H), 127.2 (C_{Ar}-H), 125.1 (C=C), 112.1 (C=C), 78.13 (C_q), 35.79 (CH_2), 34.51 (CH_2), 31.33 (C_q), 13.40 (CH_3) ppm;

The physical and spectroscopic data is in accordance to these reported in the literature. [125]

1-(1-(naphthalen-2-yl) vinyl)cyclobutan-1-ol (102g)

(according to AAV 7)



102g

Colorless liquid;

Yield = 83%;

R_f = 0.3 (silica gel, Petroleum ether/EtOAc = 90/10);

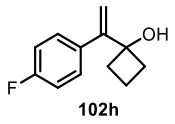
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (s, 1H, C_{Ar}-H), 7.87-7.78 (m, 3H, C_{Ar}-H), 7.63 (d, *J* = 10.1 Hz, 1H, C_{Ar}-H), 7.51-7.43 (m, 2H, C_{Ar}-H), 5.50 (s, 1H, CH), 5.48 (s, 1H, CH), 2.54 (ddd, *J* = 12.0, 8.9, 6.0 Hz, 2H, CH), 2.31 (ddd, *J* = 12.1, 9.2, 6.7 Hz, 2H, CH), 2.01 (m, 2H, CH, OH), 1.75-1.58 (m, 1H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 152.4 (C_{Ar}-H), 136.5 (C_{Ar}-H), 133.2 (C_{Ar}-H), 132.8 (C_{Ar}-H), 128.3 (C_{Ar}-H), 127.7 (C_{Ar}-H), 127.6 (C_{Ar}-H), 126.5 (C_{Ar}-H), 126.1 (C_{Ar}-H), 125.9 (C_{Ar}-H), 125.1 (C=C), 113.4 (C=C), 78.28 (C_q), 35.83 (CH_2), 13.46 (CH_2) ppm;

The physical and spectroscopic data is in accordance to these reported in the literature. [134]

1-(1-(4-fluorophenyl) vinyl)cyclobutan-1-ol (102h)

(according to AAV 7)



102h

Colorless liquid;

Yield = 80%;

R_f = 0.6 (silica gel, Petroleum ether/Et_2O = 90/10);

^{19}F NMR (376 MHz, $CDCl_3$): δ -115.1 (s) ppm;

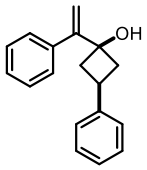
^{1}H NMR (300 MHz,$CDCl_3$): δ 7.50-7.43 (m, 2H, C_{Ar}-H), 7.04-6.96 (m, 2H, C_{Ar}-H), 5.35 (s, 1H, CH), 5.32 (s, 1H, CH), 2.44 (ddd, *J* = 12.5, 9.1, 5.7 Hz, 2H, CH_2), 2.22 (ddd, *J* = 11.9, 9.4, 6.8 Hz, 2H, CH_2), 2.06-1.93 (m, 1H, CH_2), 1.91 (s, 1H, OH), 1.67-1.55 (m, 1H, CH_2) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4 (C_{Ar}-H), 160.7 (C_{Ar}-H), 151.4 (C_{Ar}-H), 135.1 (C_{Ar}-H), 135.1 (C_{Ar}-H), 129.3 (C_{Ar}-H), 129.2 (C_{Ar}-H), 115.1 (C_{Ar}-H), 114.8 (C_{Ar}-H), 112.9 (C=C), 112.1 (C=C), 78.08 (C_q), 35.61 (CH_2), 13.32 (CH_2) ppm;

The physical and spectroscopic data is in accordance to these reported in the literature. [127]

3-phenyl-1-(1-phenylvinyl) cyclobutan-1-ol (102i)

(according to AAV 7)



(cis : trans = 80 : 20)

102i

Colorless liquid;

Yield = 76%;

R_f = 0.3 (silica gel, Petroleum ether/EtOAc = 90/10); Cis-isomer and trans-isomer (80:20, which was determined by ^{1}H NMR) could not be separated by silica gel column chromatography. Analytical data for the major cis-isomer 3-Phenyl-1-(1-phenylvinyl) cyclobutanol;

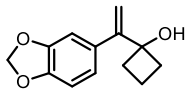
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (dd, *J* = 20.4, 8.2 Hz, 7H, C_{Ar}-H), 7.43-7.27 (m, 26H, C_{Ar}-H), 7.23 (t, *J* = 6.9 Hz, 6H, C_{Ar}-H), 5.61 (s, 2H, CH), 5.53 (s, 2H, CH), 5.36 (s, 1H, CH), 5.32 (s, 1H,CH), 3.91 (p, *J* = 9.0 Hz, 1H, CH), 3.17-2.95 (m, 8H, CH), 2.77-2.64 (m, 2H,CH), 2.52 (dtd, *J* = 31.1, 9.6, 2.5 Hz, 7H, CH), 1.97 (m, 4H, CH, OH) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5 (C_{Ar}-H), 151.4 (C_{Ar}-H), 145.1 (C_{Ar}-H), 144.7 (C_{Ar}-H), 139.0 (C_{Ar}-H), 138.8 (C_{Ar}-H), 128.4 (C_{Ar}-H), 127.7 (C_{Ar}-H), 126.7 (C_{Ar}-H), 126.0 (C_{Ar}-H), 113.7 (C=C), 112.8 (C=C), 76.05 (C_q), 73.30 (C_q), 43.67 (CH), 42.35 (CH), 33.07 (CH_2), 30.55 (CH_2) ppm;

The physical and spectroscopic data is in accordance to these reported in the literature. [134]

1-(1-(benzo[d][1,3]dioxol-5-yl)vinyl)cyclobutan-1-ol (102j)

(according to AAV 7)



102j

Colorless liquid;

Yield = 85%;

$\boldsymbol{R_f}$ = 0.4 (silica gel, Petroleum ether/EtOAc = 90/10);

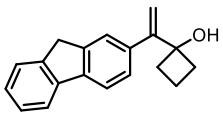
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (d, *J* = 1.6 Hz, 1H, C_{Ar}-H), 6.96 (dd, *J* = 8.1, 1.7 Hz, 1H, C_{Ar}-H), 6.75 (d, *J* = 8.1 Hz, 1H, C_{Ar}-H), 5.92 (s, 2H, O-CH_2-O), 5.27 (d, *J* = 2.6 Hz, 2H, C_{Ar}-CH_2), 2.43 (ddd, *J* = 12.4, 8.8, 5.8 Hz, 2H, CH_2), 2.21 (ddd, *J* = 12.2, 9.3, 6.7 Hz, 3H, CH, OH), 2.03-1.91 (m, 1H, CH), 1.60 (dddd, *J* = 15.7, 11.0, 8.8, 6.9 Hz, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.9 (C=C), 147.4 (C_{Ar}-H), 147.0 (C_{Ar}-H), 133.1 (C_{Ar}-H), 121.1 (C_{Ar}-H), 112.1 (C_{Ar}-H), 108.2 (C_{Ar}-H), 107.9 (C=C), 100.9 (CH_2), 78.13 (C_q), 35.68 (CH_2), 13.38 (CH_2) ppm;

The physical and spectroscopic data is in accordance to these reported in the literature. [125]

1-(1-(9H-fluoren-2-yl)vinyl)cyclobutan-1-ol (102k)

(according to AAV 7)



102k

Colorless liquid;

Yield = 96%;

$\boldsymbol{R_f}$ = 0.5 (silica gel, Petroleum ether/EtOAc = 90/10);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.5 Hz, 1H, C_{Ar}-H), 7.74 (d, *J* = 7.9 Hz, 1H, C_{Ar}-H), 7.68 (s, 1H, C_{Ar}-H), 7.54 (d, *J* = 7.4 Hz, 1H, C_{Ar}-H), 7.51 (d, *J* = 7.9 Hz, 1H, C_{Ar}-H), 7.38 (t, *J* = 7.4 Hz, 1H, C_{Ar}-H), 7.30 (t, *J* = 7.4 Hz, 1H, C_{Ar}-H), 5.43 (s, 1H, CH),

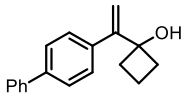
5.41 (s, 1H, CH), 3.91 (s, 2H, CH), 2.61 – 2.45 (m, 2H, CH), 2.35 – 2.24 (m, 2H, CH, OH), 2.03 (dt, *J* = 10.8, 5.5 Hz, 2H, CH), 1.74 – 1.61 (m, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.7 (C=C), 143.4 (C_{Ar}-H), 143.2 (C_{Ar}-H), 141.4 (C_{Ar}-H), 141.1 (C_{Ar}-H), 137.6 (C_{Ar}-H), 126.7 (C_{Ar}-H), 126.7 (C_{Ar}-H), 126.3 (C_{Ar}-H), 125.0 (C_{Ar}-H), 124.2 (C_{Ar}-H), 119.9 (C_{Ar}-H), 119.5 (C_{Ar}-H), 112.6 (C=C), 78.29 (C_q), 37.00 (CH_2), 35.83 (CH_2), 13.43 (CH_2) ppm;

The physical and spectroscopic data is in accordance to these reported in the literature. [125]

1-(1-([1, 1'-biphenyl]-4-yl)vinyl)cyclobutan-1-ol (102l)

(according to AAV 7)



102l

Colorless liquid;

Yield = 60%;

$\boldsymbol{R_f}$ = 0.5 (silica gel, Petroleum ether/EtOAc = 90/10);

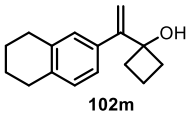
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.8 Hz, 2H, C_{Ar}-H), 7.58 (s, 4H, C_{Ar}-H), 7.45 (t, *J* = 7.5 Hz, 2H, C_{Ar}-H), 7.36 (t, *J* = 7.3 Hz, 1H, C_{Ar}-H), 5.45 (s, 1H, CH), 5.41 (s, 1H, CH), 2.57 – 2.48 (m, 2H, CH), 2.30 (q, *J* = 9.3 Hz, 2H, CH), 2.03 (ddt, *J* = 14.7, 9.4, 5.0 Hz, 1H, CH), 1.93 (s, 1H, OH), 1.67 (dq, *J* = 16.0, 7.9 Hz, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.7 (C=C), 143.4 (C_{Ar}-H), 143.2 (C_{Ar}-H), 141.4 (C_{Ar}-H), 141.1 (C_{Ar}-H), 137.6 (C_{Ar}-H), 126.7 (C_{Ar}-H), 126.1 (C_{Ar}-H), 126.3 (C_{Ar}-H), 125.0 (C_{Ar}-H), 124.2 (C_{Ar}-H), 119.9 (C_{Ar}-H), 119.1 (C_{Ar}-H), 112.6 (C=C), 78.29 (C_q), 37.00 (CH_2), 35.83 (CH_2), 13.43 (CH_2) ppm;

The physical and spectroscopic data is in accordance to these reported in the literature. [125]

1-(1-(5, 6, 7, 8-tetrahydronaphthalen-2-yl)vinyl)cyclobutan-1-ol (102m)

(according to AAV 7)



102m

Colorless liquid;

Yield = 68%;

$\boldsymbol{R_f}$ = 0.5 (silica gel, Petroleum ether/EtOAc = 90/10);

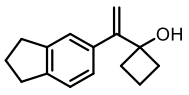
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.1 Hz, 1H, C_{Ar}-H), 7.18 (s, 1H, C_{Ar}-H), 7.03 (d, *J* = 7.8 Hz, 1H, C_{Ar}-H), 5.32 (s, 2H, CH_2), 2.77 (s, 4H, CH), 2.55 – 2.43 (m, 2H, CH), 2.30 – 2.21 (m, 2H, CH), 1.99 (tq, *J* = 9.4, 5.5 Hz, 2H, CH), 1.81 (s, 2H, OH), 1.71-1.58 (m, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.4 (C=C), 136.9 (C_{Ar}-H), 136.6 (C_{Ar}-H), 136.1 (C_{Ar}-H), 128.9 (C_{Ar}-H), 128.2 (C_{Ar}-H), 124.7 (C_{Ar}-H), 111.9 (C=C), 78.15 (C_q), 35.76 (CH_2), 29.55 (CH_2), 29.14 (CH_2), 23.23 (CH_2), 13.41 (CH_2) ppm.

The physical and spectroscopic data is in accordance to these reported in the literature. [125]

1-(1-(2, 3-dihydro-1H-inden-5-yl)vinyl)cyclobutan-1-ol (102n)

(according to AAV 7)



102n

Colorless liquid;

Yield = 85%;

$\boldsymbol{R_f}$ = 0.7 (silica gel, Petroleum ether/EtOAc = 90/10);

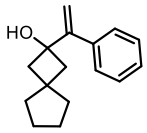
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H, C_{Ar}-H), 7.27 (d, *J* = 7.8 Hz, 1H, C_{Ar}-H), 7.21 (d, *J* = 7.8 Hz, 1H, C_{Ar}-H), 5.36 (s, 1H, CH_2), 5.34 (s, 1H, CH_2), 2.94 (td, *J* = 7.5, 3.0 Hz, 4H, CH), 2.52 (ddd, *J* = 12.1, 8.8, 5.6 Hz, 2H, CH), 2.28 (tdd, *J* = 9.3, 6.8, 3.0 Hz, 2H, CH), 2.15 -2.07 (s, 2H, CH, OH), 2.01 (m, 2H, CH), 1.73-1.64 (m, 1H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.8 (C=C), 144.2 (C_{Ar}-H), 143.7 (C_{Ar}-H), 137.1 (C_{Ar}-H), 125.6 (C_{Ar}-H), 124.1 (C_{Ar}-H), 123.6 (C_{Ar}-H), 112.1 (C=C), 78.19 (C_q), 35.78 (CH_2), 32.91 (CH_2), 32.63 (CH_2), 25.47 (CH_2), 13.39 (CH_2) ppm.

The physical and spectroscopic data is in accordance to these reported in the literature. [125]

2-(1-Phenylvinyl)spiro[3.4]octan-2-ol (102o)

(according to AAV 7)



102o

Colorless liquid;

Yield = 80%;

R_f = 0.4 (silica gel, Petroleum ether/Et_2O = 90/10);

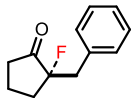
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38-1.47 (m, 6H, CH), 1.64-1.68 (m, 2H, CH), 2.07 (AB, *J* = 13.2 Hz, 2H, CH_2), 2.09 (br, 1H, OH), 2.30 (BA, *J* = 13.2 Hz, 2H, CH_2), 5.24 (d, *J* = 0.8 Hz, 1H, CH_2), 5.25 (d, *J* = 0.8 Hz, 1H, CH_2), 7.15-7.20 (m, 3H, C_{Ar}-H), 7.38-7.40 (m, 2H, C_{Ar}-H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5 (C_{Ar}-H), 139.1 (C_{Ar}-H), 128.0 (C_{Ar}-H), 127.4 (C_{Ar}-H), 127.3 (C=C), 113.1 (C=C), 73.7 (C_q), 46.6 (C_q), 40.5 (CH_2), 39.6 (CH_2), 37.9 (CH_2), 23.8 (CH_2), 23.7 (CH_2) ppm;

The physical and spectroscopic data is in accordance to these reported in the literature. [134]

2.7. Synthesis procedures for cyclopentanones 106

2-benzyl-2-fluorocyclopentan-1-one (106a)



106a

Colorless liquid;

Yield = 90%;

$\boldsymbol{R_f}$ = 0.5 (silica gel, Petroleum ether/Et_2O = 95/5);

^{19}F NMR (376 MHz, $CDCl_3$): δ -153.4 (s) ppm;

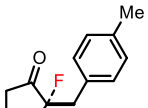
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 1H, C_{Ar}-H), 7.20 (d, *J* = 6.9 Hz, 1H, C_{Ar}-H), 3.15 (t, *J* = 14.1 Hz, 1H, CH_2), 2.90 (dd, *J* = 28.0, 14.1 Hz, 1H, CH_2), 2.48-2.39 (m, 1H, CH), 2.24 – 2.13 (m, 1H, CH), 2.07 – 1.94 (m, 3H, CH), 1.78 – 1.67 (m, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 213.0 (C=O), 134.6 (C_{Ar}-H), 134.6 (C_{Ar}-H), 130.2 (C_{Ar}-H), 128.4 (C_{Ar}-H), 127.1 (C_{Ar}-H), 98.23 (CH_2), 96.40 (CH_2), 38.81 (CH_2), 38.57 (CH_2), 35.62 (CH_2), 32.94 (CH_2), 32.73 (CH_2), 17.37 (CH_2), 17.33 (CH_2) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2984, 2935, 2371, 2324, 1603, 1476, 1463, 1234, 969, 899, 832, 746, 699 cm^{-1};

HRMS Calcd for $C_{12}H_{14}FO$ $[M + H]^+$ m/z 193.1000, Found: m/z 193.1023.

2-fluoro-2-(4-methylbenzyl)cyclopentan-1-one (106b)



106b

Colorless liquid;

Yield = 94%;

$\boldsymbol{R_f}$ = 0.5 (silica gel, Petroleum ether/Et_2O = 95/5);

^{19}F NMR (376 MHz, $CDCl_3$): δ -153.2 (s) ppm;

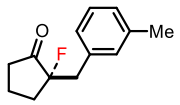
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (q, *J* = 6.1 Hz, 4H, C_{Ar}-H), 3.10 (td, *J* = 14.1, 2.1 Hz, 1H, CH), 2.87 (ddd, *J* = 27.4, 14.1, 2.1 Hz, 1H, CH), 2.48 – 2.39 (m, 1H, CH), 2.33 (d, *J* = 2.1 Hz, 3H, CH), 2.22 – 2.14 (m, 1H, CH), 2.09 – 1.93 (m, 3H, CH_3), 1.71 (dtt, *J* = 10.4, 6.8, 3.2 Hz, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 213.1 (C=O), 136.7 (C_{Ar}-H), 131.4 (C_{Ar}-H), 131.4 (C_{Ar}-H), 130.1 (C_{Ar}-H), 129.1 (C_{Ar}-H), 98.29 (CH_2), 96.46 (CH_2), 38.41 (CH_2), 38.17 (CH_2), 35.65 (CH_2), 32.91 (CH_2), 32.70 (CH_2), 21.05 (CH_2), 17.35 (CH_2), 17.31 (CH_3) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2922, 2360, 1755, 1514, 1013, 958, 825, 751 cm^{-1};

HRMS Calcd for $C_{13}H_{19}FNO$ $[M + NH_4]^+$ m/z 224.1445, Found: m/z 224.1446.

2-fluoro-2-(3-methylbenzyl)cyclopentan-1-one (106c)



106c

Colorless liquid;

Yield = 84%;

$\boldsymbol{R_f}$ = 0.5 (silica gel, Petroleum ether/Et_2O = 95/5);

^{19}F NMR (376 MHz, $CDCl_3$): δ -153.2 (s) ppm;

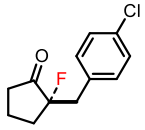
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (t, *J* = 7.5 Hz, 1H, C_{Ar}-H), 7.08 (d, *J* = 7.6 Hz, 1H, C_{Ar}-H), 7.01 (d, *J* = 11.2 Hz, 2H, C_{Ar}-H), 3.11 (t, *J* = 14.1 Hz, 1H, CH), 2.86 (dd, *J* = 27.9, 14.1 Hz, 1H, CH), 2.50 – 2.39 (m, 1H, CH), 2.33 (s, 3H, CH), 2.26 – 2.13 (m, 1H, CH), 2.09 – 1.93 (m, 3H, CH_3), 1.77-1.67 (m, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 213.0 (C=O), 138.1 (C_{Ar}-H), 134.5 (C_{Ar}-H), 131.0 (C_{Ar}-H), 128.3 (C_{Ar}-H), 127.8 (C_{Ar}-H), 127.2 (C_{Ar}-H), 98.28 (C_{Ar}-H), 96.44 (CH_2), 38.73 (CH_2), 38.49 (CH_2), 35.63 (CH_2), 32.95 (CH_2), 32.73 (CH_2), 21.38 (CH_3), 17.37 (CH_2), 17.33 (CH_2) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2921, 1755, 1609, 1433, 1013, 708 cm^{-1};

HRMS Calcd for $C_{13}H_{16}FO$ $[M + H]^+$ m/z 207.1180, Found: m/z 207.1180.

2-(4-chlorobenzyl)-2-fluorocyclopentan-1-one (106d)



106d

Colorless oil;

Yield = 70%;

$\boldsymbol{R_f}$ = 0.4 (silica gel, Petroleum ether/EtOAc = 95/5);

^{19}F NMR (376 MHz, $CDCl_3$): δ -154.02 (s) ppm;

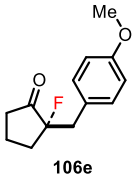
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.5 Hz, 2H, C_{Ar}-H), 7.16 (d, *J* = 8.3 Hz, 2H, C_{Ar}-H), 3.16 (t, *J* = 14.2 Hz, 1H, CH), 2.86 (dd, *J* = 28.4, 14.3 Hz, 1H, CH), 2.57 - 2.41 (m, 1H, CH), 2.31 – 2.15 (m, 1H, CH), 2.13 - 1.91 (m, 3H, CH), 1.90 - 1.72 (m, 1H, CH) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 212.5 (C=O), 133.2 (C_{Ar}-H), 133.1 (C_{Ar}-H), 131.6 (C_{Ar}-H), 131.6 (C_{Ar}-H), 128.7 (C_{Ar}-H), 98.22 (CH_2), 95.77 (CH_2), 38.11 (CH_2), 37.78 (CH_2), 35.56 (CH_2), 33.01 (CH_2), 32.72 (CH_2), 17.40 (CH_2), 17.36 (CH_2) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2987, 2949, 1489, 1249, 1093, 1013, 908, 836 cm^{-1};

HRMS Calcd for $C_{12}H_{13}ClFO$ $[M + H]^+$ m/z 227.0633, Found: m/z 227.1431.

2-fluoro-2-(4-methoxybenzyl) cyclopentan-1-one (106e)



106e

Colorless oil;

Yield = 80%;

$\boldsymbol{R_f}$ = 0.5 (silica gel, Petroleum ether/Et_2O = 95/5);

^{19}F NMR (376 MHz, $CDCl_3$): δ -153.34 ppm;

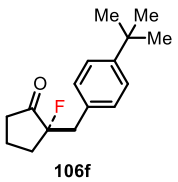
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 - 7.09 (m, 2H, C_{Ar}-H), 6.86 - 6.82 (m, 2H, C_{Ar}-H), 3.79 (s, 3H, C_{Ar}-H), 3.08 (t, *J* = 14.1 Hz, 1H, CH), 2.86 (dd, *J* = 27.3, 14.2 Hz, 1H, CH), 2.48 - 2.37 (m, 1H, CH), 2.17 (dddd, *J* = 19.5, 9.2, 6.6, 2.5 Hz, 1H, CH), 2.08 - 1.94 (m, 3H, CH), 1.76 - 1.66 (m, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 213.2 (C=O), 213.1(C_q), 158.8 (C_{Ar}-H), 131.2 (C_{Ar}-H), 126.5 (C_{Ar}-H), 113.9 (C_{Ar}-H), 98.33 (CH_2), 96.50 (CH_2), 55.24 (CH_3), 37.98 (CH_2), 37.73 (CH_2), 35.67 (CH_2), 32.88 (CH_2), 32.67 (CH_2), 17.34 (CH_2), 17.31(CH_2) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2958, 2921, 2360, 2341, 1754, 1513, 1250, 1031, 830 cm^{-1};

HRMS Calcd for $C_{13}H_{16}FO_2$ $[M + H]^+$ m/z 223.1129, Found: m/z 223.1129.

2-(4-(tert-butyl) benzyl)-2-fluorocyclopentan-1-one (106f)



106f

Colorless liquid;

Yield = 87%;

$\boldsymbol{R_f}$ = 0.5 (silica gel, Petroleum ether/Et_2O = 95/5);

^{19}F NMR (376 MHz, $CDCl_3$): δ -153.6 ppm;

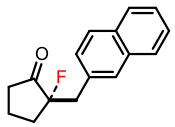
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 - 7.30 (m, 2H, C_{Ar}-H), 7.17 - 7.11 (m, 2H, C_{Ar}-H), 3.12 (t, *J* = 14.1 Hz, 1H, CH), 2.86 (dd, *J* = 28.5, 14.2 Hz, 1H, CH), 2.48 - 2.39 (m, 1H, CH), 2.26 - 2.14 (m, 1H, CH), 2.08 - 1.95 (m, 3H, CH), 1.78 - 1.70 (m, 1H, CH), 1.31 (s, 9H, CH);

^{13}C NMR (101 MHz, $CDCl_3$): δ 213.2 (C=O), 149.9 (C_{Ar}-H), 131.5 (C_{Ar}-H), 131.5 (C_{Ar}-H), 129.9 (C_{Ar}-H), 125.4 (C_{Ar}-H), 98.35 (CH_2), 96.51 (CH_2), 38.23 (C_q), 37.99 (CH_2), 35.60 (CH_2), 34.45 (CH_2), 32.93 (CH_2), 32.71 (CH_2), 31.34 (CH_3), 17.35 (CH_3), 17.32 (CH_3) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2960, 2868, 1756, 1364, 1198, 1067, 1002, 921, 854, 756, 674 cm^{-1};

HRMS Calcd for $C_{16}H_{25}FNO$ $[M + NH_4]^+$ m/z 249.1600, Found: m/z 249.1250.

2-fluoro-2-(naphthalen-2-ylmethyl) cyclopentan-1-one (106g)



106g

Colorless liquid;

Yield = 80%;

R_f = 0.4 (silica gel, Petroleum ether/Et_2O = 95/5);

^{19}F NMR (376 MHz, $CDCl_3$): δ -152.8 ppm;

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 – 7.75 (m, 3H, C_{Ar}-H), 7.69 – 7.65 (m, 1H, C_{Ar}-H), 7.52 – 7.44 (m, 2H, C_{Ar}-H), 7.34 (dt, *J* = 8.3, 1.3 Hz, 1H, C_{Ar}-H), 3.32 (t, *J* = 14.1 Hz, 1H, CH), 3.07 (dd, *J* = 27.4, 14.1 Hz, 1H, CH), 2.53 – 2.41 (m, 1H, CH), 2.26 – 2.11 (m, 1H, CH), 2.12 – 1.91 (m, 3H, CH), 1.79 – 1.68 (m, 1H, CH) ppm;

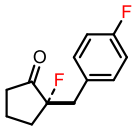
^{13}C NMR (75 MHz, $CDCl_3$): δ 212.9 (C=O), 133.4 (C_{Ar}-H), 132.5 (C_{Ar}-H), 132.3 (C_{Ar}-H), 132.2 (C_{Ar}-H), 129.0 (C_{Ar}-H), 128.3 (C_{Ar}-H), 128.1 (C_{Ar}-H), 127.7 (C_{Ar}-H), 126.2 (C_{Ar}-H),

125.8 (C_{Ar}-H), 98.66 (C_{Ar}-H), 96.21 (CH_2), 38.97 (CH_2), 38.64 (CH_2), 35.66 (CH_2), 33.06 (CH_2), 32.78 (CH_2), 17.45 (CH_2), 17.40 (CH_2) ppm;

IR (film) $\tilde{\nu}_{max}$ = 3483, 3060, 2980, 2050, 1799, 1575, 1430, 1306, 1240, 965, 713 cm^{-1};

HRMS Calcd for $C_{16}H_{15}FO$ $[M]^+$ m/z 242.1107, Found: m/z 242.1176.

2-fluoro-2-(4-fluorobenzyl) cyclopentan-1-one (106h)



106h

Colorless liquid;

Yield = 92%;

$\boldsymbol{R_f}$ = 0.6 (silica gel, petroleum ether/EtOAc = 91/9);

^{19}F NMR (376 MHz, $CDCl_3$): δ -115.7, -154.1 ppm;

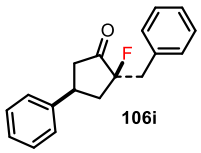
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (dd, *J* = 8.2, 5.6 Hz, 2H, C_{Ar}-H), 6.99 (t, *J* = 8.6 Hz, 2H, C_{Ar}-H), 3.13 (t, *J* = 14.3 Hz, 1H, CH_2), 2.85 (dd, *J* = 28.4, 14.4 Hz, 1H, CH_2), 2.51 – 2.40 (m, 1H, CH), 2.20 (dtd, *J* = 15.8, 7.3, 6.3, 2.8 Hz, 1H, CH), 2.10 – 1.89 (m, 3H, CH), 1.75 (dh, *J* = 16.9, 5.3 Hz, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 212.7 (C=O), 160.9 (C_{Ar}-H), 131.8 (C_{Ar}-H), 131.7 (C_{Ar}-H), 130.4 (C_{Ar}-H), 130.3 (C_{Ar}-H), 130.3 (C_{Ar}-H), 115.5 (C_{Ar}-H), 115.2 (C_{Ar}-H), 37.91 (CH_2), 37.67 (CH_2), 35.58 (CH_2), 32.93 (CH_2), 32.72 (CH_2), 17.37 (CH_2), 17.33 (CH_2) ppm;

IR (film) $\tilde{\nu}_{max}$ = 3478, 3055, 2979, 2898, 1759, 1509, 1223, 1161, 1013, 844, 759, 697 cm^{-1};

HRMS Calcd for $C_{12}H_{13}F_2O$ $[M + H]^+$ m/z 211.0929, Found: m/z 211.0932.

2-benzyl-2-fluoro-4-phenylcyclopentan-1-one (106i)



106i

Colorless liquid;

Yield = 80%;

cis: trans = 80:20;

R_f = 0.4 (silica gel, petroleum ether/Et_2O = 95/5);

^{19}F NMR (376 MHz, $CDCl_3$): δ -148.64, -153.52 ppm;

Analytical data for the major cis-isomer **106j**:

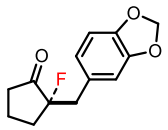
^{1}H NMR (400 MHz,$CDCl_3$): δ 7.71 - 7.66 (m, 2H, C_{Ar}-H), 7.46 - 7.24 (m, 2H, C_{Ar}-H), 7.19 (d, *J* = 7.4 Hz, 6H, C_{Ar}-H), 3.35 (t, *J* = 13.5 Hz, 1H, CH_2), 3.22 (t, *J* = 14.6 Hz, 3H, CH_2), 3.14 - 2.92 (m, 8H, CH), 2.77 (dd, *J* = 20.1, 8.6 Hz, 4H, CH), 2.69 - 2.61 (m, 3H, CH), 2.54 (dd, *J* = 19.2, 11.2 Hz, 3H, CH), 2.26 - 2.11 (m, 3H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 212.3 (C=O), 141.9 (C_{Ar}-H), 141.0 (C_{Ar}-H), 134.3(C_{Ar}-H), 133.8 (C_{Ar}-H), 130.7(C_{Ar}-H), 128.9(C_{Ar}-H), 128.6(C_{Ar}-H), 128.5 (C_{Ar}-H), 127.4 (C_{Ar}-H), 127.2 (C_{Ar}-H), 127.1 (C_{Ar}-H), 126.9 (C_{Ar}-H), 126.6 (C_{Ar}-H), 99.40 (C_{Ar}-H), 97.48 (C_{Ar}-H), 96.67 (C_{Ar}-H), 94.79 (C_{Ar}-H), 43.27 (CH_2), 43.26 (CH_2), 40.77 (CH), 40.53 (CH), 40.32 (CH_2), 40.12 (CH_2), 39.72 (CH_2), 39.47 (CH_2), 37.20 (CH_2), 36.96 (CH_2), 35.74 (CH_2), 35.67 (CH_2) ppm;

IR (film) $\tilde{\nu}_{max}$ = 3058, 2850, 2600, 2163, 1979, 1798, 1486, 1004, 740, 688 cm^{-1};

HRMS Calcd for $C_{18}H_{18}FO$ $[M + H]^+$ m/z 269.1336, Found: m/z 269.1337.

2-(benzo[d][1,3]dioxol-5-ylmethyl)-2-fluorocyclopentan-1-one (106j)



106j

Colorless liquid;

Yield = 87%;

$\boldsymbol{R_f}$ = 0.3 (silica gel, petroleum ether/Et_2O = 91/9);

^{19}F NMR (376 MHz, $CDCl_3$): δ -153.6 ppm;

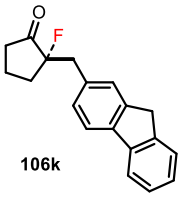
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (d, *J* = 7.9 Hz, 1H, C_{Ar}-H), 6.70 (s, 1H, C_{Ar}-H), 6.65 (s, 1H, C_{Ar}-H), 5.94 (s, 2H, CH_2), 3.05 (t, *J* = 14.3 Hz, 1H, CH), 2.81 (dd, *J* = 27.7, 14.3 Hz, 1H,CH), 2.48 – 2.39 (m, 1H, CH), 2.24 – 2.14 (m, 1H, CH), 2.07 – 1.94 (m, 3H, CH), 1.78 – 1.68 (m, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 212.9 (C=O), 147.7 (C_q), 146.7 (C_{Ar}-H), 128.1 (C_{Ar}-H), 123.3 (C_{Ar}-H), 110.5 (C_{Ar}-H), 108.2 (C_{Ar}-H), 101.0 (CH_2), 98.25 (CH_2), 96.41 (CH_2), 38.45 (CH_2), 38.21 (CH_2), 35.61 (CH_2), 32.88 (CH_2), 32.66 (CH_2), 17.36 (CH_2), 17.32 (CH_2) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2988, 2892, 2794, 1745, 1489, 1443, 1306, 1215, 1136, 971, 892, 717, cm^{-1};

HRMS Calcd for $C_{13}H_{14}FO_3$ $[M + H]^+$ m/z 237.0921, Found: m/z 237.0923.

2-((9H-fluoren-2-yl) methyl)-2-fluorocyclopentan-1-one (106k)



106k

Colorless liquid;

Yield = 96%;

R_f = 0.5 (silica gel, petroleum ether/Et_2O = 91/9);

^{19}F NMR (376 MHz, $CDCl_3$): δ -152.9 ppm;

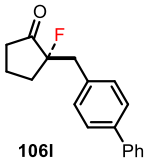
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.5 Hz, 1H, C_{Ar}-H), 7.72 (d, *J* = 7.8 Hz, 1H, C_{Ar}-H), 7.54 (d, *J* = 7.4 Hz, 1H, C_{Ar}-H), 7.39 (s, 1H, C_{Ar}-H), 7.37 (d, *J* = 7.4 Hz, 1H, C_{Ar}-H), 7.31 (d, *J* = 6.8 Hz, 1H, C_{Ar}-H), 7.27 (d, *J* = 9.8 Hz, 1H, C_{Ar}-H), 7.21 (d, *J* = 7.7 Hz, 1H, C_{Ar}-H), 3.88 (s, 2H, CH), 3.22 (t, *J* = 14.1 Hz, 1H, CH), 2.99 (dd, *J* = 27.3, 14.1 Hz, 1H, CH), 2.45 (ddd, *J* = 19.2, 8.6, 5.7 Hz, 1H, CH), 2.28 – 2.12 (m, 1H, CH), 2.04 (ddd, *J* = 30.9, 16.3, 7.5 Hz, 3H, CH), 1.73 (dq, *J* = 12.7, 6.2 Hz, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 213.1 (C=O), 143.6 (C_q), 143.2 (C_{Ar}-H), 141.3 (C_{Ar}-H), 140.7 (C_q), 133.1 (C_{Ar}-H), 133.0 (C_{Ar}-H), 128.8 (C_{Ar}-H), 126.9 (C_{Ar}-H), 126.8 (C_{Ar}-H), 126.7 (C_{Ar}-H), 125.0 (C_{Ar}-H), 119.8 (C_{Ar}-H), 119.7 (C_{Ar}-H), 98.40 (C_{Ar}-H), 96.57 (C_{Ar}-H), 39.00 (CH_2), 38.75 (CH_2), 36.85 (CH_2), 35.69 (CH_2), 32.99 (CH_2), 32.78 (CH_2), 17.40 (CH_2), 17.36 (CH_2) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2988, 2892, 2149, 1753, 1455, 1400, 1010, 836, 745 cm^{-1};

HRMS Calcd for $C_{19}H_{18}FO$ $[M + H]^+$ m/z 281.1336, Found: m/z 281.1337.

2-([1, 1'-biphenyl]-4-ylmethyl)-2-fluorocyclopentan-1-one (106l)



106l

Colorless liquid;

Yield = 95%;

R_f = 0.5 (silica gel, Petroleum ether/Et_2O = 91/9);

^{19}F NMR (376 MHz, $CDCl_3$): δ -153.54 ppm;

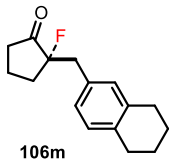
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.1 Hz, 2H, C_{Ar}-H), 7.54 (d, *J* = 8.2 Hz, 2H, C_{Ar}-H), 7.44 (t, *J* = 7.5 Hz, 2H, C_{Ar}-H), 7.35 (t, *J* = 7.3 Hz, 1H, C_{Ar}-H), 7.29 (d, *J* = 8.0 Hz, 2H, C_{Ar}-H), 3.20 (t, *J* = 14.1 Hz, 1H, CH), 2.94 (dd, *J* = 28.2, 14.1 Hz, 1H, CH), 2.55 – 2.41 (m, 1H, CH), 2.29 – 2.16 (m, 1H, CH), 2.14 – 1.96 (m, 3H, CH), 1.78 (dt, *J* = 8.9, 6.0 Hz, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 212.9 (C=O), 140.6 (C_q), 140.0 (C_{Ar}-H), 133.7 (C_{Ar}-H), 133.6 (C_{Ar}-H), 130.6 (C_{Ar}-H), 128.8 (C_{Ar}-H), 127.3 (C_{Ar}-H), 127.1 (C_{Ar}-H), 127.0 (C_{Ar}-H), 98.24 (C_{Ar}-H), 96.41 (C_{Ar}-H), 38.43 (CH_2), 38.18 (CH_2), 35.64 (CH_2), 33.02 (CH_2), 32.80 (CH_2), 17.42 (CH_2), 17.39 (CH_2) ppm;

IR (film) $\tilde{\nu}_{max}$ = 3485, 3032, 2981, 2920, 2890, 1751, 1486, 1004, 739, 687 cm^{-1};

HRMS Calcd for $C_{18}H_{18}FO$ $[M + H]^+$ m/z 269.1336, Found: m/z 269.1337.

2-fluoro-2-((5,6,7,8-tetrahydronaphthalen-2-yl)methyl)cyclopentan-1-one (106m)



106m

Colorless liquid;

Yield = 85%;

***R*$_f$** = 0.6 (silica gel, Petroleum ether/Et_2O = 91/9);

^{19}F NMR (376 MHz, $CDCl_3$): δ -153.46 ppm;

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (d, *J* = 7.6 Hz, 1H, C_{Ar}-H), 6.91 (d, *J* = 10.9 Hz, 2H, C_{Ar}-H), 6.90 (s, 1H, C_{Ar}-H), 3.07 (t, *J* = 14.1 Hz, 1H, CH), 2.89 – 2.78 (m, 1H, CH), 2.74 (s,

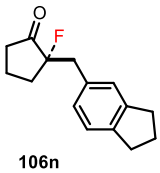
4H, CH), 2.43 (ddd, *J* = 19.5, 8.5, 5.8 Hz, 1H, CH), 2.24 – 2.14 (m, 1H, CH), 2.06 (t, *J* = 6.6 Hz, 1H, CH), 1.98 (dd, *J* = 20.0, 5.6 Hz, 2H, CH), 1.81 – 1.68 (m, 6H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 213.2 (C=O), 137.2 (C_{Ar}-H), 135.9 (C_{Ar}-H), 131.4 (C_{Ar}-H), 130.9 (C_{Ar}-H), 129.2 (C_{Ar}-H), 127.3 (C_{Ar}-H), 98.36 (C_q), 38.39 (CH_2), 38.15 (CH_2), 35.64 (CH_2), 32.93 (CH_2), 32.71 (CH_2), 29.37 (CH_2), 29.05 (CH_2), 23.20 (CH_2), 23.16 (CH_2), 17.38 (CH_2), 17.34 (CH_2) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2925, 2857, 1754, 1503, 1436, 1163, 1002, 827, 748 cm^{-1};

HRMS Calcd for $C_{16}H_{20}FO$ $[M + H]^+$ m/z 247.1493, Found: m/z 247.1495.

2-((2, 3-dihydro-1H-inden-5-yl)methyl)-2-fluorocyclopentan-1-one (106n)



106n

Colorless liquid;

Yield = 87%;

***R*$_f$** = 0.6 (silica gel, Petroleum ether/Et_2O = 91/9);

^{19}F NMR (376 MHz, $CDCl_3$): δ -153.40 ppm;

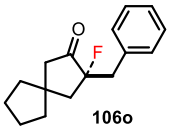
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, *J* = 7.6 Hz, 1H, C_{Ar}-H), 7.07 (s, 1H, C_{Ar}-H), 6.96 (d, *J* = 7.5 Hz, 1H, C_{Ar}-H), 3.11 (t, *J* = 14.1 Hz, 1H, CH), 2.93 - 2.82 (m, 6H, CH), 2.48 - 2.39 (m, 1H, CH), 2.24 - 2.14 (m, 1H, CH), 2.11 - 2.03 (m, 3H, CH), 1.99 (dq, *J* = 14.5, 7.5, 6.7 Hz, 2H, CH), 1.78 - 1.68 (m, 1H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 213.2 (C=O), 144.6 (C_{Ar}-H), 143.0 (C_{Ar}-H), 132.2 (C_{Ar}-H), 128.0 (C_{Ar}-H), 126.2 (C_{Ar}-H), 124.2 (C_{Ar}-H), 98.41 (C_q), 38.63 (CH_2), 38.38 (CH_2), 35.65 (CH_2), 32.92 (CH_2), 32.79 (CH_2), 32.53 (CH_2), 25.46 (CH_2), 17.37 (CH_2) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2948, 2845, 1754, 1491, 1437, 1163, 1002, 825, 731 cm^{-1};

HRMS Calcd for $C_{15}H_{18}FO$ $[M + H]^+$ m/z 233.1336, Found: m/z 233.1338.

3-fluoro-3-(4-methylbenzyl)spiro[4.4]nonan-2-one (106o)



106o

Colorless liquid;

Yield = 50%;

R_f = 0.8 (silica gel, petroleum ether/Et_2O = 95/5);

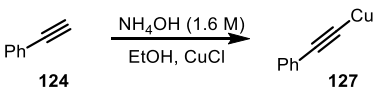
^{19}F NMR (376 MHz, $CDCl_3$): δ -145.34 ppm;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14-7.06 (m, 5H, C_{Ar}-H), 3.16 (t, *J* = 13.8 Hz, 1H, CH_2), 2.89-2.74 (m, 1H, CH), 2.46-2.36 (m, 2H, CH), 2.33 (s, 3H, CH), 2.15-2.07 (m, 1H, CH), 2.06-1.93 (m, 2H, CH), 1.62 (dddd, *J* = 19.0, 9.5, 5.3, 2.3 Hz, 4H, CH) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 212.8 (C=O), 131.8 (C_{Ar}-H), 130.2 (C_{Ar}-H), 129.7 (C_{Ar}-H), 99.08 (C_{Ar}-H), 97.26 (C_{Ar}-H), 50.21 (CH_2), 44.58 (CH_2), 44.37 (CH_2), 43.73 (CH_2), 39.71 (CH_2), 39.54 (CH_2), 39.40 (CH_2), 39.39 (CH_2), 39.01 (CH_2), 29.71 (CH_2), 24.07 (C_q), 23.87 (CH_2), 21.07 (CH_2) ppm;

IR (film) $\tilde{\nu}_{max}$ = 2924, 2853, 1755, 1453, 1030, 727, 700 cm^{-1};

Synthese procedures for copper phenylacetylide (127)



124 **127**

To a solution of CuI (20.0 mmol, 3.8 g, 2.0 equiv.) in a mixture of NH_4OH (28% NH_3

solution, 1.6 M, 50 mL) and EtOH (30 mL) was added the phenylacetylene **124** (10.0 mmol) with dropwise. The deep blue reaction mixture was stirred under argon overnight at room temperature and the yellow precipitate was collected by filtration and then washed with NH_4OH (10% NH_3 solution, 3 × 50 mL), H_2O (3 × 50 mL), EtOH (3 × 50 mL), and Et_2O (3 × 50 mL). The bright yellow solid was then dried under high vacuum overnight to afford the desired copper acetylide **127**, which was used in the next step without further purification.

The physical and spectroscopic data is in accordance to these reported in the literature. [103]

IV. Abbreviations

Ad	Adamantyl
Add.	Additives
Aq.	Aqueous
Ar	Aryl (substituted aromatic ring)
BINOL	1,1'-bi-2,2'-naphthol
Bipy	2, 2'-bipyridyl
Bn.	Benzyl
Boc.	*t*-butoxycarbonyl
Bu	Butyl
Bz	Benzoyl
Cata	Catalyst
Conc. (c)	Concentrated
$CDCl_3$	Chloroform-*d*
C_6D_6	Benzene-*d6*
CuI	Copper (I) iodide
DCM	Dichloromethane
DMF	Dimethylformamide
d.r.	Diastereomer ratio
Dest	Destilliert (Distilled)
DIPEA	Diisopropylethylamine
DIAD	Diisopropylazodicarboxylate
DMSO	Dimethyl sulfoxide
$(DHQ)_2PHAL$	Bis(dihydroquinino)phthalazine
$(DHQD)_2PHAL$	Bis(dihydroquinidino)phthalazine
DMAD	Dimethyl acetylene dicarboxylate
Equiv.	Equivalent
e.e.	Enantiomeric excess

e.r.	Enantiomeric ratio
EtOH	Ethanol
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EWG	Electron-withdrawing group
Et_3N	Triethylamine
ESI	Electronspray ionization
Et	Ethyl-
GC-MS	Gas chromatography-mass spectrometry
HOMO	Highest occupied molecular orbital
HMBC	Heteronuclear Multiple Bond Correlation
HRMS	High-resolution mass spectrometry
h	Hours (length of reaction time)
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HPLC	High-pressure liquid chromatography
HSQC	Heteronuclear Single Quantum Coherence
IR	Infrared spectroscopy
i-Pr	Isopropyl
I_2	Iodine
LiOH	Lithium hydroxide
LUMO	lowest unoccupied molecular orbital
Me	Methyl
Ms.	Mesyl (methane sulfonyl)
$MgSO_4$	Magnesium sulfate
m.p.	Melting point
MeCN	Acetonitrile
MeOH	Methanol
min.	Minute
NBS	*N*-bromosuccinimide
n.r.(n.d.)	No reaction(not detected)

$NaHCO_3$	Sodium bicarbonate
$Na_2S_2O_3$	Sodium thiosulfate
Na_2SO_4	Sodium sulfate
NMR	Nuclear Magnetic Resonance
PE	Petrol ether (bp. 40-65 ℃)
r.t.	Room temperature
R_f	Retention factor
R	R-configuration
S	S-configuration
THF	Tetrahydrofuran
Sat.	Saturate
$SOCl_2$	Thionyl chloride
Ts.	(Tos) *p*-toluenesulfonyl
T	Temperature
*t*Bu	*Tert*-butyl
*t*BuLi	*Tert*-butyl Lithium
TLC	Thin layer chromatography
TBAF	Tetra-*n*-butyl ammonium fluoride
TFA	Trifluoroacetic acid
R.S.M. (r.s.m.)	Recovery of the starting material
UV	Ultraviolet

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VII. Publications

1. Wang, W. -Y.,[1] Ayan, D.,[1] Hypervalent λ^3-Iodane Catalyzed Bromonium-Induced Reactions for the Preparation of Bicyclic Isoxazoles. *In Preparation*.

2. Wang, W. -Y.,[1] Zhao, P. -Y.,[1] Hypervalent λ^3-Fluoro Iodane Triggered Unusual Semipinacol Rearrangements: Efficient Synthesis of α-Quaternary Fluoroketones. *In Preparation.*

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