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Asymmetric Catalysis

Axially Chiral 1,1′-Binaphthyl-2-Carboxylic Acid (BINA-Cox) as Ligands for Titanium-Catalyzed Asymmetric Hydroalkoxylation

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Abstract: Axially chiral, enantiopure 1,1′-binaphthyl-2-carboxylic acids (BINA-Cox) have recently been introduced as chiral ligands for transition metal catalysis. Together with equimolar, co-catalytic amounts of $Ti(OiPr)_4$ and water they form an in situ catalyst that performs the asymmetric catalytic hydroalkoxylation of 2-allylphenols to 2-methylcoumarans at high temperature (240 °C, microwave heating). The synthesis of reference ligand 2′-MeO-BINA-Cox (**L1**) has been optimized and performed at molar scale. Synthetic routes have been developed to access a variety of substituted BINA-Cox ligands (>30 examples), which have been tested for ligand effects on the reference asymmetric cyclization of 2-allylphenol. The substrate range of asymmetric catalytic hydroalkoxylation has been explored through systematic substrate structure variations to define scope and limitations of the titanium-catalyzed process. The new substrates 2-(1-vinylcycloalkyl)phenols (**1j**, **1k**), 2-(2-vinylphenyl)propan-2-ol (**1t**), and 2′-vinyl-[1,1′-biphenyl]-2-ol (**1u**) are shown to undergo asymmetric catalytic cyclization to benzodihydrofurans and benzo[*c*]chromene, respectively.

Introduction

Chiral steering ligands for asymmetric catalysis with transition metal compounds mostly rely on phosphane, phosphite, heterocyclic imine, amine, imine, *N*-heterocyclic carbene, alkene, alcohol or phenol donors, and combinations thereof.[1] Chiral carboxylic acids are currently much less developed, even if their potential is evident through uses of $Rh_2(O_2CR^*)_4$ complexes based on α-amidocarboxylic acids as catalysts in asymmetric metal-carbenoid induced reactions (Figure 1),[2] or of similar α-amidocarboxylic acids in asymmetric palladium-catalyzed C–H-coupling reactions.[3,4] Aside from a plethora of applications of bifunctional aminocarboxylic acids in enamine type organocatalysis,[5] unifunctional chiral carboxylic acids have been explored as metal-free chiral Brønsted acid catalysts,[6] and among those, designer 1,1′-binaphthyl-2,2′-dicarboxylic acids (BINA-DiCox) with 3,3′-diarylsubstitution have shown particular versatility.[7–9] Axially chiral 1,1-binaphthyl-2-monocarboxylic acids including MeO-BINA-Cox[10,11] and MNCB (2-{2′-methoxy-1′-naphthyl}-3,5-dichlorobenzoic acid)[12] have been synthetically developed and investigated for use as chiral derivatizing reagents for absolute configuration determination by NMR spectroscopy,[12,13] as chiral inductors in polymer chemistry,[14,15] and as building blocks for accessing chiral ligands.[9b,16–18]

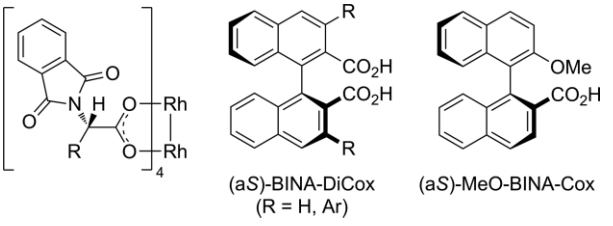
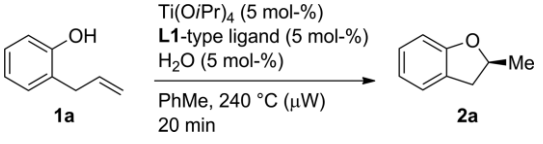


Figure 1. Examples of chiral carboxylic acids used in asymmetric catalysis, either as ligands for transition metals, or as chiral organocatalysts.

We have recently described an intramolecular asymmetric catalytic hydroalkoxylation of 2-allylphenols (**1**) to 2-methylcoumarans (**2**) that is catalyzed by a peculiar titanium complex generated by mixing $Ti(OR)_4$, the axially chiral carboxylic acid MeO-BINA-Cox (**L1**) and H_2O in a 1:1:1 ratio.[19] The process is an example of asymmetric catalytic hydrofunctionalization, and a rare example of asymmetric catalysis with high enantioselectivity at the exceptionally high reaction temperature of 240 °C (*HOT-CAT*, homogeneous thermal catalysis; Scheme 1).[20]



Scheme 1. Asymmetric titanium-carboxylate catalyzed hydroalkoxylation of 2-allylphenol.

The ligand-effect in the titanium-carboxylate-catalyzed reaction is critical, and preliminary ligand variation studies covering

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a number of chiral *O,O*-, *N,N*- or *O,N*- potentially chelate-forming ligands failed to induce notable activity or any enantioselectivity. Another round of ligand screening that focused on combinations of titanium alkoxide with a variety of simple bifunctional chiral carboxylic acids (including proline, *N*-anisoylprolines (*o*-, *m*-, *p*-anisoyl isomers), mandelic acid, mandelic acid *O*-methyl ether, camphoric acid, camphoric acid monoamides) likewise failed to show catalytic activity.[21] After such unsuccessful forays into alternative basic ligand structures, it transpired that the 1,1′-biaryl-2-carboxylic acid skeleton should be conserved. A first successful ligand variation involved the substitution of H-6′ in 2-MeO-BINA-Cox (**L1**), by a *tert*-butyl group (**L18**), which slightly increased both activity and enantioselectivity of the model reaction.[19] The goal for further ligand variation studies was to retain the biaryl-2′-alkoxy-2-carboxylic acid substructure and substitute any available position. Since the number of readily accessible, enantiopure biaryl-carboxylic acids is limited, new synthetic routes had to be developed to access the desired products, either by de novo asymmetric synthesis, or by substitution of the more readily available enantiopure MeO-BINA-Cox (**L1**).

Here, we first present the various synthetic approaches that we have followed to prepare a variety of C_1-symmetric axially chiral, enantiopure biarylcarboxylic acids. Next, their evaluation as ligands in titanium-catalyzed asymmetric hydroalkoxylation in the model cyclization of 2-allylphenol to 2-methylcoumaran will be compared; finally, we present studies towards the extension of the substrate range in the titanium-carboxylate catalyzed asymmetric catalytic hydroalkoxylation.

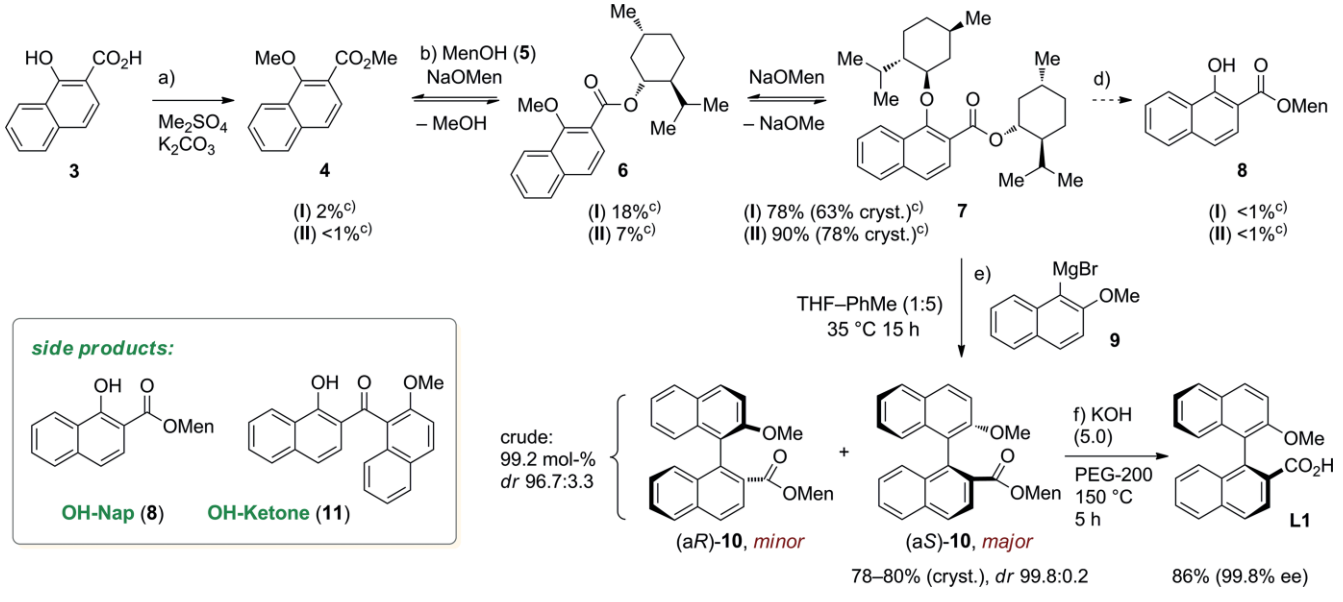
Results and Discussion

Scaled Synthesis of MeO-BINA-Cox (L1)

Syntheses of unsymmetrical 1,1′-binaphthyl-2-carboxylic acids mostly proceed along a few key routes, exemplified by:[22] (I) Coupling approaches, such as Ullmann coupling of 1-halo-2-naphthoic acid derivatives to BINA-DiCox derivatives,[23] or cross-coupling of 1-metalated 2-methylnaphthalene to 2-methyl-1,1-binaphthyls,[22] followed by oxidation ($CH_3 \rightarrow CO_2H$).[11] (II) S_NAr reactions of 1-naphthyl Grignard reagents with 1-alkoxy-2-naphthoates or 1-alkoxy-2-naphthyl-oxazolines, developed by Meyers,[24] Cram,[10] and Miyano,[25] which afford enantiomerically or diastereomerically enriched BINA-Cox derivatives if chiral alkoxy leaving groups are present.[26] (III) Partial syntheses of BINA-DiCox or BINA-Cox derivatives from 2,2′-BINOL by alkoxycarbonylation of sulfonates,[22,27,28] reductive carboxylation of phosphates,[29] or alternatively via Sandmeyer cyanation of the bis-diazonium salt from 2,2-diamino-1,1′-binaphthyl.[23b] (IV) Progress has also been achieved in asymmetric catalytic syntheses of biaryl-2-carboxylic acids (or potential precursor aldehydes), as for example through Suzuki biaryl couplings,[30] oxidative phenol coupling,[31] phenol–quinone coupling,[32] alkyne trimerization,[33] or asymmetric aldol condensation.[34]

An evaluation of such pathways pointed to Miyano's synthesis of (a*S*)-2′-methoxy-(1,1′-binaphthyl)-2-carboxylic acid (MeO-BINA-Cox; **L1**) as the best option for establishing an economic, scalable and enantioselective route to binaphthyl-2-carboxylic acid derivatives, and that **L1** could then serve as synthetic platform to access modified ligand structures.

The Miyano synthesis of **L1** involves a key S_NAr-reaction of 1-naphthylmagnesium bromide (**9**) with menthyl 1-menthyloxy-2-napthoate (**7**; Scheme 2),[25] in which the etheric menthyloxy leaving group is responsible for induction,[10] and the menthyl ester suppresses acyl substitution through shielding of the ester carbonyl.[35] The methodology has been applied by other groups,[14,16a–16c,17] and we also got satisfactory results at small scale. Various issues emerged upon scale-up, which were resolved step by step: Methylation of acid **3** to methoxyester **4**



Scheme 2. Synthesis of (a*S*)-2′-methoxy-(1,1′-binaphthyl)-2-carboxylic acid (MeO-BINA-Cox; **L1**). a) Me_2SO_4 (2.1 equiv.), K_2CO_3 (2.2 equiv.), acetone, 50 °C, 7 h; 96 %. b) MenOH (2.5 equiv.), NaOMen (0.5 equiv.), DMF, (**II**). c) (**I**) 250 mmol scale, 60 °C, 2 h static conditions, then 2.5 h of slow solvent distillation; (**II**) 750 mmol scale, 60 °C, 1 h static conditions, 3 h slow solvent distillation, new solvent addition, 2.5 h slow distillation. d) Side reaction. e) **9** (1.2 equiv.), toluene, 35 °C, 15 h. f) KOH (5.0 equiv.), PEG-200, 150 °C; 5 h. Men = menthyl, based on menthol or (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexanol.

with methyl iodide in DMF[25] is uneconomic. Equally good results were obtained with Me_2SO_4–K_2CO_3 in acetone (Scheme 2, a). The methoxy groups of **4** next are exchanged with (1*R*)-menthol (**5**) under basic conditions. The reported procedure uses three molar equivalents of sodium menthoxide to push the alkoxy-exchange equilibrium[36] towards product **7**.[25] The handling and use of NaH for generating the menthoxide base becomes unsafe and wasteful at large scale. We considered performing a catalytic alkoxide exchange with substoichiometric amounts of base, since the exchange product methoxide can be regenerated to sodium menthoxide by reaction with menthol and release of methanol. To drive the reaction towards product **7**, methanol as the most volatile component may be removed from the reaction equilibrium.

In our experiments, sodium menthoxide (NaOMen) was generated by stirring 50 mol-% of sodium metal in excess (2.5 equivalents) molten menthol (**5**) at 190 °C.[37] After cooling, the exchange reaction was performed in DMF solution by addition of **4**. NMR analyses showed that a rapid transesterification to methoxy-menthyl ester **6** occurs, followed by the slower S_NAr-alkoxy-exchange to **7**. Dealkylation to **8** occurs as side-reaction at higher temperature, but remains insignificant (<1 mol-% **8**) at ≤60 °C. A dynamic vacuum (15 mbar) was applied to induce slow distillation of MeOH–DMF from the reaction mixture, presumably as an azeotrope.[38] Plenty of product **7** emerged in the process, but a portion of **6** remained unreacted (Scheme 2, **I**). Renewed addition of DMF to the concentrated reaction mixture, followed by a second dynamic vacuum distillation raised the conversion to 90 mol-% (Scheme 2, **II**).[39] Crystallization of the reaction mixture from ethanol gave pure **7** at molar scale in 78 % yield, matching the result of the reaction with excess base.[25]

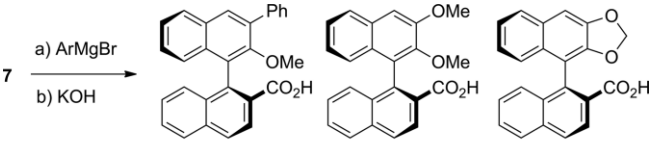
The precursor 1-bromo-2-methoxynaphthalene required for the key S_NAr-reaction (via Grignard reagent **9**) has often been prepared by methyl iodide alkylation from commercial 1-bromo-2-naphthol.[40] A more economic access at large scale is by bromination of the fragrant compound 2-methoxynaphthalene, which is high-yielding and selective when performed in acetic acid as solvent (see Table S3 for variations).[41]

We were now in a position to approach the critical, diastereoselective S_NAr coupling step of **7** and Grignard reagent **9** to give (a*S*)-**10**. The scale-up of the reaction met with some difficulties, starting with the limited solubility of **9**, which complicated its transfer to the reaction vessel and required using large amounts of solvent. In the actual S_NAr reaction with **7**, incomplete conversion was often noted even after extending the reaction time to several days. Heating such reactions with the aim to raise the conversion of **7** induced dealkylation to **8** instead. Unfortunately, neither the original methodological work[25,42] nor later applications[14,16a–16c,17] reported on the impact of specific reaction parameters on the reaction. To learn about effects of specific variables on stereoselectivity and yield, data from published examples[17,25] was collected and supplemented with selected new experiments, in which we analyzed the composition of crude reaction mixtures by qNMR methods (Table S4; Scheme 2, c). The strategy of Miyano et al. to work in a low-polarity medium (Et_2O–PhH; Table S4, entry I, II)[25,43] at high dilution (0.05 M), while seemingly optimal to support the chelated transition state of the stereoselective reaction,[25,26b] is inconvenient for scale-up considering the resulting large reaction volumes. Hoveyda et al. had obtained equally good results in THF–PhH at 0.25 M (entry III),[17] which implies that neither the low polarity of co-solvent ether nor high dilution are necessary. To circumvent solubility issues with Grignard reagent **9**, we generated the latter in situ from aryl bromide and magnesium in the presence of substrate **7**, but this resulted in a low yield of **10**, and reductive C–O-cleavage in **7** to **8** became the major reaction pathway (Scheme 2, d; Table S4, entries 2, 3).[44] It emerged that reagent **9** is best prepared separately at 1 mol/L in THF–toluene (1:5) and transferred while still hot (at 50 °C, to prevent crystallization) into a solution of **7** in toluene. Remarkable analytical yields of 99 % of **10** with a *dr* (a*S*:a*R*) of 97:3 were thus achieved at a reaction concentration of 0.5 M (based on initial **7**) by applying a slight excess of **9** at 35 °C (Scheme 2, e and Table S4, entries 5–8). Precipitation of the crude product and recrystallization gave very satisfactory yields of (a*S*)-**10** (*dr* ≥99.8:0.2) at scales up to 0.4 mol with no need for chromatography (Scheme 2, e; Table S4, entry 8).

Finally, saponification of ester **10** to MeO-BINA-Cox (**L1**) with 50–70 equivalents of KOH in hot (80 °C) ethanol is wasteful at large scale. To speed up hydrolysis, we intensified the reaction conditions by working in polyethylene glycol (PEG-200) at 150 °C, which effected hydrolysis within a few hours with only 5 equivalents of base (Scheme 2, f; for additional tests of conditions, see Table S5). The product was precipitated by acidification and recrystallized to raise the *ee* of (a*S*)-**L1** to ≥99.7 %, as determined by Fukushi's ^1H NMR shift method with nicotine as chiral base.[45] This step was also readily scaled with one example performed at 0.25 mol and providing 80 g of **L1**. The overall yield of **L1** from **3** was 51 % over 5 steps, and all purification steps are performed either by distillation or recrystallization, with no need for chromatography.

Structural Modifications of MeO-BINA-Cox Ligands

The singular success of MeO-BINA-Cox (**L1**) as ligand in the titanium catalyzed intramolecular asymmetric hydroalkoxylation (cf. Scheme 1)[19] created a demand for incremental structure variations of the basic ligand structure, whose defining element is an axially chiral 1,1′-biaryl-2′-alkoxy-2-carboxylic acid. The following sections present various synthetic approaches towards such modified structures.



Scheme 3. De novo asymmetric synthesis of **L2–4** from **7**. a) ArMgBr (0.8–1.0); THF, 66 °C, 1 h for **L2**, PhMe, 50 °C, 60 h for **L3**, THF–PhMe (1:3), 80 °C, 1 h for **L4**. b) KOH (5.0); EtOH, 80 °C, 48 h for **L2**, PEG-200, 150 °C, 5 h for **L3**, PEG-200, 150 °C, 20 h for **L4**.

De Novo Asymmetric Syntheses of 1,1′-Biaryl-2-carboxylic Acids

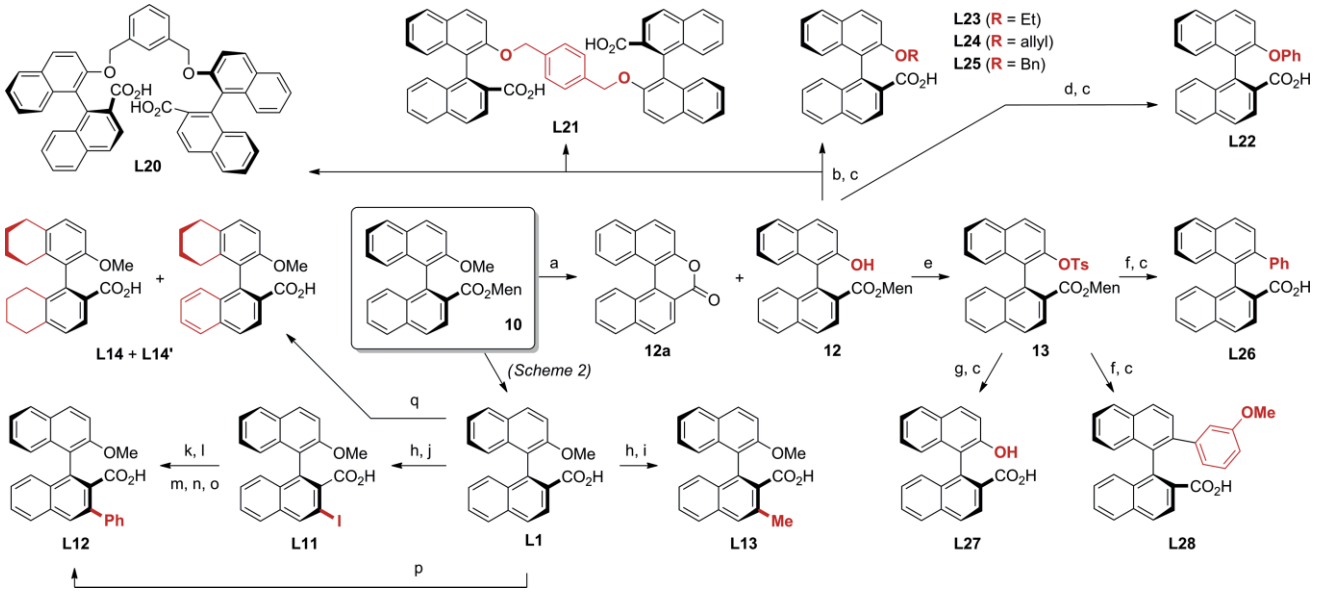
A few target structures with variations at C-3′ of the alkoxynaphthalene subunit were accessed following the Cram–Miyano-S_NAr route from **7** and the respective alkoxy-bromonaphthalene derived Grignard reagents. The syntheses, performed in analogy to that of **L1**, tended to proceed sluggishly and with lower stereoselectivity. Even so, the major diastereomers could be obtained in all cases and were saponified to the enantiopure target acids **L2**–**4** (Scheme 3). The sparse results of those syntheses did not recommend further exploration of the de novo asymmetric synthesis approach. It was used once more to access the chiral carboxylic acid and NMR shift reagent MNCB (**L5**) as another potential ligand for catalytic hydroalkoxylation (Table 1), following Fukushi's synthetic route.[45]

Transformation of the 2′-Methoxy Group

Based on the well-developed route to **L1**, either the latter or its precursor **10** recommended themselves as synthetic platform for structure variations (Scheme 4). Dealkylation of **10** with BBr_3 at 0 °C or r.t. returned lactone **12a**, which suffers fast racemization at ambient temperature.[46] At –78 °C the same reagent permitted demethylation to give diastereomerically and enantiomerically pure ester **12**, whose successive Williamson etherification and saponification return various 2′-alkoxy-BINA-Cox ligands **L23–25** (Scheme 4, b, c). Notably, alkylation with α,α′-dibromoxylenes gave tethered bis-carboxylic acids **L20** and **L21**. Phenoxy derivative **L22** was accessed via Chan-Lam coupling,[47,48] after initial attempts at Ullmann coupling had failed. No epimerization occurred in the alkylation or arylation of **12**, whose substitution products were diastereomerically pure. Absence of racemization under the conditions of saponification was further proven for the free acids by ^1H NMR spectroscopy with nicotine as chiral shift reagent.[45] Tosylate **13** derived from **12** was prepared with the intention to explore cross coupling approaches towards 2′-aryl-substituted derivatives of MeO-BINA-Cox. Nickel-catalyzed Suzuki coupling ($Ni(COD)_2$, PCy_3, K_3PO_4) of **13** with phenyl boronic acid,[49] followed by saponification, initially returned hydroxyacid **L27**, besides target **L26** (17 %) and hydro-de-metalation product (a*S*)-1,1′-binaphthyl-2-carboxylic acid (**L32**; 6 %). Repeat experiments with careful exclusion of water provided the desired coupling product in superior selectivity. It was then saponified to **L26** (Scheme 4, f and c). An analogous coupling with 3-methoxyphenylboronic acid gave **L28**, which reintroduces a methoxy group into the ligand periphery.

Ligand Syntheses via Metalation or Reduction of L1

According to Metz et al., H-3 of MeO-BINA-Cox (**L1**) was regioselectively lithiated with *sec*-BuLi–TMEDA[50] and then alkylated with MeI to give **L13** (Scheme 4, h, i).[51] An analogous metalation followed by quenching with iodine gave **L11**, whose direct Suzuki coupling with phenyl boronic acid to **L12** failed, but was realized at the stage of its methyl ester. Unfortunately, the resulting ester resisted standard saponification and thus was laboriously converted to **L12** via $LiAlH_4$ reduction, IBX-oxidation and Lindgren[52] $NaClO_2$ oxidation. More efficiently, a phenyl



Scheme 4. Synthesis of MeO-BINA-Cox derivatives from **10**. a) BBr_3, CH_2Cl_2, –78 °C, 5 h, 82 % **12**. b) Alkyl bromide, K_2CO_3, MeCN, 82 °C. c) KOH, EtOH, 80 °C, 24–72 h. **L20**: 72 % (2 steps); **L21**: 64 % (2 steps); **L22**: 73 % (2 steps); **L23**: 62 %, 82 %; **L24**: 83 %, 60 %; **L25**: 72 %, 56 %; **L26**: 68 %, 84 %; **L27**: 32 % (2 steps); **L28**: 57 %. d) Ph-$B(OH)_2$, $Cu(OAc)_2$, NEt_3, CH_2Cl_2, MS 4 Å, r.t., 16 h. e) TsCl, DMAP, NEt_3, CH_2Cl_2, 0 °C → r.t., 18 h, 88 %. f) Ar-$B(OH)_2$, K_3PO_4, $Ni(COD)_2$, PCy_3, THF, MS 4 Å, 45/50 °C, 60/48 h; to **L26**: 68 %/**L28**: 84 %, respectively. g) Conditions as in f), but with "wet" base and no MS 4Å present; hydrolysis occurred as side-reaction. h) *sec*-BuLi, TMEDA, THF, –78 °C. i) MeI, 22 %.[51] j) I_2, THF, –78 °C → r.t., 24 h, 48 %. k) K_2CO_3, MeI, acetone, 56 °C, 16 h. l) Na_2CO_3, Ph-$B(OH)_2$, $[PdCl_2(PPh_3)_2]$, THF–H_2O (1:1), 50 °C, 18 h. m) $LiAlH_4$, THF, 0 °C → 65 °C, 16 h. n) IBX, DMSO, r.t., 4 h. o) H_2O_2 aq., $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, MeCN–H_2O (1:1), 50 °C, 18 h; 22 % (5 steps).[54] p) Ag_2CO_3, K_2CO_3, $Pd(OAc)_2$, *N*-acetylglycin, PhI–HOAc, 90 °C, 3 d, 51 %. q) Ni–Al alloy, 1 % aq. NaOH, H_2O–*i*PrOH (7:1), 90 °C, 24 h, 90 % (**14**:**14′** = 1:1).

Full Paper
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group was introduced at C-3 of **L1** following a protocol for Pd-catalyzed *ortho*-C–H-arylation[53] to give **L12** in a single step (Scheme 4, p).

Hydrogenation of **L1** with in situ activated Raney-Nickel in aqueous 2-propanol[55] led to a 1:1 mixture of tetrahydro- and octahydrogenated derivatives **L14/L14′**, whose ratio remained unchanged when the mixture was exposed once more to the hydrogenation conditions. The two components could not be separated either by chromatography or fractional crystallization.

S_EAr Functionalization of MeO-BINA-Cox Esters

Friedel-Crafts type functionalization at methoxynaphthalene C-6′ were performed on methyl ester **15** as substrate and succeeded in case of alkylation with *tert*-butyl chloride[56] or acylation with acetyl chloride[15] to provide **L17** and **L18**, respectively, after saponification (Scheme 5, b–d). When the evaluation of ligand **L18** in catalysis returned superior results over **L1**, we thought it worthwhile to study the effect of 1-adamantyl as typical dispersion energy donor substituent (DED[57]). Its introduction at C-6′ was attempted through $InCl_3$-catalyzed Friedel-Crafts alkylation of menthyl ester **10** with 1-bromoadamantane.[58] Curiously, adamantylated acid **L19** was the major product from this reaction besides the expected ester. It appears that HBr, which is released in the alkylation step also cleaves the menthyl ester by dealkylation, and this was supported by detecting both menthyl- (δ_H = 3.99) and neomenthyl bromide (δ_H = 4.67) in the crude reaction mixture. Saponification was thus spared in the synthesis of **L19**. The absence of racemization under S_EAr reaction conditions was checked for **L17** and **L18** through ^1H NMR analysis with nicotine as shift reagent.[45]

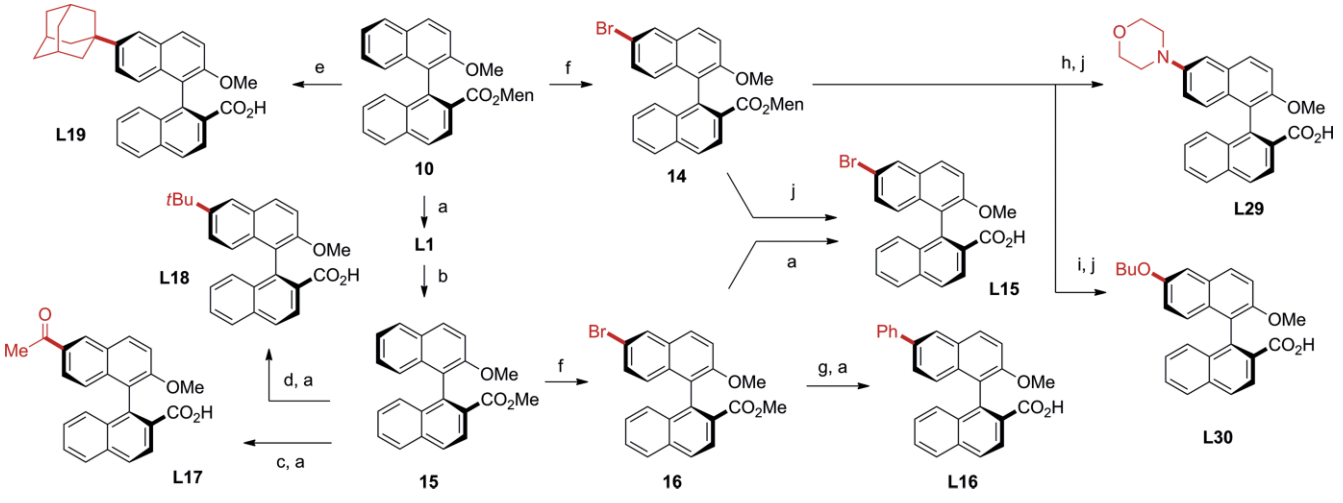
Cross-Coupling of 6′-Bromoester

Bromination of either menthyl (**10**) or methyl (**15**) esters of MeO-BINA-Cox proceeded in the C-6′ position to give monobromides **14** or **16** in excellent yields. Either ester was saponified to bromoacid **L15**. Standard coupling methodologies for heteronucleophiles (amines, alcohols) with **14** gave access to 6′-amino- (**L29**)[59] or 6′-alkoxy- (**L30**)[60] substituted MeO-BINA-Cox after saponification (Scheme 5, h–j). Brominated ester **16** was also arylated by Suzuki coupling and furnished 6′-phenyl acid **L16** after saponification (Scheme 5, g, a).

Ligand Effects in Titanium-Catalyzed Asymmetric Hydroalkoxylation

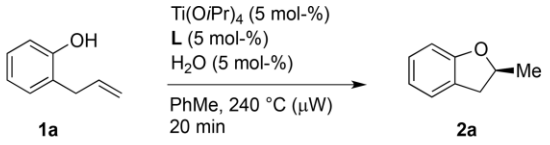
The cycloisomerization of 2-allylphenol (**1a**) to 2-methylcoumaran (**2a**) served as reference reaction for comparing the performance of ligands **L2**–**L34** in titanium-carboxylate catalyzed asymmetric hydroalkoxylation by determining ligand effects on catalyst activity and stereoselectivity (Table 1).[19] We opted for a short reaction time of 20 min, such that the analytical yields of **2a** reflect relative catalytic activities. The reaction is generally sensitive to variations in the reaction temperature, the water-content of substrates and solvent and the purity of starting allyl phenol **2a**. As a means of quality control and to ascertain the integrity of the reaction setup, the standard reaction with **L1** was repeated with each new experiment series. Any notable deviation in either yield or enantioselectivity of **2a** pointed to problems with either reagents or the microwave unit. The temperature sensor of the latter was also regularly recalibrated.

In spite of the thermally forcing conditions of this reaction ("HOT-CAT", homogeneous thermal catalysis), initial blank experiments with titanium(IV)alkoxide in the absence of carboxylic acid ligand show very little substrate conversion (entry 1), and carboxylic acid **L1** in the absence of titanium precursor gave no conversion at all (entry 2). Standard catalytic runs with **L1** gave (2*S*)-2-methylcoumaran (**2a**) in yields that increased with the holding time at 240 °C (entries 3a vs. 3b).

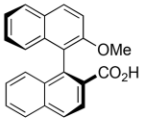
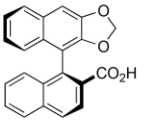
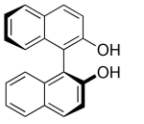
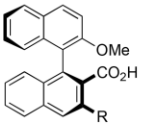
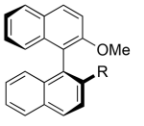
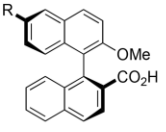
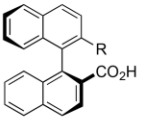
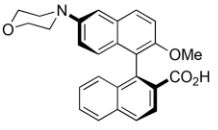
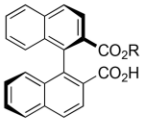
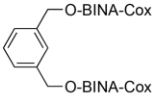
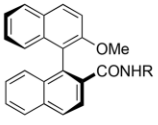
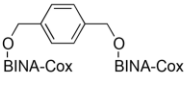
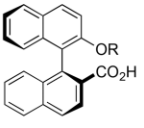
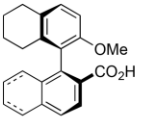
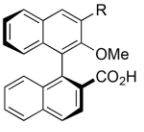
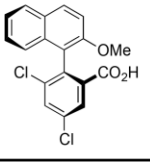


Scheme 5. Syntheses of ligands **L15–19**, **L29** and **L30** from esters **10**/**15** of MeO-BINA-Cox (**L1**). a) KOH, EtOH, 80 °C, 18–21 h; **L15**: 83 %; **L16**: 92 %; **L17**: 37 %; **L18**: 82 %; see Scheme 2 for **L1**. b) K_2CO_3, MeI, acetone, 56 °C, 2 h, 94 %. c) MeCOCl, $AlCl_3$, CH_2Cl_2, 0 °C → r.t., 45 min, 91 %. d) *t*BuCl, $AlCl_3$, CH_2Cl_2, 0 °C → r.t., 60 h, 72 %. e) 1-AdBr, $InCl_3$, CH_2Cl_2, 60 °C, 14 h, 53 % (in situ ester cleavage). f) Br_2, HOAc, r.t., 4–29 h, 98 % for **14**, 84 % for **16**. g) Na_2CO_3, Ph-B(OH)$_2$, $PdCl_2(PPh_3)_2$, THF–H_2O (1:1), 50 °C, 18 h, 65 %. h) morpholine, $Pd(OAc)_2$, XPhos, NaO*t*Bu, PhMe, 110 °C, 1 h. i) *n*BuOH, K_3PO_4, CuI, 8-hydroxyquinoline, 110 °C, 48 h. j) KOH, PEG-200, 150 °C, 2–8 h. **L15**: 55 %; **L29**: 20 % (2 steps); **L30**: 78 % (2 steps). XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

Table 1. Structure variations of **L1** and their effects on the asymmetric catalytic hydroalkoxylation of **1a** to **2a**.[a]



1a **2a**

Entry	Ligand	Ln	Yield[b] [%]	ee[c] [%]	Entry	Ligand	Ln	Yield[b] [%]	ee[c] [%]
1[d]		no ligand	1	–					
2[e]		**L1**, no $Ti(OR)_4$	0	–	22[f]		**L4**	56	43
3a		**L1**	54	75					
3b[f]		**L1**	75–84	71–75					
4[f]		**L10** (H = Na)	0	–					
5		**L8**	10	0	23		**L13** (R = Me)	80	57
					24		**L11** (R = I)	22	35
					25		**L12** (R = Ph)	2	5
6		**L9** (R = OMe)	15	0	26		**L17** (R = COMe)	0	–
7[f]		**L31** ($R = NH_2$)	13	0	27		**L15** (R = Br)	52	72
					28[f]		**L30** (R = O*n*Bu)	73	73
					29a		**L18** (R = *t*Bu)	71	80
					29b[f]		**L18**	79	78
					30[f]		**L19** (R = 1-Ad)	85	78
					31		**L16** (R = Ph)	60	76
8[g]		**L32** (R = H)[h]	18	4	32		**L29**	55	70
9		**L27** (R = OH)	5	n.d.					
10		**L26** (R = Ph)	13	20					
11		**L28** (R = *m*-An)	9	20					
12		**L6** (R = H)	10	36	33a		**L20**	1	13
13		**L7** (R = Me)	3	0	33b[i]		**L20**	10	70
14		**L33** (R = H)	8	0	34a		**L21**	2	14
15		**L34** (R = *t*Bu)	14	0	34b[i]		**L21**	6	67
16		**L23** (R = Et)	29	51	35[f]		**L14/L14'**	36	20
17		**L24** (R = All)	30	49					
18		**L25** (R = Bn)	21	36					
19		**L22** (R = Ph)	24	36					
20		**L2** (R = Ph)	23	49	36		**L5**	38	71
21[f]		**L3** (R = OMe)	68	46					

[a] Conditions: 2-allylphenol (1.5 mmol), PhMe (3 mL); $Ti(OiPr)_4$ (5 mol-%). [b] Yield of **2a** determined by qNMR analysis. [c] *ee* of **2a** determined by chiral HPLC of purified product. [d] Without H_2O. [e] Without $Ti(OiPr)_4$. [f] Reaction time 50 min. [g] Reaction time 30 min. [h] 45 % *ee*. [i] 2.5 mol-% of chiral ligand (-CO_2H:Ti ratio 1:1). n.d. = not determined; *m*-An = *meta*-anisyl or 3-(C_6H_4OMe); Ad = adamantyl.

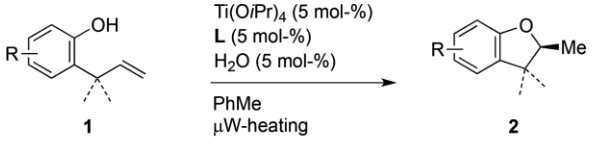
The influence of polar functional groups in the ligand sphere upon catalytic activity was explored with suitably modified structures: Converting **L1** to its sodium salt **L10** quenches the catalytic activity of the in situ catalyst with $Ti(OiPr)_4$ and water (entry 4). This negative buffering effect points to the importance of a minimal acidity level within the reaction system. Runs with variously functionalized 1,1-binaphthyl-derivatives (entries 2–15) imply that the presence of a single carboxyl (entry 8), or chelation by two coordinating donors (-CO_2H, -OR, -NH_2, -CONHR > CO_2R; entries 5–7, 9, 12–15) are minimal require-

ments for catalytic activity. However, enantioselectivity is only achieved with free carboxyls (entries 3, 8, 12), and high activity and selectivity are only reached by combining one carboxyl with a weakly coordinating 2′-methoxy group (entry 3). Replacing 2′-methoxy with sterically active non-donors retains some selectivity at low activity (entries 10,11). Shifting of the methoxy group from the 2′-position into the periphery by inserting a 2′-*meta*-anisyl group is ineffective (entry 11). Increasing the size of the 2′-alkoxy-group beyond methoxy successively reduces catalyst activity and selectivity (entries 16–19).

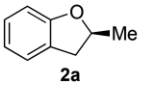
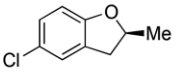
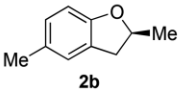
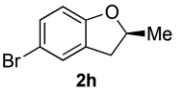
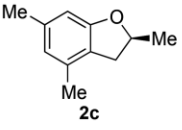
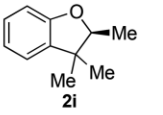
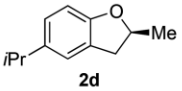
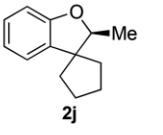
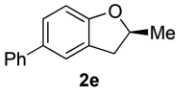
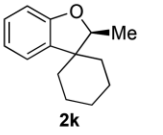
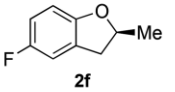
Attaching a group to the 3′-position (while retaining 2′-alkoxy) reduces catalyst activity and selectivity (entries 20–22). Substitution at C-3 in the naphthoic acid fragment has similar effects (entries 23–25), although the small methyl group boosts catalyst activity at somewhat reduced selectivity (entry 23). The increased activity of **L13** might be a consequence of the σ-donor effect of methyl. By placing specific groups into the remote 6′-position of the MeO-BINA-Cox core structure, their electronic influence can be studied with minimal disturbance of the coordination sphere around the metal. Entries 26–31 show that electron-rich +σ and +π groups induce high activity and enantioselectivity similar to, and sometimes surpassing that obtained with **L1** (entries 29, 30). The most successful groups are the bulky ones, and thus a steric (or: dispersion donor) influence on catalyst properties cannot be discounted, besides the electron donor effect. In any case, the π-acceptor group of **L17** completely suppresses catalyst activity (entry 26).

The in situ catalyst from Ti(O*i*Pr)$_4$, **L*n*** and H_2O is presumably a multinuclear titanium-μ-oxo species.[19] Tethered dicarboxylic acids **L20** and **L21** were prepared to potentially bridge metal centers more effectively than separate units of **L1**. Their low catalytic activity points to a steric misfit of the tethering unit, however (entries 33, 34). The partially hydrogenated ligand mixture **L14/L14′** displayed lowered activity and selectivity (entry 35), whereas replacing the naphthoic with a dichlorobenzoic acid subunit (**L5**)[12,45] was well tolerated; the lower activity vs. **L1** is consistent with assuming a deactivating σ-acceptor effect exerted by chlorine (entry 36).

Table 2. Asymmetric catalytic cyclization of variably substituted 2-allylphenols (**1**) to coumarans (**2**).[a]



1 2

Entry	1	Ln	T [°C]	t [min]	Product (2)	yield[b] [%]	ee[c] [%]	Entry	1	Ln	T [°C]	t [min]	Product (2)	yield[b] [%]	ee[c] [%]
1a	**1a**	**L1**	240	50		84	75	7a	**1g**	**L1**	240	50		90	62
1b		**L18**	220	50		81	85	7b		**L18**	220	50		88	73
1c		**L18**	240	50	**2a**	92	80	7c		**L18**	240	50	**2g**	93	69
2a	**1b**	**L1**	240	50		71	72	8a	**1h**	**L1**	240	50		71	62
2b		**L18**	220	50		78	81	8b		**L18**	240	50		86	73
2c		**L18**	240	50	**2b**	79	75						**2h**		
3a	**1c**	**L1**	240	50		88	78	9a	**1i**	**L1**	190	20		48[e]	71
3b		**L18**	220	50		88	87	9b		**L1**	220	20		76	71
3c		**L18**	240	50	**2c**	93	84	9c		**L1**	240	20		88[e]	66
								9d		**L5**	240	20		63	53
								9e		**L13**	240	20	**2i**	64	50
4a	**1d**	**L1**	240	50		51	61	10a	**1j**	**L1**	220	20		84[e]	68
4b[d]		**L18**	240	50		83	77	10b		**L1**	240	50		74[e]	65
					2d								**2j**		
5a	**1e**	**L1**	240	50		0	–	11a	**1k**	**L1**	220	20		55[e]	64
5b		**L18**	240	50		31	59	11b[f]		**L1**	240	20		55[e]	60
					2e			11c[f]		**L1**	240	50		48[e]	61
6	**1f**	**L1**	240	50		56	72						**2k**		
					2f										

[a] Conditions: allylphenol (1.5 mmol), toluene (3 mL); Ti(O*i*Pr)$_4$ was added using an Eppendorf pipette or as a 0.15 M stock solution in toluene (0.5 mL per experiment). [b] Isolated yields after work-up by column chromatography except otherwise stated. [c] *ee* values were determined by chiral HPLC of the purified reaction product. [d] Conditions: substrate (0.95 mmol), Ti(O*i*Pr)$_4$ (8 mol-%), **L18** (8 mol-%), H_2O (8 mol-%), toluene (3 mL). [e] Yields were determined by qNMR analysis using tetradecane as internal standard. [f] Reaction scale: substrate (1.4 mmol), toluene (3 mL). n.d. = not determined.

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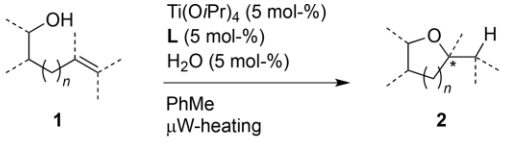
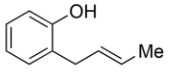
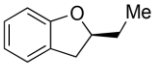
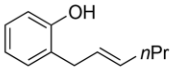
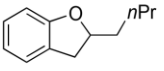
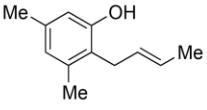
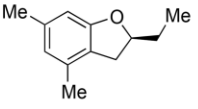
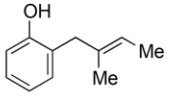
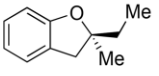
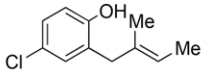
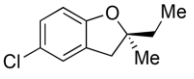
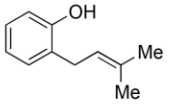
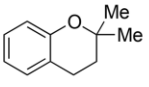
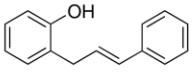
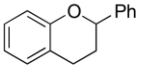
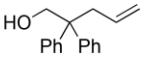
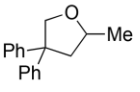
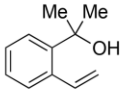
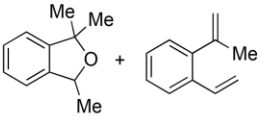
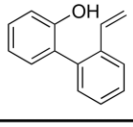
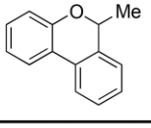
Substrate Scope of Asymmetric Cycloisomerization

The cyclization of 2-allylphenols (**1**) to 2-methylcoumarans (**2**) was the original assay used for the discovery of the $Ti(OiPr)_4$–**L1**–H_2O catalyst system; results with various core-substituted 2-allylphenols were already reported in our communication[19] and are included in Table 2 for completeness. The catalytic runs for the substrate scope were typically performed with **L1** and

Table 3. Extended substrate range of intramolecular asymmetric catalytic hydroalkoxylation.[a]



1 2

Entry	Substrate (**1**)	**1**	**Ln**	T [°C]	t [min]	Product (**2**)	**2**	Yield[b] [%]	ee[c] [%]
1		**1l**	**L1**	250	20		**2l**	8	30
2		**1m**	**L1**	250	20		**2m**	0	–
3		**1n**	**L1**	250	20		**2n**	traces	n.d.
4		**1o**	**L1**	250	20		**2o**	76	n.d.[d]
5		**1p**	**L1**	250	20		**2p**	56[e]	n.d.
6		**1q**	**L1**	250	20		**2q**	63	n.a.
7		**1r**	**L1**	250	20		**2r**	<3[e,f]	n.d.
8		**1s**	**L1**	240	20		**2s**	6	0
9a 9b 9c		**1t**	**L1** **L19**	220 220	50 30		**2t +2t'**	32 + 62[e] 32 + 26[e]	52[g] 71[g]
10a[h] 10b[i]		**1u**	**L1** **L1**	240 240	20 30		**2u**	11[e] 44[e]	34 24

[a] Conditions: allylphenol (1.5 mmol), toluene (3 mL); $Ti(OiPr)_4$ was added using an Eppendorf pipette or as a 0.15 M stock solution in toluene (0.5 mL per experiment). [b] Isolated yields after work-up by column chromatography except otherwise stated. [c] *ee* values were determined by chiral HPLC of the purified reaction product. [d] *ee*-value could not be determined due to contamination of the purified product by side-products. [e] Yields were determined by qNMR analysis using tetradecane as internal standard. [f] Yields could not be determined precisely and do not exceed the given value. [g] *ee* was determined by chiral GC analysis of the purified reaction product. [h] Reaction scale: substrate (1.38 mmol), toluene (3 mL). [i] Reaction scale: substrate (0.73 mmol), toluene (3 mL). n.d. = not determined; n.a. = not applicable.

Full Paper
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additional selected examples with **L18**, or other ligands. The heating phase was extended to 50 minutes in order to approach complete conversion of substrates.

2-Allylphenol Substrates

Results obtained with methylated and halogenated allylphenols are shown in Table 2 (entries 1–8). Besides simple allylphenol (**1a**), the alkylated analogues **1b,c** cyclized in excellent yields at enantiomeric ratios of er 85:15–90:10 (entries 1–3). Sterically demanding substituents *para* to phenolic hydroxyl (**1d,e**) are less well tolerated (entries 4, 5b), and **1e** only showed conversion with the more active catalyst incorporating **L18** (entry 5b). Halogenated 2-allylphenols **1f–h** cyclize fairly well, but at slightly lower enantiomeric excesses (entries 6–8). Reactions performed at 220 °C tend to be more selective, but also lower yielding (cf. entries 1b, 2b, 3b vs. 1c, 2c, 3c). The highest enantioselectivity was achieved with substrate **1c** in combination with ligand **L18** (entry 3b).

Cycloisomerizations typically profit from the Thorpe-Ingold effect.[61] The geminal dimethylallyl-phenol **1i** was prepared with this in mind and tested additionally with ligands **L13** and **L5**, which gave lower yields and *ee*-values (entries 9), consistent with the ligand screen of **1a** (Table 1). Spirocyclic cycloalkyl derivatives **1j,k** cyclized successfully with yields of **1j** surpassing those of **1k** (entry 10 vs. 11) at stable enantiomeric excesses slightly below **1a**. The lower yields obtained with those substrates are ascribed to competing homo-1,5-rearrangements giving regioisomeric coumarans (Scheme S1). The extent of rearrangement was lower for the titanium catalyst than in the previously reported results with $Al(OiPr)_3$ as (achiral) catalyst.[62]

Further Extension of the Substrate Range

To probe further variations of the substrates for titanium-catalyzed (asymmetric) hydroalkoxylation we next concentrated on allylphenols bearing additional substituents within the alkene unit. Crotylphenol (**1l**) showed little conversion under standard conditions with **L1**, and lower enantioselectivity (Table 3, entry 1); **1m** with a further extended allyl chain failed to cyclize entirely (entry 2). Core-methylation of crotylphenol to **1n** likewise did not improve reactivity (entry 3). Based on those results, we assumed that there is a detrimental steric effect of alkene substitution but were next surprised to find catalytic activity restored with the still higher substituted 2,3-dimethyl-allyl-substrates **1o** and **1p** (entries 4, 5). The presence of inseparable side products prevented a reliable determination of the *ee* of the reaction products. Cyclization of **1q** and **1r** took a different path in that *6-endo-trig* cyclization to chromans was preferred (entries 6, 7); chroman **2q** is achiral. Aliphatic alkenol **1s** cyclized only with difficulty (entry 8). With substrate **1t** we found a new type of substrate for the reaction, whose asymmetric *5-exo-trig* cyclization also illustrates compatibility of tertiary alkanol substrates (entries 9). Finally, a *6-exo-trig* cyclization could also be realized asymmetrically with 2′-vinyl-1,1′-biphenyl-2-ol **1u**, which bears an alkene and a phenolic moiety on separate phenyl groups; product **2u** was obtained in limited yield and enantioselectivity, however (entries 10).

Substrates Failing to Cyclize

Additional substrates that failed to cyclize will be shortly discussed: 2-Allylphenols with substituents *ortho* to hydroxyl fail in the model reaction (Figure 2). A methyl group is sufficient to suppress the catalysis (**1aa**), disregarding more hindered substrates (**1ab**, **1ac**). The presence of polar, coordinating or π-acceptor groups, even remote ones, is another limitation, judging from the inactivity of substrates **1ad** and **1af**–**1ai**. The case of 2-prop-1-enylphenol (**1aj**) is of interest, since this compound could principally be formed by isomerization from **1a**. The *5-endo-trig* cyclization of **1aj** to **2a** was not observed under catalytic reaction conditions, even though the starting material was fully converted. This points to a relatively fast polymerization of **1aj** under reaction conditions, which also explains why the latter is not observed as side-product in the model cyclization **1a**→**2a**, where it escapes analytical detection through fast polymerization.

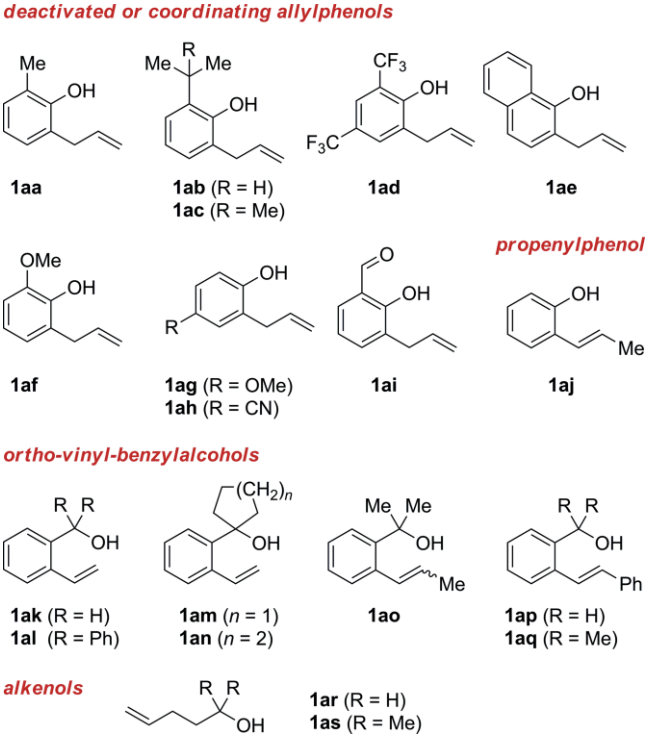

Figure 2. Substrates **1aa-as**, which did not cyclize under the standard reaction conditions of the asymmetric titanium catalyzed hydroalkoxylation.

The group of *ortho*-alkenyl-benzyl alcohols (**1t**, **1ak**–**1ao**) has their reactive centers homologously shifted relative to allylphenols. Unlike for α,α-dimethylcarbinol **1t**, which cyclized to coumaran **2t** under standard conditions (cf. Table 3, entries 9), experiments with **1ak**–**1am** returned only starting material. The formal introduction of a β-methyl group into **1t** prevented cyclization in the resulting **1ao**, which suffered elimination of water to give a dialkenylbenzene instead (Scheme S2). The 2-styryl alcohols **1ap** and **1aq** failed to cyclize under conditions of the model catalysis. In another attempt at converting aliphatic alkenols (cf. **1s** in Table 3, entry 8), both substrates **1ar** and **1as** failed to cyclize.

Full Paper
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Conclusions

The present work extends our studies of the high-temperature asymmetric catalytic cyclization of 2-allylphenols to 2-methylcoumarans.[19] The chiral carboxylic acid ligand in the novel titanium alkoxide–carboxylic acid–water in situ catalyst is preferrably an axially chiral biaryl-2-carboxylic acid with a methoxy group in the 2′-position. Ligand structure variations for structure-activity studies of the catalyst were conveniently realized at the stage of enantiopure MeO-BINA-Cox (**L1**) as platform chemical. The asymmetric synthesis of **L1** was improved by determining key reaction parameters in all steps and adapting the reaction conditions to molar scales with no need for chromatography. A new protocol for saponification of sterically hindered, resilient esters in hot PEG-200 at elevated temperature was introduced, which permits the saponification of hindered esters in short reaction time with only a moderate excess of base. More than 30 novel axially chiral biaryl-2-carboxylic acids have been synthesized in enantiopure form and tested as ligands in the titanium-catalyzed asymmetric cycloisomerization of 2-allylphenol to 2-methylcoumaran. Compared with **L1**, an increase of catalytic activity was observed in ligands having electron-donating and sterically demanding substituents at the remote 6′-position (**L18**, **L19**).

Extensions of the substrate scope of the asymmetric catalytic hydroalkoxylation reaction with non-activated alkenes have been explored. Alkylated and halogenated allylphenols, as well as allylphenols having aryl or alkyl groups attached to the alkene unit or to the α-allylic (benzylic) position were tolerated in the catalytic reaction, although with various levels of success regarding the yield and enantiomeric excess of the products. New examples of asymmetric catalytic hydroalkoxylation reactions have been identified, such as the cyclization of 2′-vinylphenyl-(1,1-dialkyl)methanol (cf. **1t**) or of 2′-vinyl-1,1′-biphenyl-2-ol (**1u**) to 1,3-dihydrobenzofuran (**2t**) or 6*H*-benzo[*c*]chromene (**2u**), respectively.

Based on the ready access to **L1**, we plan to isolate and study the chiral titanium carboxylate complexes that appear to catalyze the hydroalkoxylation reaction. In combination with the findings from the substrate structure variations, we hope to gain insight into the mechanism of this peculiar reaction.

Experimental Section

General remarks. Unless otherwise specified, all reagents were obtained from commercial suppliers and used without further purification. 2-Allylphenol (**1a**) was distilled in high vacuum (short-path distillation) and stored under exclusion of air in the dark; typical water content 200 ppm. K_2CO_3 was dried in high vacuum with heating to 120 °C. K_3PO_4 was finely powdered and dried in high vacuum at 100 °C. Commercial KOH flakes (85 % content) were ground to a fine powder before use. Solvents for synthesis were commercially obtained and used without purification. Solvents for column chromatography were of technical grade and used after distillation. Water-free solvents were obtained by passing commercial solvents through a column of dry Al_2O_3 and storing under argon over 4 Å molecular sieves. Residual water was analyzed by coulometric Karl-Fischer titration.

Abbreviations: The term (1*R*)-menthyl denotes (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl, or (–)-menthyl (in the older literature), within a menthyloxy group. PEG is polyethylene glycol.

Chromatography. Column chromatography (CC) was performed on silica gel 60 (35–70 µm particle size) with 0.2 bar positive air pressure. Thin layer chromatography (TLC) was performed on glass plates coated with silica gel 60 F_{254} and visualized with UV light (254 nm) and by staining with Mostain [10 g $(NH_4)_6[Mo_7O_{24}]\cdot 4H_2O$, 0.2 g $Ce(SO_4)_2\cdot 4H_2O$, 190 mL H_2O; 12 mL H_2SO_4 (conc.) added last with stirring].

Microwave Syntheses were carried out in an Anton Paar Monowave 300 reactor equipped with a MAS 24 autosampler. The temperature was monitored by an external IR thermometer, which was regularly calibrated against an internal optical ruby thermo-probe. Specified reaction times correspond to the holding time at target temperature.

Analytical data: NMR spectra were recorded at ambient temperature (19–25 °C). Chemical shifts (δ) are given in ppm. ^{1}H NMR spectra are internally referenced to tetramethylsilane (TMS, δ_H = 0.00) or residual solvent peak ($CHCl_3$: δ_H = 7.26; [D_5]-DMSO: δ_H = 2.50). ^{13}C NMR spectra are referenced to solvent ($CDCl_3$, δ_C = 77.16; [D_6]-DMSO, δ_C = 39.52). Quantitative ^{1}H NMR analysis (qNMR) was performed with a prolonged relaxation delay (d1) of 20 s, with either tetradecane (δ_H = 0.88) or 1,1,2,2-tetrachloroethane (δ_H = 5.90) or trichloroethene (δ_H = 6.45) as internal standard. The symbol Ψ denotes a "pseudo"-signal (appearing as). Chiral HPLC analysis was performed on Chiralcel OJ or OD stationary phases (250 × 4.6 mm). EI HRMS were recorded using a DFS High Resolution MS, ESI HRMS using a LTQ FT Ultra, equipped with a Fourier-transform ion cyclotron resonance (FT-ICR) MS detector.

General procedures

General procedure for saponification of biarylcarboxylic acid esters with KOH in EtOH (GP-1A): To a solution of 1.00 equiv. ester and KOH (85 % content) in EtOH (5–10 mL/mmol), a little water was added (ca. 0.2 mL/mmol) and the reaction mixture was heated to reflux overnight (bath 100 °C). After cooling to r.t. and addition of H_2O and Et_2O, the layers were separated. The aqueous layer was acidified using aqueous 2 M HCl and extracted with several portions of Et_2O. The organic layers were combined and washed with aqueous 2 M HCl and saturated aqueous NaCl. After drying over Na_2SO_4 and filtration, the solvent was evaporated giving the crude reaction product.

General procedure for saponification of biarylcarboxylic acid esters with KOH in EtOH (GP-1B): To a solution of 1.00 equiv. ester and solid KOH (85 % content) in EtOH (5–10 mL/mmol), a little water (0.2 mL/mmol) was added and the reaction mixture was heated to reflux overnight (bath 100 °C). After cooling to r.t. and addition of H_2O and Et_2O, the layers were separated. The organic layer was extracted with saturated aqueous LiOH, then discarded. The combined aqueous layers were acidified with aqueous 2 M HCl and extracted with several portions of Et_2O. The combined extracts were dried with Na_2SO_4. After filtration, the solvent was evaporated to give the crude product. Note: use of aqueous LiOH can be beneficial for bringing carboxylate into the aqueous layer, in case the potassium salt is partially soluble in the organic layer.

General procedure for saponification of biarylcarboxylic acid esters with KOH in PEG-200 (GP-1C): The ester (1.00 equiv.) and solid KOH (85 % content; 5.00 equiv.) were added to PEG-200 (ca. 5 mL/mmol) at r.t. The reaction mixture was heated to 150 °C with stirring for the indicated time. After cooling to r.t. and addition of H_2O, aqueous 6 M HCl and EtOAc, the layers were separated and

the aqueous layer was extracted with EtOAc (2–3 ×). The combined organic phases were washed with H_2O (5 ×), dried with $MgSO_4$ and filtered. After removal of the solvent in vacuo, the crude residue was dissolved in a small amount of CH_2Cl_2 and a defined amount of trichloroethene was added as an internal standard for qNMR analysis. After the NMR analysis, solvent and internal standard were removed in vacuo to give the crude reaction product.

General procedure for determining the enantiomeric excess of biarylcarboxylic acids (GP-2). The enantiomeric excess of chiral carboxylic acids was determined by an NMR chiral shift method using (–)-nicotine as chiral base according to Fukushi:[45] A sample of the chiral carboxylic acid (15–30 μmol, 1.0 equiv.) was dissolved in $CDCl_3$ and (–)-nicotine (10 μL, 60 μmol, 2–4 equiv.) was added. The ^{1}H NMR spectrum was recorded using a relaxation delay (d1) of 20 seconds. For MeO-BINA-Cox derivatives, the methoxy signals for enantiomeric anions appear at different chemical shifts (e.g., $\Delta\delta_H$ 0.05 for **L1**). Integration of the methoxy singlets – by means of deconvolutive peak analysis, if necessary – gave the relative amounts of diastereomeric ion pairs (*dr*), from which the *ee* of the acid is derived.

General procedure for asymmetric catalytic hydroalkoxylation (GP-3). Under argon, the ligand (0.05 equiv.) was combined with titanium(IV) isopropoxide (0.05 equiv.; a stock solution in toluene may be used) in a borosilicate glass vial. H_2O (0.05 equiv.) was added to the lower vessel wall by micro-syringe, followed by dry toluene (3 mL). The resulting mixture was stirred for 10 min at 60 °C. The substrate (1.00 equiv.) was added and the mixture was heated in a microwave reactor to the target temperature, where it was held for the indicated reaction time. After cooling, an internal standard (tetradecane) was added to the crude reaction mixture and an aliquot was removed for qNMR analysis. The reaction mixture was placed on top of a solvent-filled silica gel column for purification by CC. Enantiomeric excess was determined by chiral HPLC analysis of chromatographically purified reaction product.

Scaled-up synthesis of MeO-BINA-Cox (L1)

Methyl 1-methoxy-2-naphthoate (4): A three-necked 4 L round-bottom flask was charged with 1-hydroxy-2-naphthoic acid (**3**; 400 g, 2.13 mol, 1.00 equiv.), acetone (2 L) and dimethyl sulfate (424 mL, 4.48 mol, 2.10 equiv.; *CAUTION*).[a)] To the mechanically stirred suspension,[b)] potassium carbonate (648 g, 4.69 mol, 2.20 equiv.) was added in portions over the course of 5 h. The internal reaction temperature was initially kept at 20 °C by an external water bath, to which ice was added as needed. After half the amount of the base had been added, the reaction mixture was warmed by the reaction heat, and the water bath was additionally heated to 50 °C.[c)] After completion of the base addition, the reaction mixture was stirred for 2 h at 50 °C, when TLC indicated consumption of both starting material (**3**) and the intermediary methyl 1-hydroxynaphthoate (R_f 0.49; EtOAc–hexanes, 1:10). After cooling to r.t., aqueous 25 % NH_3 (100 mL) and H_2O (1.2 L) were added slowly with continued stirring.[d)] The top organic layer was removed[e)] from the aqueous layer. The aqueous layer was extracted with Et_2O (2 ×) and the combined organic layers were washed with saturated aqueous NaCl (2 ×). After drying ($MgSO_4$) and filtration, solvents were evaporated. The crude oil was distilled (118–122 °C, oil-pump vacuum, ca 0.1 mbar) to give bright-yellow liquid (442 g, 96 %). *Notes*: a) Safety measures for the case of spilling of dimethyl sulfate or bursting of the reaction vessel were taken. The reaction vessel was placed into a water bath in a metallic pan, and aqueous 25 % ammonia was kept in reach for decontamination of spills. b) Motor-driven mechanical stirring is required at large scale. c) Stirring of the heated suspension proved to be considerably easier than of the cooled reaction mixture. External ice-cooling may not be necessary at all, if K_2CO_3 is added at a rate to keep the temperature of the water bath below the boiling point of the reaction mixture. d) The addition of ammonia (*EXOTHERM!*) is a safety-measure to quench excess dimethyl sulfate by alkylation, which renders the ensuing work-up more safely. e) Since no sufficiently large separatory funnel was available, phase separation was effected by transfer of the upper organic layer through PTFE tubing under a positive nitrogen pressure. The lower aqueous phase was extracted by mechanical stirring with new solvent added to the reaction vessel. R_f 0.35 (EtOAc–hexanes, 1:10). B. p. 118–122 °C (ca. 0.1 mbar). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.98 (s, 3 H), 4.07 (s, 3 H), 7.53–7.60 (m, 2 H), 7.61 (d, J = 8.8 Hz, 1 H), 7.85 (dd, J = 8.9, 6.4 Hz, 2 H), 8.28 (d, J = 7.6 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 52.32, 63.47, 119.27, 123.69, 123.71, 126.60, 126.74, 127.95, 128.40, 128.65, 136.85, 158.37, 166.75. Known compound, CAS 6039–59–4.

(1*R*)-Menthyl 1-(1*R*)-menthyloxy-2-naphthoate (7): (1*R*)-Menthol (**5**; 351.6 g, 2.25 mol, 3.00 equiv.) was placed in a 1 L three-necked glass vessel and heated to 100 °C. Sodium (8.63 g, 0.375 mol, 0.50 equiv.) was added to the melt and the reaction temperature raised to 190 °C with intense magnetic stirring. Gas evolution was monitored with a silicon bubbler. After consumption of the liquid metal (3 h), the reaction mixture was cooled to 60 °C, then diluted with dry DMF (200 mL). Methyl 1-methoxynaphthyl-2-carboxylate (**4**; 163 g, 0.750 mol, 1.00 equiv.) was added at 50 °C with stirring. After 1 h at 50 °C, the temperature was raised to 60 °C and 160 mL of a DMF–MeOH mixture was slowly distilled out of the vessel over the course of 5 h by applying a dynamic vacuum (15 mbar). Another portion of dry DMF (160 mL) was added to the thickened and foaming reaction solution, while the reaction mixture was kept at 60 °C. The slow distillation was continued at 15 mbar for 2 h (120 mL of DMF–MeOH distillate). The mixture, having thickened to the extent that stirring became impossible, was cooled to r.t. and aqueous 6 M HCl (60 mL) and H_2O (100 mL) were added. After separation of the layers, the aqueous layer was extracted with Et_2O (3 ×). The combined organic layers were washed with aqueous 2 M NaOH (2 ×), saturated aqueous NaCl (2 ×) and H_2O (2 ×), then dried ($MgSO_4$) and filtered. After evaporation in vacuo, the oily residue was taken up in EtOH (400 mL), which induced crystallization of colorless crystalline solid overnight at r.t. Filtration and washing with cooled (0 °C) MeOH gave 272 g (78 %) of colorless crystals. R_f 0.46 (EtOAc–hexanes, 1:20). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.73 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 7.0 Hz, 4 H), 0.89–0.99 (m, 2 H), 0.93 (d, J = 7.1 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H), 1.02 (d, J = 6.9 Hz, 3 H), 1.05 (d, J = 7.0 Hz, 3 H), 1.05–1.26 (m, 4 H), 1.52–1.67 (m, 4 H), 1.70–1.76 (m, 4 H), 2.04 (sept × d, J = 7.0, 2.6 Hz, 1 H), 2.18 (dtd, J = 11.9, 4.0, 1.6 Hz, 1 H), 2.67 (sept × d, J = 7.0, 2.2 Hz, 1 H), 4.33 (td, J = 10.4, 4.1 Hz, 1 H), 5.03 (td, J = 10.9, 4.4 Hz, 1 H), 7.45–7.56 (m, 3 H), 7.67 (d, J = 8.6 Hz, 1 H), 7.79 (dd, J = 7.8, 1.4 Hz, 1 H), 8.32 (dd, J = 8.3, 1.4 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.57, 16.78, 21.05, 21.60, 22.23, 22.24, 23.44, 23.51, 25.84, 26.39, 31.62, 31.68, 34.46, 34.59, 39.98, 41.18, 47.28, 49.64, 74.59, 82.11, 121.15, 122.39, 124.46, 126.00, 126.22, 127.73, 127.85, 130.12, 136.24, 154.10, 166.76. Known compound, CAS 129656–73–1.

1-Bromo-2-methoxynaphthalene. This was obtained by bromination of 2-methoxynaphthalene in acetic acid.[41a] Attempts to diminish the solvent volume by partially replacing HOAc with CH_2Cl_2 (1:1), in which starting material and product are well soluble, led to a significantly reduced yield (76 % at the 1.25 mol scale). This was due to lower chemoselectivity, with partial over-bromination to 1,6-dibromo-2-methoxynaphthalene, besides leaving unreacted starting material. *Procedure*: To a suspension of 2-methoxynaphthalene (198 g, 1.25 mol, 1.00 equiv.) in acetic acid (1 L), a solution of brom-

ine (65.0 mL, 1.25 mol, 1.00 equiv.) in acetic acid (250 mL) was added at r.t. over the course of 2.5 h. After addition of ca. 80 mL of the solution, the starting material had completely dissolved; after addition of ca. 120 mL, product crystallization set in. After the addition was completed, H_2O (500 mL) was added dropwise with stirring to the reaction mixture to complete the crystallization. The resulting suspension was filtered, and solids were washed with H_2O to neutrality. The resulting colorless solid was left to dry in an open dish in the fume hood for 1 day, giving 276 g (93 %) of colorless crystals. R_f 0.46 (EtOAc–hexanes, 1:10). M. p. 84.7–86.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.00 (s, 3 H), 7.24 (d, J = 8.9 Hz, 1 H), 7.38 (ddd, J = 8.0, 6.8, 1.1 Hz, 1 H), 7.55 (ddd, J = 8.4, 6.7, 1.2 Hz, 1 H), 7.76 (d, J = 9.2 Hz, 1 H), 7.79 (d, J = 9.1 Hz, 1 H), 8.21 (d, J = 8.6 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 57.22, 108.84, 113.79, 124.46, 126.28, 127.88, 128.18, 129.10, 129.97, 133.28, 153.91. Known compound, CAS 3401–47–6.

(1*R*)-Menthyl (a*S*)-2′-methoxy-(1,1′-binaphthyl)-2-carboxylate ((a*S*)-10). Under argon, a solution of 1-bromo-2-methoxynaphthalene (119 g, 500 mmol, 1.25 equiv.) in dry toluene (460 mL) was added to magnesium (14.6 g, 600 mmol, 1.50 equiv.) in dry THF (90 mL) in portions; initiation of the reaction was assured after the first addition. The reaction temperature was kept at 40–50 °C by means of an external water bath to prevent either over-reaction at elevated or crystallization of the Grignard reagent at lower temperature. After completion of the addition, the reaction solution was heated to 55 °C for another 1 h. The resulting Grignard solution was transferred (while warm) continuously or in several portions through PTFE tubing into a solution of (1*R*)-menthyl 1-(1*R*)-menthyloxynaphthyl-2-carboxylate (**7**; 186 g, 400 mmol, 1.00 equiv.) in dry toluene (220 mL) kept at r.t. by a water bath, also ensuring that no magnesium-metal was transferred. The reaction mixture was stirred at 35 °C for 15 h, then the reaction was quenched by addition of aqueous 6 M HCl (100 mL), saturated aqueous NH_4Cl (200 mL) and H_2O (300 mL). The layers were separated, the aqueous layer was extracted with EtOAc (3 ×) and the combined organic layers were washed with aqueous 2 M NaOH (2 ×) and saturated aqueous Na_2CO_3 (2 ×), dried ($MgSO_4$) and filtered. Volatiles were removed in a rotatory evaporated and the residue was dissolved in MeOH (900 mL). A colorless solid crystallized from the brown crude reaction mixture overnight at r.t., which was filtered and washed with cooled (0 °C) MeOH. Recrystallization from boiling EtOH (1200 mL) with toluene (80 mL) added to increase solubility gave 145 g (78 %) colorless solid (> 99.7 % *de*). R_f 0.39 (EtOAc–hexanes, 1:10). ^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.22 (td, J = 12.2, 10.9 Hz, 1 H), 0.49 (d, J = 7.0 Hz, 3 H), 0.50–0.60 (m, 1 H), 0.64 (d, J = 6.5 Hz, 3 H), 0.66–0.69 (m, 1 H), 0.71 (d, J = 7.0 Hz, 3 H), 0.82 (m, 1 H), 1.19 (m, 1 H), 1.34 (m, 1 H), 1.47 (m, 3 H), 3.74 (s, 3 H), 4.48 (td, J = 10.8, 4.4 Hz, 1 H), 6.96 (d, J = 8.5 Hz, 1 H), 7.16 (ddd, J = 8.3, 6.7, 1.3 Hz, 1 H), 7.28 (m, 2 H), 7.35 (m, 1 H), 7.41 (d, J = 9.0 Hz, 1 H), 7.52 (ddd, J = 8.1, 6.6, 1.3 Hz, 1 H), 7.84 (d, J = 7.9 Hz, 1 H), 7.93 (d, J = 8.1 Hz, 1 H), 7.98 (m, 2 H), 8.13 (d, J = 8.6 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 15.83, 21.06, 21.99, 22.92, 25.66, 31.12, 34.20, 39.68, 46.69, 56.52, 74.41, 113.30, 122.41, 123.58, 124.97, 126.52, 126.62, 126.66, 127.61, 127.63, 127.82, 127.98, 128.10, 129.14, 129.38, 129.94, 133.07, 134.31, 135.19, 136.59, 154.32, 167.59. Known compound, CAS 116741–64–1.

(a*S*)-2′-Methoxy-(1,1′-binaphthyl)-2-carboxylic acid (MeO-BINACox; L1). (1*R*)-Menthyl (a*S*)-2′-methoxy-(1,1′-binaphthyl)-2-carboxylate (**10**; 70.0 g, 150 mmol, 1.00 equiv.) and finely powdered 85 % KOH (49.5 g, 750 mmol, 5.00 equiv.) were added to PEG-200 (750 mL) at r.t. The mixture was heated to 150 °C with stirring and kept at that temperature for 5 h. Reaction progress was followed by TLC (EtOAc–hexanes, 1:10 + 1 % HOAc; product R_f 0.17). After cooling to r.t., the reaction was quenched by addition of H_2O (200 mL), aqueous 6 M HCl (400 mL) and EtOAc (300 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 300 mL). The combined organic phase was washed with H_2O (5 × 300 mL) and dried with $MgSO_4$. After filtration and evaporation of the solvent, the sticky residue was suspended in MeOH (150 mL), the homogenized suspension filtered through a glass filter and sucked dry in vacuo. The material was recrystallized from boiling EtOH (ca. 90 mL) to give 44.2 g (86 %) of colorless solid (≥99.8 % *ee*, by GP-2). R_f 0.17 (EtOAc–hexanes, 1:10 + 1 % HOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.62 (s, 3 H), 6.86 (d, J = 8.5 Hz, 1 H), 7.14 (ddd, J = 8.3, 6.8, 1.4 Hz, 1 H), 7.20–7.27 (m, 2 H), 7.29 (ddd, J = 8.1, 6.8, 1.1 Hz, 1 H), 7.32 (d, J = 9.1 Hz, 1 H), 7.51 (ddd, J = 8.1, 6.1, 1.8 Hz, 1 H), 7.87 (d, J = 8.1 Hz, 1 H), 7.91 (d, J = 8.2 Hz, 1 H), 7.96 (m, 2 H), 8.12 (d, J = 8.7 Hz, 1 H), 10.93 (br. s, 1 OH). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 56.72, 113.72, 121.55, 123.61, 124.92, 126.62, 126.60, 126.85, 127.81, 127.87, 128.03, 128.08 (2C), 128.13, 129.06, 129.73, 133.05, 133.88, 135.63, 138.13, 154.28, 171.87. Known compound.

Synthesis of selected chiral biaryl carboxylic acids (Ln)

(1*R*)-Menthyl (a*S*)-2′-hydroxy-[1,1′-binaphthyl]-2-carboxylate (12). Under argon, a solution of (1*R*)-menthyl (a*S*)-2′-methoxy-(1,1′-binaphthyl)-2-carboxylate (**10**; 2.53 g, 5.32 mmol, 1.00 equiv.) in dry CH_2Cl_2 (60 mL) was cooled to –78 °C. BBr_3 (1 M in CH_2Cl_2; 10.8 mL, 10.8 mmol, 2.00 equiv.) was added dropwise over 15 min and the reaction mixture was stirred at –78 °C for 5 h. Saturated aqueous LiOH (15 mL) was added and the mixture warmed to r.t. After addition of H_2O (20 mL), the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL) and the combined organic layers were washed with saturated aqueous NaCl (100 mL). After drying (Na_2SO_4) and filtration, the solvent was removed in vacuo. The crude product was purified by CC (SiO_2, EtOAc–hexanes, 1:40→1:4) to give 2.01 g (82 %) colorless solid. ^{1}H NMR (360 MHz, $CDCl_3$): δ = –0.05 (q, J = 12.0 Hz, 1 H), 0.41 (d, J = 6.9 Hz, 3 H), 0.66 (d, J = 7.0 Hz, 3 H), 0.67 (d, J = 6.5 Hz, 3 H), 0.76–0.90 (m, 2 H), 1.16–1.28 (m, 1 H), 1.34–1.55 (m, 5 H), 4.53 (td, J = 10.6, 4.5 Hz, 1 H), 4.85 (br. s, 1 OH), 6.88 (dd, J = 8.4, 1.1 Hz, 1 H), 7.17 (ddd, J = 8.3, 6.8, 1.3 Hz, 1 H), 7.23–7.42 (m, 4 H), 7.57 (ddd, J = 8.2, 6.3, 1.8 Hz, 1 H), 7.78–7.86 (m, 1 H), 7.90 (d, J = 8.9 Hz, 1 H), 7.97 (d, J = 8.2 Hz, 1 H), 8.07 (s, 2 H). ^{13}C NMR (91 MHz, $CDCl_3$): δ = 15.90, 20.82, 21.98, 23.10, 25.91, 31.18, 34.15, 39.70, 46.63, 75.20, 117.86, 118.40, 123.50, 124.61, 126.08, 126.75, 127.11, 127.69, 127.97, 128.19, 128.37, 129.19, 129.37, 129.89, 132.32, 132.51, 132.94, 134.18, 135.27, 151.14, 167.75. ESI HR-MS calcd. for $[C_{31}H_{33}O_3]^+$: 453.2424, found 453.2424. ESI HR-MS calcd. for $[C_{31}H_{31}O_3]^-$: 451.2279, found 451.2285.

(a*S*)-2′-Ethoxy-[1,1′-binaphthyl]-2-carboxylic acid (L23).

(1*R*)-Menthyl (a*S*)-2′-ethoxy-[1,1′-binaphthyl]-2-carboxylate. A solution of (1*R*)-menthyl (a*S*)-2′-hydroxy-[1,1′-binaphthyl]-2-carboxylate (**12**; 250 mg, 552 µmol, 1.00 equiv.) in dry MeCN (3 mL) was stirred with K_2CO_3 (122 mg, 884 µmol, 1.60 equiv.) and ethyl bromide (410 µL, 5.52 mmol, 10.0 equiv.) at 30 °C for 3 d. Remaining ethyl bromide was quenched by addition of NEt_3 (0.7 mL) and stirring for a few minutes. H_2O (30 mL) and Et_2O (30 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (30 mL). The combined organic layers were washed with aqueous 2 M HCl (2 × 15 mL), H_2O (20 mL) and saturated aqueous NaCl (20 mL). After drying (Na_2SO_4) and filtration, the solvent was removed in vacuo to give 164 mg (62 %) slightly yellow solid. ^{1}H NMR (360 MHz, $CDCl_3$): δ = –0.17 (ψ-q, J = 12.1 Hz, 1 H), 0.50 (d, J = 6.9 Hz, 3 H), 0.56 (td, J = 12.2, 3.0 Hz, 1 H), 0.60–0.75 (m, 1 H), 0.65 (d, J = 6.5 Hz, 3 H), 0.70 (d, J = 7.0 Hz, 3 H), 0.81 (td, J = 12.8, 3.1 Hz,

1 H), 1.02 (t, *J* = 7.0 Hz, 3 H), 1.12–1.54 (m, 5 H), 3.95–4.09 (m, 2 H), 4.49 (td, *J* = 10.8, 4.4 Hz, 1 H), 6.98 (d, *J* = 8.3 Hz, 1 H), 7.16 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1 H), 7.23–7.32 (m, 2 H), 7.32–7.42 (m, 2 H), 7.51 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1 H), 7.82 (d, *J* = 8.1 Hz, 1 H), 7.90–8.01 (m, 3 H), 8.12 (d, *J* = 8.6 Hz, 1 H). ^{13}C NMR (91 MHz, $CDCl_3$): δ = 15.14, 15.89, 21.03, 21.99, 22.98, 25.67, 31.15, 34.23, 39.75, 46.73, 64.89, 74.41, 114.85, 122.91, 123.00, 123.55, 125.09, 126.48, 126.48, 126.50, 127.51, 127.79, 127.81, 128.01, 129.18, 129.23, 129.98, 133.14, 134.46, 135.15, 136.82, 153.76, 167.67. ESI HR-MS calcd. for $[C_{33}H_{37}O_3]^+$ ($[M + H]^+$): 481.2737, found 481.2738.

(a*S*)-2′-Ethoxy-[1,1′-binaphthyl]-2-carboxylic acid (L23). (1*R*)-Menthyl (a*S*)-2′-ethoxy-[1,1′-binaphthyl]-2-carboxylate (160 mg, 333 µmol, 1.00 equiv.) and 85 % KOH (934 mg, 14.1 mmol, 42.5 equiv.) in EtOH (5 mL) were combined for 48 h according to GP-1A. The crude reaction product was purified by CC (SiO_2, EtOAc–hexanes, 1:4) to give 93 mg (82 %) colorless solid (≥95 % *ee*, by GP-2). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.0 Hz, 3 H), 4.01 (q, *J* = 7.0 Hz, 2 H), 6.92 (d, *J* = 8.5 Hz, 1 H), 7.19 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1 H), 7.22–7.34 (m, 3 H), 7.39 (d, *J* = 9.0 Hz, 1 H), 7.55 (ddd, *J* = 8.1, 6.4, 1.6 Hz, 1 H), 7.88 (d, *J* = 8.2 Hz, 1 H), 7.95 (d, *J* = 8.2 Hz, 1 H), 7.99 (t, *J* = 8.2 Hz, 2 H), 8.15 (d, *J* = 8.7 Hz, 1 H), 8.62 (br. s, 1 OH). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.92, 65.06, 115.01, 121.92, 123.72, 125.02, 126.53, 126.66, 126.78, 127.90, 128.00, 128.03, 128.07 (2 C), 128.10, 129.06, 129.77, 133.01, 134.00, 135.50, 137.79, 153.47, 170.64. ESI HR-MS calcd. for $[C_{23}H_{17}O_3]^-$: 341.1183, found 341.1182.

The allyloxy (L24) and benzyloxy (L25) derivatives were analogously prepared starting from 12; see the supporting information.

(1*R*)-Menthyl (a*S*)-2′-tosyloxy-[1,1′-binaphthyl]-2-carboxylate (13). Under argon, (1*R*)-menthyl (a*S*)-2′-hydroxy-[1,1′-binaphthyl]-2-carboxylate (**12**; 600 mg, 1.36 mmol, 1.00 equiv.), tosyl chloride (278 mg, 1.46 mmol, 1.10 equiv.) and DMAP (32.5 mg, 266 µmol, 0.20 equiv.) in dry CH_2Cl_2 (10 mL) was cooled to 0 °C. NEt_3 (220 µL, 1.60 mmol, 1.20 equiv.) was added and the reaction mixture stirred at 0 °C for 2 h, then at r.t. for 18 h. Saturated aqueous NH_4Cl (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic layers were washed with aqueous 2 M NaOH (20 mL) and saturated aqueous NaCl (20 mL). After drying (Na_2SO_4) and filtration, the solvent was removed in vacuo to give 708 mg (88 %) yellow solid. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.09 (q, *J* = 12.1 Hz, 1 H), 0.55 (d, *J* = 6.9 Hz, 3 H), 0.60–0.94 (m, 3 H), 0.70 (d, *J* = 6.5 Hz, 3 H), 0.77 (d, *J* = 7.0 Hz, 3 H), 1.12–1.30 (m, 1 H), 1.45–1.63 (m, 4 H), 2.27 (s, 3 H), 4.54 (td, *J* = 10.6, 4.2 Hz, 1 H), 6.79 (d, *J* = 8.1 Hz, 2 H), 7.01 (ψ-d, *J* = 8.3 Hz, 3 H), 7.08 (d, *J* = 8.4 Hz, 1 H), 7.13–7.28 (m, 2 H), 7.42 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1 H), 7.49 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1 H), 7.76 (d, *J* = 9.0 Hz, 1 H), 7.82–7.95 (m, 3 H), 8.00 (d, *J* = 8.9 Hz, 1 H), 8.04 (d, *J* = 8.9 Hz, 1 H). ^{13}C NMR (91 MHz, $CDCl_3$): δ = 16.02, 21.03, 21.70, 22.02, 23.03, 25.77, 31.22, 34.20, 40.03, 46.75, 74.75, 121.19, 126.02, 126.35, 126.44, 126.78, 126.98, 127.26, 127.56, 127.71, 128.05, 128.12, 128.39, 128.47, 129.19, 129.54, 129.94, 131.75, 132.77, 133.53, 133.93, 133.96, 134.83, 144.21, 145.35, 166.59. ESI HR-MS calcd. for $[C_{38}H_{39}O_5S]^+$ ($[M + H]^+$): 607.2513, found 607.2519. ESI HR-MS calcd. for $[C_{38}H_{38}O_5S + NH_4]^+$: 624.2778, found 624.2782.

(a*S*)-2′-Phenyl-[1,1′-binaphthyl]-2-carboxylic acid (L26)

(1*R*)-Menthyl (a*S*)-2′-phenyl-[1,1′-binaphthyl]-2-carboxylate. Under argon, a solution of phenylboronic acid (604 mg, 4.95 mmol, 10.0 equiv.) in dry THF (8 mL) was added to K_3PO_4 (1.05 g, 4.95 mmol, 10.0 equiv.) and degassed with an argon bubbling (15 min). $Ni(COD)_2$ (20.0 mg, 74.3 µmol, 0.15 equiv.) and PCy_3 (83.0 mg, 297 µmol, 0.60 equiv.) were added, followed by (1*R*)-menthyl (a*S*)-2′-tosyloxy-[1,1′-binaphthyl]-2-carboxylate (**13**; 300 mg, 495 µmol, 1.00 equiv.). The reaction mixture was heated to 45 °C for 48 h. After filtration, EtOAc (25 mL) and H_2O (25 mL) were added to the filtrate and the layers were separated. The aqueous layer was extracted with EtOAc (25 mL) and the combined organic layers were washed with saturated aqueous NaCl (2 × 25 mL). After drying (Na_2SO_4) and filtration, the solvent was removed in vacuo. The crude product was purified by CC (SiO_2, EtOAc–hexanes, 1:20) to give 172 mg (68 %) colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.05 (q, *J* = 12.1 Hz, 1 H), 0.53 (d, *J* = 6.9 Hz, 3 H), 0.67 (d, *J* = 7.0 Hz, 3 H), 0.69 (d, *J* = 6.5 Hz, 3 H), 0.76–0.88 (m, 2 H), 1.14–1.37 (m, 2 H), 1.41–1.54 (m, 4 H), 4.54 (td, *J* = 10.6, 4.4 Hz, 1 H), 6.94–6.98 (m, 3 H), 7.11–7.30 (m, 6 H), 7.37–7.45 (m, 2 H), 7.61 (d, *J* = 8.5 Hz, 1 H), 7.78 (d, *J* = 8.2 Hz, 1 H), 7.85 (d, *J* = 8.6 Hz, 1 H), 7.92 (d, *J* = 8.2 Hz, 1 H), 8.01 (d, *J* = 8.8 Hz, 2 H). ^{13}C NMR (91 MHz, $CDCl_3$): δ = 15.86, 21.01, 22.01, 22.91, 25.76, 31.20, 34.16, 39.86, 46.66, 74.78, 125.76, 126.04, 126.47, 126.51, 126.53, 126.55, 127.45, 127.49, 127.93, 127.97, 128.00, 128.02, 128.25, 129.12, 130.84, 132.80, 132.85, 133.44, 134.71, 134.86, 138.70, 141.92, 167.51. EI HR-MS calcd. for $[C_{36}H_{36}O_2]^+$: 512.2710, found 512.2703.

(a*S*)-2′-Phenyl-[1,1′-binaphthyl]-2-carboxylic acid (L26). The above ester (167 mg, 326 µmol, 1 equiv.) was saponified with 85 % KOH (2.19 g, 33.2 mmol, 102 equiv.) in EtOH (6 mL) over 24 h, followed by addition of $LiOH·H_2O$ (625 mg, 26.1 mmol, 80.0 equiv.) and continued saponification for 24 h according to GP-1B. The crude product was purified by CC (SiO_2, EtOAc–hexanes, 1:4) to give 103 mg (84 %) yellowish solid (≥ 95 % *ee* by GP-2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.87–6.95 (m, 4 H), 6.96–7.01 (m, 1 H), 7.07 (d, *J* = 8.5 Hz, 1 H), 7.21–7.31 (m, 2 H), 7.34 (d, *J* = 8.5 Hz, 1 H), 7.45 (ddd, *J* = 8.1, 6.6, 1.2 Hz, 1 H), 7.50 (ddd, *J* = 8.1, 6.6, 1.2 Hz, 1 H), 7.55 (d, *J* = 8.4 Hz, 1 H), 7.83 (d, *J* = 8.6 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 8.7 Hz, 1 H), 7.97 (d, *J* = 8.2 Hz, 1 H), 8.02 (d, *J* = 8.5 Hz, 1 H), 10.03 (br. s, 1 OH). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 125.77, 126.28, 126.41, 126.53, 126.58, 126.96, 127.53, 127.92, 128.04, 128.08, 128.11, 128.13, 128.17, 128.29, 128.45, 128.91, 132.62, 132.95, 133.53, 134.08, 135.11, 138.93, 140.69, 141.63, 171.10. ESI HR-MS calcd. for $[C_{27}H_{17}O_2]^-$: 373.1234, found 373.1233.

(a*S*)-2′-Methoxy-3-phenyl-[1,1′-binaphthyl]-2-carboxylic acid (L12). *Synthesis by C–H-arylation from MeO-BINA-Cox (**L1**)*:[53] To a mixture of **L1** (328 mg, 1.00 mmol, 1.00 equiv.), Ag_2CO_3 (303 mg, 1.10 mmol, 1.10 equiv.), K_2CO_3 (138 mg, 1.00 mmol, 1.00 equiv.), $Pd(OAc)_2$ (22.5 mg, 0.10 mmol, 0.10 equiv.) and *N*-acetylglycin (23.4 mg, 0.20 mmol, 0.20 equiv.) under argon, iodobenzene (1.30 mL, 12.0 mmol, 12.0 equiv.) and HOAc (1.00 mL, 18.0 mmol, 18.0 equiv.) were added in one portion each at r.t. The reaction was heated to 90 °C for 3 d. After cooling to r.t., aqueous 1 M HCl (5 mL) was added and the mixture was filtered through celite, followed by washing of the filter cake with EtOAc (3 × 25 mL). After separation of the layers, the aqueous layer was extracted with EtOAc (2 × 25 mL) and the combined organic phase was washed with saturated aqueous NaCl (10 mL), dried ($MgSO_4$), and filtered. Purification of the crude product by CC (SiO_2, EtOAc–hexanes, 1:10 + 1 % HOAc) and recrystallization from MeOH (1.5 mL) gave 206 mg (51 %) yellow solid (≥95 % *ee* by GP-2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59 (s, 3 H), 7.04 (d, *J* = 8.4 Hz, 1 H), 7.15–7.39 (m, 8 H), 7.45–7.59 (m, 3 H), 7.84 (d, *J* = 8.1 Hz, 1 H), 7.88–8.04 (m, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 56.84, 113.75, 120.33, 123.86, 125.56, 126.86, 126.90, 126.96, 127.48, 127.51, 127.86, 128.38, 128.47, 128.82, 128.89, 129.01, 130.31, 131.73, 132.17, 133.50, 133.85, 134.23, 137.16, 140.77, 154.95, 172.85. ESI HR-MS calcd. for $[C_{28}H_{19}O_3]^-$: 403.1340, found 403.1343.

(a*S*)-6′-Adamantyl-2′-methoxy-(1,1′-binaphthyl)-2-carboxylic acid (L19). Under argon, a suspension of (1*R*)-menthyl (a*S*)-2′-meth-

oxy-(1,1′-binaphthyl)-2-carboxylate (**10**; 4.67 g, 10.0 mmol, 1.00 equiv.), 1-bromoadamantane (2.15 g, 10.0 mmol, 1.00 equiv.) and indium(III) chloride (111 mg, 0.50 mmol, 0.05 equiv.)[58] in dry CH_2Cl_2 (20 mL) was stirred at 60 °C for 14 h. The crude reaction product obtained by evaporation of the solvent was purified by CC (SiO_2, EtOAc–hexanes, 1:10→EtOAc–hexanes + HOAc 1:10 + 1 %). The resulting yellow solid was dissolved in Et_2O and the organic layer was extracted with aqueous 2 M NaOH (3 ×). The combined aqueous layers were washed with Et_2O (2 ×), acidified with aqueous 6 M HCl and extracted with Et_2O. Drying ($MgSO_4$), filtration and removal of the solvent in vacuo gave 2.460 g (53 %) slightly yellow solid (≥99.7 % *ee* by GP-2). R_f 0.22 (EtOAc–hexanes, 1:10 + 1 % HOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.70–1.85 (m, 6 H), 1.96 (d, *J* = 2.9 Hz, 6 H), 2.10 (m, 3 H), 3.70 (s, 3 H), 6.84 (d, *J* = 9.0 Hz, 1 H), 7.18–7.28 (m, 3 H), 7.37 (d, *J* = 9.0 Hz, 1 H), 7.53 (ddd, *J* = 8.1, 6.3, 1.6 Hz, 1 H), 7.74 (d, *J* = 2.0 Hz, 1 H), 7.88–8.05 (m, 3 H), 8.16 (d, *J* = 8.7 Hz, 1 H), 8.58 (br. s, 1 OH). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 29.10, 36.21, 37.01, 43.20, 56.82, 113.56, 121.07, 122.91, 124.59, 125.08, 126.59, 126.81, 127.93, 128.00, 128.02, 128.04, 128.09, 129.17, 129.86, 132.16, 133.07, 135.58, 138.06, 146.42, 153.94, 171.20. ^{13}C APT NMR (101 MHz, $CDCl_3$): δ = 29.09 (CH), 36.19 (C), 37.00 (CH_2), 43.20 (CH_2), 56.78 (CH_3), 113.57 (CH), 121.18 (C), 122.88 (CH), 124.59 (CH), 124.98 (CH), 126.58 (CH), 126.77 (CH), 127.89 (C), 127.97 (CH), 128.00 (CH), 128.01 (CH), 128.07 (CH), 129.15 (C), 129.74 (CH), 132.14 (C), 133.08 (C), 135.58 (C), 138.25 (C), 146.32 (C), 153.93 (C), 171.97 (CO_2H). EI HR-MS calcd. for $[C_{32}H_{30}O_3]^+$: 462.2189, found 462.2187.

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