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Chiral 2-(2-hydroxyaryl)alcohols (HAROLs) with a 1,4-diol scaffold as a new family of ligands and organocatalysts

Ömer Dilek[a,b], Mustafa A. Tezeren[a,b], Tahir Tilki[b], Erkan Ertürk*[,a]

[a] Institute of Chemical Technology, TÜBITAK Marmara Research Center, 41470 Gebze, Kocaeli, Turkey

[b] Department of Chemistry, Süleyman Demirel University, 32260 Isparta, Turkey

E-mail address of the corresponding author: erkan.erturk@tubitak.gov.tr (E. Ertürk)

Fax: +90-262-641 2309

Tel: +90-262-677 3893

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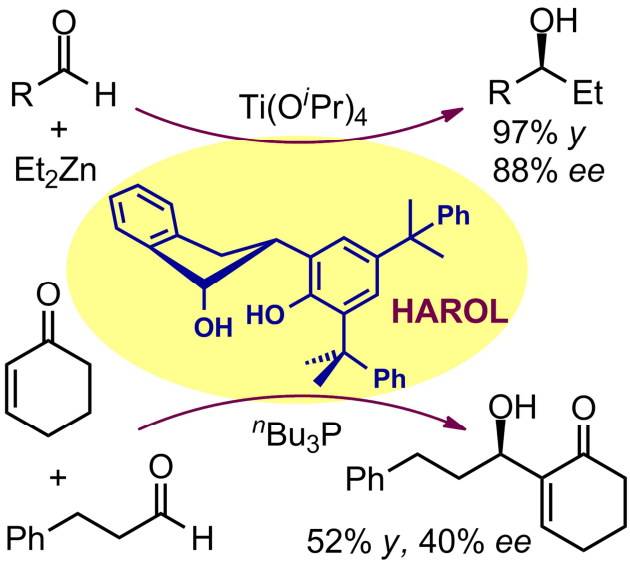
Graphical Abstract



Abstract

Efficient and modular syntheses of chiral 2-(2-hydroxyaryl)alcohols (HAROLs), novel 1,4-diols carrying one phenolic and one alcohol hydroxyl group, have been developed which led to generation of a small library of structurally diverse HAROLs in enantiomerically pure form. Of the different HAROLs examined, a HAROL based on the indan backbone exhibited the highest activity and enantioselectivity in the 1,2-addition of certain organometallic compounds to aldehydes in the presence of $Ti(O^iPr)_4$ (up to 97% *y*, 88% *ee*) and performed as a hydrogen-bond donor organocatalyst in the Morita-Baylis-Hillman reaction, promoted by trialkylphosphines.

Key Words

Chiral 1,4-diols, Chiral ligands, Hydrogen-bond donor organocatalysts, Diethylzinc addition, Morita-Baylis-Hillman reaction

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1. Introduction

Chiral compounds in enantiomerically pure form are intensely desired due to the fact that not only biological systems, in most cases, recognize a pair of enantiomers as different substances, but also enantiopure molecules offer new opportunities as functional materials.[1,2] Over the last three decades, catalytic asymmetric synthesis has proven to be the most efficient tool for providing pure enantiomers. Consequently, the development of novel chiral compounds, especially for catalytic applications, continues to be a most vibrant field of research.[1] In this regard, enantiomerically pure diols, such as TADDOLs,[3] hydrobenzoins[4] as well as BINOLs[5], have played a significant role in enantioselective catalysis and materials science[2c,4b,6] as chiral ligands, organocatalysts, chiral luminophores etc. Whereas the majority of works with chiral diols have dealt with their use as chiral ligands in combination with metals in asymmetric catalysis,[3,4,5b-c,7] there have also been some reports in which chiral diols themselves serve as suitable hydrogen-bond donor (HBD) organocatalysts for certain asymmetric transformations.[8,9] For instance, chiral diols have been reported to perform in some reactions with a high degree of activity and enantioselectivity, such as the Morita-Baylis-Hillman reaction,[9a,b] epoxide ring-opening,[9c,d] hetero Diels-Alder reactions,[9e-i] aldol-type reactions,[9k,l] as well as some other transformations.[9m,n] As such, diols have become an appealing structural motif for organocatalysis in recent years.[10,11]

Xu and his co-workers recently reported the synthesis of chiral Ar-BINMOLs (1,1′-binaphthalene-2-α-arylmethan-2′-ols) possessing both axial and sp^3 point chirality (Figure 1)[12] which were shown to be efficient and highly enantioselective chiral ligands for the asymmetric 1,2-addition reactions of some organometallic compounds to aldehydes.[13-18] In some cases, up to >99% enantiomeric excesses were achieved for the 1,2-addition of organozinc,[14] organolithium,[15] organomagnesium,[16] and organoaluminum[17] reagents to aldehydes by employing a catalytic amount of ArBINMOLs (e.g. 5 mol%) and a super-stoichiometric amount of $Ti(O^iPr)_4$ (e.g. 2.50-6.00 equiv). Additionally, Xu and co-workers demonstrated that chiral ArBINMOLs can also act as supramolecular HBD organocatalysts for the enantioselective Michael addition of anthrone to (*E*)-β-nitrostyrene, furnishing the corresponding adduct in good yields, albeit moderate enantiomeric excesses were detected.[14] Despite their utility as catalysts, ArBINMOL-type structures are rather limited to the 1,1′-binaphthalene-unit, due to the synthetic approach developed. On the other hand, a modular synthesis of targets is regarded as a very advantageous approach, because it leads to the generation of a library of compounds with structural diversity, thereby enhancing the hit rate of the purpose.[19] Encouraged by the remarkable successes of ArBINMOLs as chiral ligands and by the potential catalytic applications of diols in general, we set out to prepare new chiral 1,4-diols posessing one phenolic and one

alcohol hydroxyl (-OH) group. Herein, we report efficient and modular syntheses of structurally-diverse 2-(2-hydroxyaryl)alcohols (HAROL*s*) as well as their use as chiral ligands and organocatalysts (Figure 1).

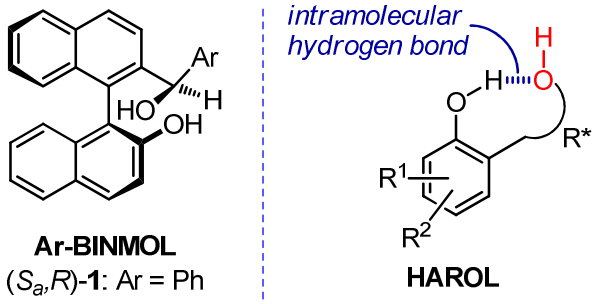
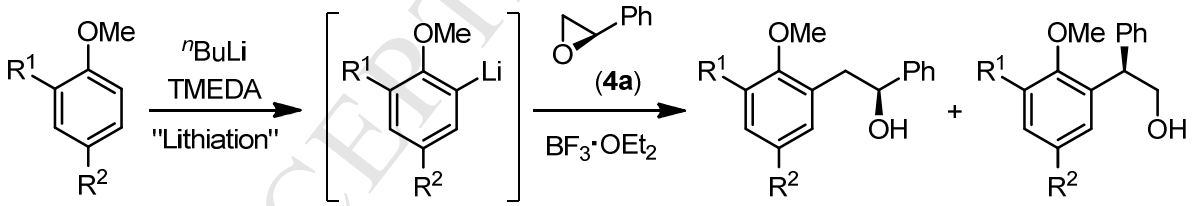


Figure 1. Structures of Ar-BINMOLs and **h**ydroxy**ar**ylalcoh**ol**s (HAROLs).

2. Results and discussion

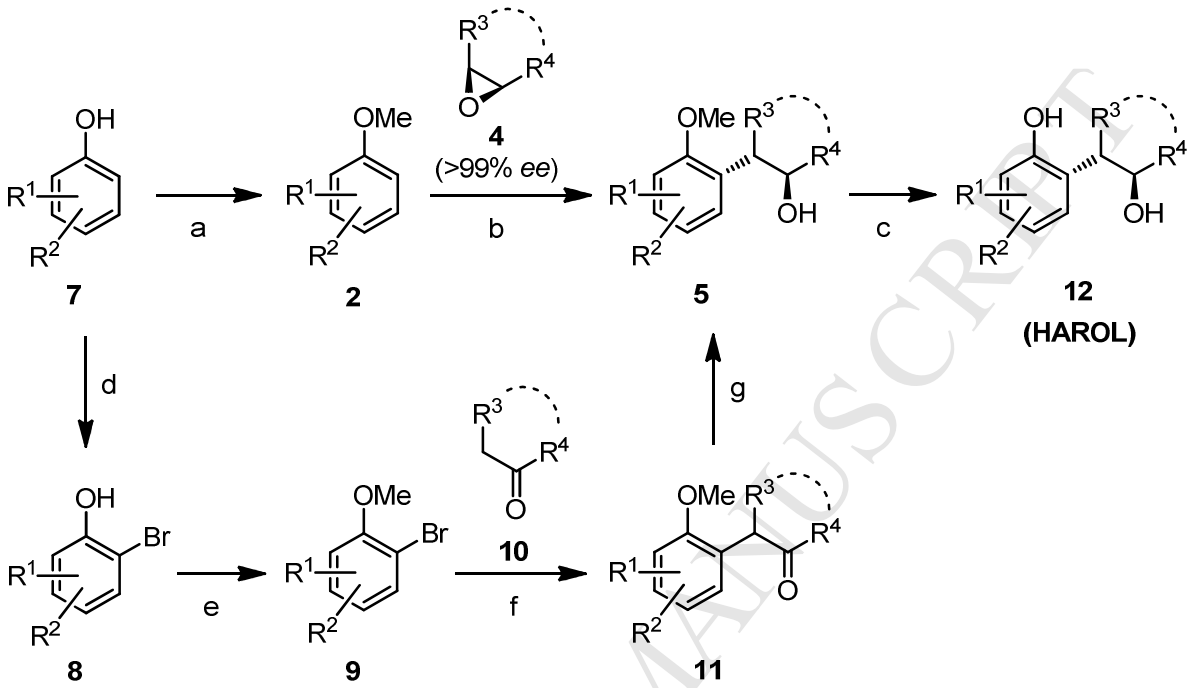
In our previous work, we reported on the regioselective ring-opening of epoxides with *ortho*-lithioanisoles in the presence of $BF_3{\cdot}OEt_2$ as the Lewis acid catalyst (Scheme 1).[20] This method enabled us to prepare 2-(2-methoxyaryl)alcohols (**5** and **6**) in high yields and regioselectivities. It was also shown that the enantiomerically pure 2-(2-methoxyaryl)alcohols **5a** and **6a** could be obtained by employing (*R*)-(+)-styrene oxide (**4a**). Thus, the protected form of 2-(2-hydroxyaryl)alcohols (HAROL*s*) could be accessed in a one-pot fashion. However, substrate scope of this methodology has found to be rather limited to monosubstituted terminal epoxides and bicyclic epoxides, such as styrene oxide and cyclohexene oxide.



Scheme 1. Stereospecific ring-opening of (*R*)-(+)-styrene oxide (**4a**) with *o*-lithioanisoles (**3**) catalyzed by $BF_3{\cdot}OEt_2$.

Synthetic analysis suggested that precursors for 2-(2-hydroxyaryl)alcohols (HAROL*s*) (**5**) could be effectively prepared via two ways as sketched in Scheme 2. Besides regioselective ring-opening of epoxides with *ortho*-lithioanisoles (upper side of Scheme 2), palladium-catalyzed α-arylation of ketones (**10**) with *ortho*-bromoanisoles (**9**) and enantioselective reduction of the resulting ketones (**11**) stood out as an effective way to access the HAROL

precursors **5** (lower side of Scheme 2). These two synthetic pathways were expected to provide structurally diverse HAROLs in an efficient manner.



Scheme 2. Syntheses of **h**ydroxy**ar**ylalcoh**ol**s (HAROLs): (a) Methylation; (b) (1) Lithiation, (2) $BF_3{\cdot}OEt_2$; (c) Demethylation; (d) *ortho*-Bromination; (e) Methylation; (f) Pd-catalyzed α-arylation; (g) Enantioselective reduction.

Unsubstituted anisole **2a** was obtained from commercial sources. The anisoles **2b–d** had to be prepared from the corresponding phenols **7b-d** through the usual methylation with dimethyl sulfate (Scheme 3). The somewhat special anisole **2e** (8-phenyl-1-methoxynaphthalene) was synthesized starting from 1-naphthol (**7e**) by exploiting the Pd-catalyzed arylation and subsequent methylation.[21]

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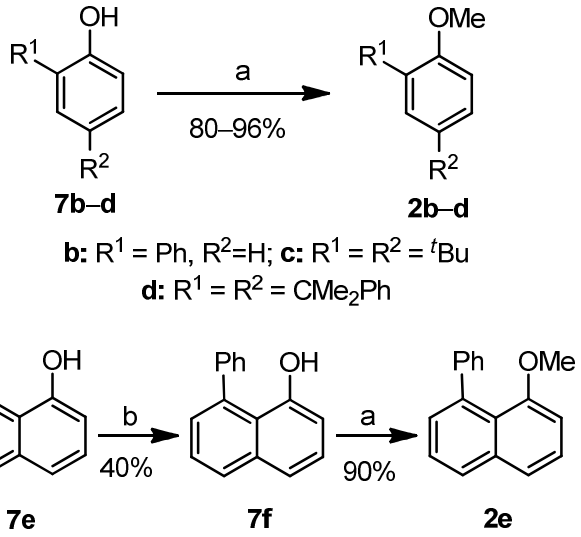
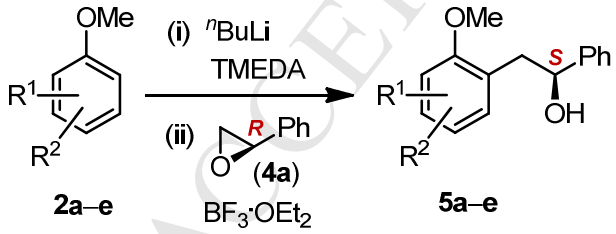
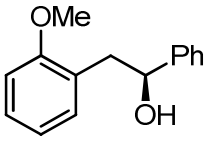


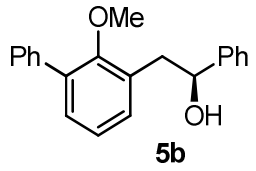
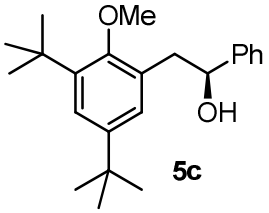
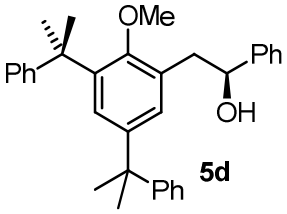
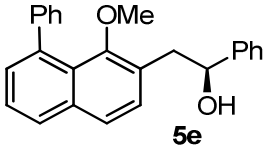
Scheme 3. Synthesis of anisoles. *Reagents and conditions:* (a) Me_2SO_4, K_2CO_3, acetone, reflux, 16 h, N_2; (b) PhI (1.20 equiv), $Pd(OAc)_2$ (2.5 mol%), Cs_2CO_3 (1.20 equiv), DMF, 125 ℃, 16 h, N_2.

With the anisole compounds **2a–e** in hand, their *ortho*-lithiated derivatives were reacted with (*R*)-(+)-styrene oxide (**4a**) to give the corresponding ring-opened products **5a–e** (Table 1). In this way, the enantiomerically pure (*S*)-2-(2-methoxyaryl)alcohols **5a–e** were obtained in satisfactory yields. As the ring-opening reaction of enantiopure **4a** with the *ortho*-lithioanisoles **3 a–e** is a stereospecific process proceeding via an S_N2 mechanism, the absolute configurations of **5 a-e** were assigned as *S*. It should be noted that only the desired regioisomers of the ring-opened products (such as **5a**) are shown in Table 1. The other regioisomers (such as **6a**) that are formed by the attack of *o*-lithioanisoles at the more substituted carbon atom of (*R*)-(+)-styrene oxide (**4a**) are not shown in Table 1.

Table 1. Synthesis of 2-(2-methoxyaryl)alcohols (**5a–e**) via the ring-opening of (*R*)-(+)-styrene oxide (**4a**) with *o*-lithioanisoles in the presence of $BF_3{\cdot}OEt_2$.

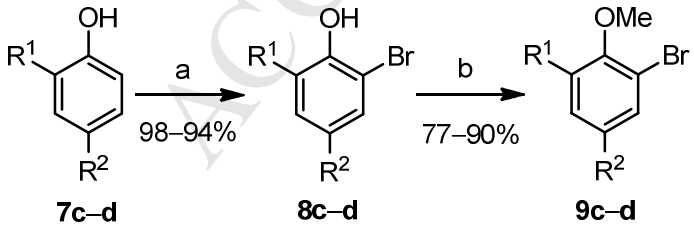


Entry	2	Product	Yield (%)[a]
1[b]	**2a**	 **5a**	83

2[c]	**2b**	 **5b**	66
3[c]	**2c**	 **5c**	68
4[c]	**2d**	 **5d**	60
5[b]	**2e**	 **5e**	53

[a] Yield of the isolated regioisomers **5a–e**.
[b] Reaction conditions: (i) **2a** or **2e** (3.00 equiv), ^{n}BuLi (3.00 equiv), TMEDA (0.60 equiv), THF, 0 ℃ → rt, 3 h; (ii) **4a** (1.00 equiv), $BF_3{\cdot}OEt_2$ (2.50 equiv), –78 ℃, 1 h, N_2.
[c] Reaction conditions: (i) **2b–d** (5.00 equiv), ^{n}BuLi (5.00 equiv), TMEDA (1.00 equiv), Et_2O, 0 ℃ → rt, 16 h; (ii) **4a** (1.00 equiv), $BF_3{\cdot}OEt_2$ (5.00 equiv), –78 ℃, 1 h, N_2.

Next, *o*-bromoanisoles that were needed for the Pd-catalyzed arylation of ketones were prepared starting from the corresponding phenols (Scheme 4). *Ortho*-monobromination of the phenols **7c–d** with molecular bromine in dichloromethane and the subsequent methylation of the *ortho*-bromophenols **8c–d** as before, allowed access to the bromoanisoles **9c–d** in high yields as shown in Scheme 4.



7c–d **8c–d** **9c–d**

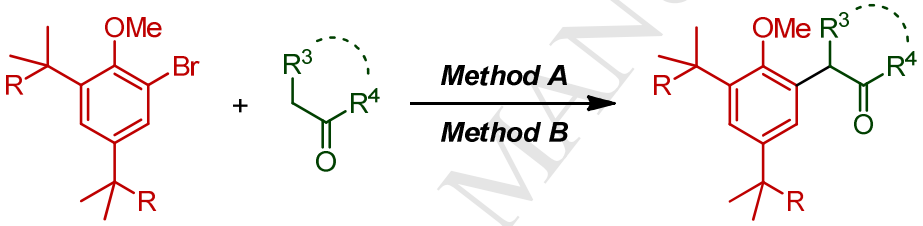
c: $R^1 = R^2 = {}^{t}Bu$; **d:** $R^1 = R^2 = CMe_2Ph$

Scheme 4. Synthesis of *o*-bromoanisoles **9c–d**. *Reagents and conditions:* (a) Br_2 (1.00 equiv), DCM, 0 ℃, 2 h, N_2; (b) Me_2SO_4 (1.30 equiv), K_2CO_3 (1.40 equiv), acetone, reflux, 16 h, N_2.

The *o*-bromoanisoles **9c–d** were then subjected to the palladium-catalyzed Buchwald-Hartwig α-arylation,[22] with ketones **10a–e** (Table 2). There have been several variants of the

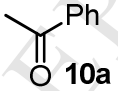
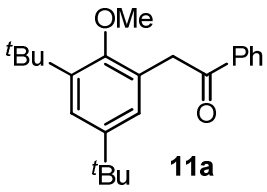
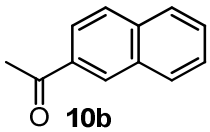
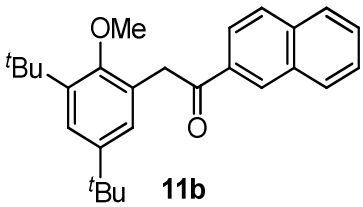
original Buchwald-Hartwig α-arylation conditions, reported in the literature over the last two decades. Among them, considering the air stability and easy availability of the triphenylphosphine ligand we first employed the $Pd(OAc)_2$-triphenylphosphine couple as the catalyst and cesium carbonate as the base in DMF at 150 °C (entry 1).[22f] The original Buchwald-Hartwig procedure consisting of the $Pd(OAc)_2$-tri-*tert*-butylphosphine couple and sodium *tert*-butoxide in THF at room temperature was then tested for our substrates as well (entry 2).[22a-d] The former was found to be effective in the coupling of the *o*-bromoanisole **9c** with acetophenone (**10a**) to some extent, giving the desired product **11a** in 68% yield. Nonetheless, the latter not only furnished the product **11a** with higher yield (72%), but also allowed us to purify the product more easily. So, 2-(2-methoxyaryl)ketones (**11a–f**) could be synthesized in yields ranging from 72% to 93%, by employing the original Buchwald-Hartwig catalytic system.

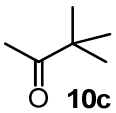
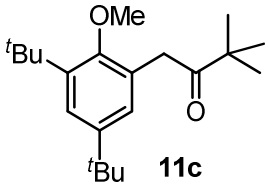
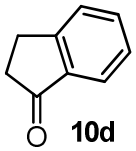
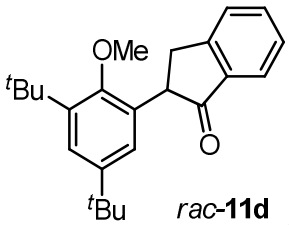
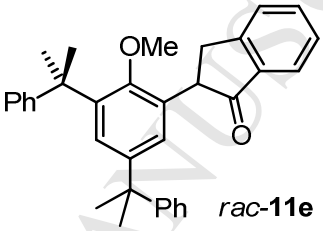
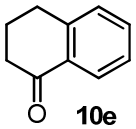
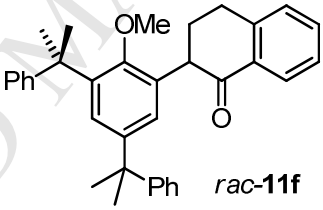
Table 2. Synthesis of α-(2-methoxyaryl)ketones (**11a–f**) via Buchwald-Hartwig α-arylation.



9c–d **10a–e** **11a–f**

c: R = Me; **d:** R = Ph

Entry	9	Ketone	Product	Yield (%)[a]
1[b]	**9c**	 **10a**	 **11a**	68
2[c]	**9c**	**10a**	**11a**	72
3[c]	**9c**	 **10b**	 **11b**	75

4[c]	**9c**	 **10c**	 **11c**	86
5[c]	**9c**	 **10d**	 *rac*-**11d**	83
6[c]	**9d**	**10d**	 *rac*-**11e**	76
7[c]	**9d**	 **10e**	 *rac*-**11f**	93

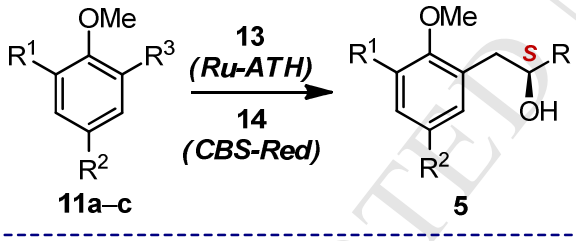
Method A: **9c** (1.00 equiv), **10a** (1.10 equiv), Cs_2CO_3 (2.50 equiv), $Pd(OAc)_2$ (2 mol%), PPh_3 (8 mol%), DMF, 150 ℃, 2 h, N_2. *Method B:* **9** (1.00 equiv), **10** (1.10 equiv), NaO^tBu (2.50 equiv), $Pd(OAc)_2$ (2 mol%), $P(^tBu)_3$ (2 mol%), THF, rt, 16 h, N_2.
[a] Isolated yield.
[b] Method A was applied.
[c] Method B was applied.

Asymmetric reduction of ketones is a powerful tool for the synthesis of secondary alcohols in enantiomerically enriched form. Asymmetric transfer hydrogenation (ATH) with the Noyori-Ikariya RuCl(*p*-cymene)[(*S,S*)-TsDPEN] catalyst (**13**) in the presence of 5:2 HCO_2H/Et_3N azeotropic mixture as the solvent and hydrogen source (Ru-ATH)[23] as well as the asymmetric reduction of ketones with proline-derived oxazoborolidine catalysts, e.g. (*R*)-(+)-2-methyl-CBS-oxazoborolidine (**14**), in the presence of borane complexes as the hydrogen source (CBS-Red)[24a] have played a pivotal role in the synthesis of chiral secondary alcohols. In numerous cases, both methods have been proven to be effective and highly enantioselective for laboratory-scale synthesis of chiral secondary alcohols from ketones. Moreover, the mechanisms of the both techniques, Ru-ATH[23c] and CBS-Red[24a], have been unequivocally provided. In case of ATH of ketones by employing the ruthenium(II) complex **13** in the presence of formic acid-

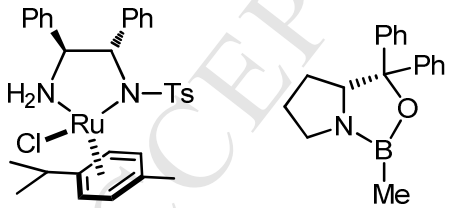
triethylamine mixture, **13** is first transformed to a 18e ruthenium hydride complex (RuH[(*S,S*)-TsNCH(C_6H_5)CH(C_6H_5)NH_2]–(η^6-cymene)) through a triethylamine-promoted elimination and a subsequent hydrogen abstraction from formic acid. This 18e ruthenium hydride complex then effects the enantioselective reduction of ketones by the simultaneous delivery of the hydridic RuH and protic NH to a C=O group through a six-membered pericyclic mechanism; i.e. "bifunctional metal-ligand catalysis" takes place.[23c] As for CBS-Red, its established mechanism evidenced by experimental findings as well as theoretical calculations in turn involves that the oxazoborolidine **14** acts as a bifunctional organocatalyst, thereby activating the carbonyl oxygen via Lewis acid catalysis as well as borane (hydride source) via Lewis base catalysis.[24a] Apart from their efficiencies and enantioselectivities, reliable stereochemical models for diastereomeric transition states have also been developed for both methods which allows us to predict the absolute configurations of the alcohol products with a high degree of certainty. The Noyori-Ikariya catalyst in Ru-ATH distinguishes the aryl and alkyl group attached to the carbonyl functionality and preferentially forms a favored diastereomeric transition state with the ketone substrate.[23c] On the other hand, oxazoborolidine catalyst **14** selectively forms a diastereomorphic ternary transition state complex with ketones and boranes by recognizing the organyl groups attached to the carbonyl functionality depending on their bulkiness.[24a] Accordingly, Ru-ATH and CBS-Red were applied to our test substrate **11a** by employing the commercially available RuCl(*p*-cymene)[(*S,S*)-TsDPEN] (**13**) and (*R*)-(+)-2-methyl-CBS-oxazoborolidine (**14**) as catalysts, respectively (Table 3). Although both Ru-ATH with **13** and CBS-Red with **14** were found to give the alcohol **5c** in excellent enantioselectivities (98% and 97% *ee*, respectively) they dramatically differed in their catalytic activities (Table 3, entries 1 and 2). Thus, CBS-Red gave the alcohol **5c** in almost quantitative yield (95%, entry 2) whereas Ru-ATH afforded it in modest yield (35%, entry 1). All attempts to increase the reduction yield of Ru-ATH with **13** by increasing the amount of the catalyst, by changing the hydrogen source from HCO_2H/Et_3N to HCO_2H/DABCO as well as ^{i}PrOH/KOH, and by employing solvents such as THF and DMF did not lead to any improvement.[23d] Absolute configurations of the alcohol products obtained from **11a** through Ru-ATH with **13** and CBS-Red with **14** were examined by comparing the sign of their optical rotations with the authentic sample **5c** that was prepared by us through the stereospecific ring-opening of (*R*)-(+)-styrene oxide (**4a**) with *ortho*-lithiated 2,4-di-*tert*-butylanisole (**2c**) in the presence of $BF_3{\cdot}OEt_2$ (Table 1, entry 3). Interestingly, it was determined that both catalytic systems, Ru-ATH with **13** and CBS-Red with **14**, gave the chiral secondary alcohol **5c** with the same absolute configuration (*S*) as depicted in Table 3 (entries 1 and 2). These stereochemical outcomes from the reduction of **11a** fit well with the mechanistic models developed for Ru-ATH and CBS-Red explained above: In the Ru-ATH, the phenyl- and the benzyl substituents attached to the C=O linkage of **11a** were recognized as the aryl- and alkyl groups,

respectively. On the other hand, the (*R*)-CBS catalyst **14** distinguishes the phenyl substituent as the bulkier group than the benzyl group of the ketone **11a**, thereby delivering the (*S*)-configured product (**5c**) preferentially. This observation is also in good accordance with a literature report, in which reduction of deoxybenzoin with borane dimethyl sulfide complex in the presence of (*R*)-CBS catalyst **14** led to the (*S*)-configured product.[24b] Note that the ketone **11a** might be considered as a derivative of deoxybenzoin. Thereafter, we were able to prepare the chiral alcohols **5f** and **5g** in almost enantiomerically pure form through the CBS-Red with **14** in excellent yields (entries 3 and 4). Inspection of the stereochemical working model for CBS-Red suggests that the absolute configurations of the secondary alcohols **5f** and **5g** are the same as for **5c**.

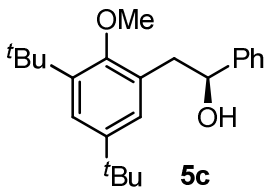
Table 3. Synthesis of chiral 2-(2-methoxyaryl)alcohols (**5**) through enantioselective reduction.

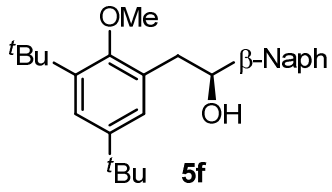
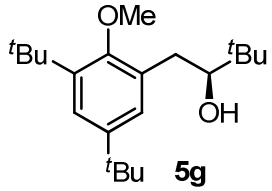


11a–c **5**



13 **14**

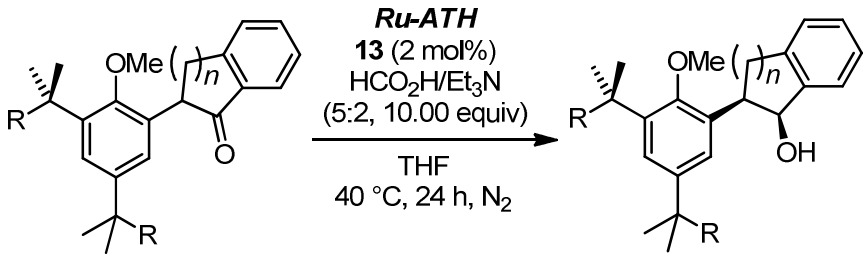
Entry	11	5	Yield (%)[a]	*ee* (%)[b]
1[c]	**11a**	 **5c**	35	98
2[d]	**11a**	**5c**	95	97

3[d]	**11b**	 **5f**	96	97
4[d]	**11c**	 **5g**	94	98

Ru-ATH: **13** (2 mol%), HCO_2H/Et_3N (5:2, 10.00 equiv HCO_2H), 40 ℃, 24 h, N_2. *CBS-Red:* **14** (5 mol%), $BH_3 \cdot SMe_2$ (1.00 equiv), THF, 0 ℃ →rt, 1 h, N_2.
[a] Isolated yield.
[b] Enantiomeric excesses.
[c] Ru-ATH was applied.
[d] CBS-Red was applied.

We next turned our attention to the asymmetric reduction of racemic 2-(2-methoxyaryl)indan-1-one and 2-(2-methoxyaryl)tetral-1-one derivatives (*rac*-**11d–f**) (Scheme 5). Ru-ATH was thought to be suitable for asymmetric reduction of these bicyclic α-aryl-substituted racemic ketones, through a dynamic kinetic resolution (DKR) process, thus facilitating the generation of the corresponding chiral alcohols in high yields. Note that ATH of very similar substrates, such as (±)-2-methylindan-1-one and (±)-2-methyltetral-1-one, through DKR process under the Ru-ATH conditions was recently demonstrated to be feasible.[23d–f] Although the conversions of *rac*-**11d–f** into the *cis*-alcohols **5h–j** via the Ru-ATH with **13** were determined to be modest, the chiral secondary alcohols **5h–j** could be obtained with excellent enantiomeric excesses in this way (99–96% *ee*). Enantiomeric excesses of the remaining ketones **11d–f** recovered after Ru-ATH were also checked by HPLC on a chiral column and determined to be 0%. This observation clearly shows that the ketones **11d–f** do racemize under Ru-ATH conditions and that Ru-ATH via DKR process is possible. But, we were not able to isolate the product in higher yields and enantiomeric excesses despite all efforts by doing some modifications of the Ru-ATH conditions as reported in the literature.[23d] The structures and the relative stereochemistries of the **5h–j** were assigned from ^1H and ^{13}C NMR as well as NOE-DIFF spectroscopic data which will be discussed below. We have not been able to grow single crystals of **5h–j** for X-ray analysis so far. Other chiroptical techniques, such as ORD, CD and the Octant rule, for determining the absolute configurations of **5h–j** were considered not to be applicable to the remaining ketones **11d–f** recovered after Ru-ATH, because they were determined to be racemic. However, we could suggest the formation of (1*S*,2*R*)-configured **5h–j** after careful application of the stereochemical model for Ru-ATH that was discussed before. This is also in good accordance with the sense of enantioselection in Ru-ATH of very similar compounds, such

as racemic 2-substituted indan-1-ones and tetral-1-ones, under the very similar reaction conditions.[23d–e]



rac-**11d** (R = Me, n = 1)
rac-**11e** (R = Ph, n = 1)
rac-**11f** (R = Ph, n = 2)

5h (R = Me, n = 1) 27% *y*, 98% *ee*
5i (R = Ph, n = 1) 50% *y*, 96% *ee*
5j (R = Ph, n = 2) 25% *y*, 99% *ee*

Scheme 5. Synthesis of chiral cyclic 2-(2-methoxyaryl)alcohols via Ru-ATH with **13**.

After the effective preparations of chiral 2-(2-methoxyaryl)alcohols **5a–j**, we explored a suitable demethylation procedure in order to synthesize our potential HAROL catalysts (Scheme 6). Boron tribromide (BBr_3) was the first choice for demethylation of **5c**, using different solvents (e.g. DCM, THF, and toluene) at different temperatures. In most cases, unidentified products formed except in one case, in which the corresponding dihydrobenzofuran was formed in almost quantitative yield according to ^{1}H NMR spectra, upon the treatment of **5c** with BBr_3 in DCM at –78 °C. However, it was determined to be labile and decomposed rapidly during column chromatographical purification on silica gel. On the other hand, treatment of **5c** with ethanethiol-sodium *tert*-butoxide couple in DMF afforded **12c** in 65% isolated yield in a practical way (Scheme 6). This demethylation technique was then applied to other 2-(2-methoxyaryl)alcohols, thus providing HAROLs in good yields (97–65%). As such, the synthesis of structurally different HAROLs with the 1,4-diol scaffold was accomplished by two different synthetic pathways.

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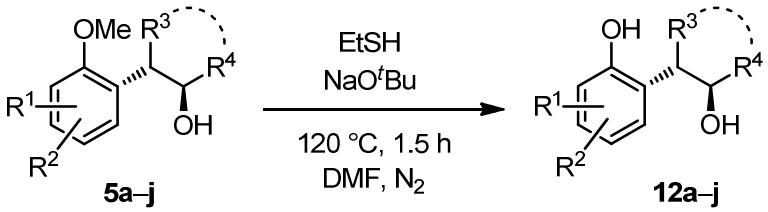
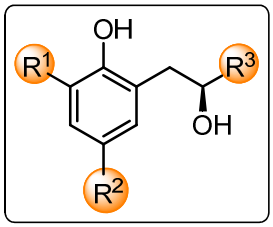
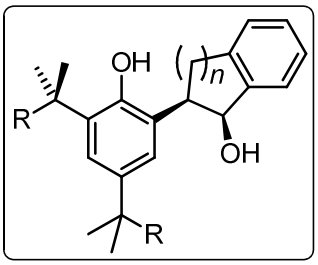
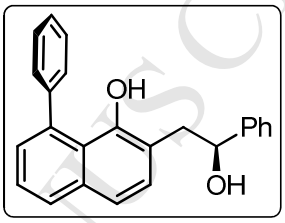




12a ($R^1 = R^2 = H$, $R^3 = Ph$) 82% *y*, >99% *ee*
12b ($R^1 = Ph$, $R^2 = H$, $R^3 = Ph$) 85% *y*, >99% *ee*
12c ($R^1 = R^2 = {}^t Bu$, $R^3 = Ph$) 65% *y*, >99% *ee*
12d ($R^1 = R^2 = CMe_2Ph$, $R^3 = Ph$) 78% *y*, >99% *ee*
12f ($R^1 = R^2 = {}^t Bu$, $R^3 = \beta$-Naph) 76% *y*, 97% *ee*
12g ($R^1 = R^2 = {}^t Bu$, $R^3 = {}^t Bu$) 97% *y*, 98% *ee*



12h (R = Me, n = 1) 73% *y*, 98% *ee*
12i (R = Ph, n = 1) 90% *y*, 96% *ee*
12j (R = Ph, n = 2) 84% *y*, 99% *ee*



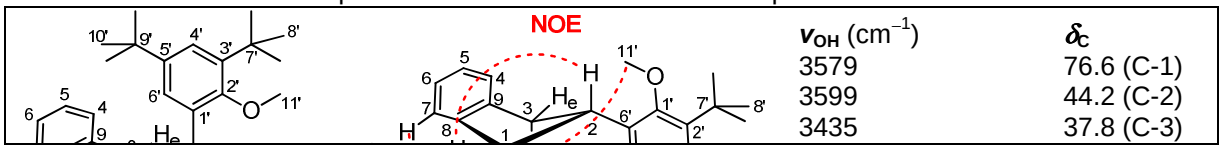
12e 80% *y*, >99% *ee*

Scheme 6. Preparation of the **HAROLs 12a–j** via demethylation. *Conditions:* **5** (1.00 equiv), EtSH (8.00 equiv), NaO^{t}Bu (3.00 equiv), DMF (ca. 5 mL for 1.0 mmol of **5**), 120 ℃, 1.5 h, N_2.

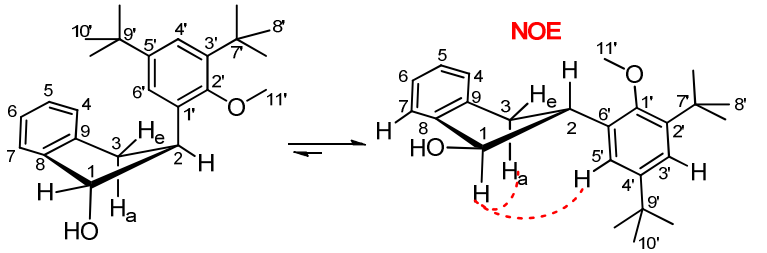
After reduction of the cyclic ketones *rac*-**11d–f** by Ru-ATH (Scheme 5), two diastereomers could be formed, i.e. it might theoretically have been expected that *cis*- and *trans*-configured diastereomers could be obtained. As observed in numeorus cases in the literature,[23d-f] Ru-ATH of 2-substituted racemic ketones delivers *cis*-configured secondary alcohols predominantly. Nonetheless, the relative stereochemistries of the **5h–j** were determined on the basis of ^1H, ^{13}C (APT), and NOE-DIFF NMR spectra as well as FT-IR spectral data. For conclusive assignments of spectral data, conformation of the structure should be investigated carefully. As is well known, substituted indanes are non-planar, usually assume envelope conformation, and exhibit a much more restricted geometry compared to the isolated five-membered ring, depending on the type of substituent. The racemic *cis*- and *trans*- 2-arylindanols *rac*-**5h** and *rac*-**18** were prepared through the reduction of *rac*–**11d** with $NaBH_4$ and they were separated by column chromatography (Table 4, see Supplementary Data). At this point, it should be noted that conformational analysis of *cis*- and *trans*-2-phenyl-indan-1-ol, structurally very similar to *rac*-**5h** and *rac*-**18**, was reported on the basis of their ^1H and ^{13}C NMR spectra.[25a] It was also reported that FT-IR spectra of *cis*- and *trans*-2-phenyl-indan-1-ol are distinctive from each other and shown to be suitable for their conformational analysis.[25b] Among the possible two extremes of

rac-**5h** and *rac*-**18** (***C1*** and ***C2*** conformers), ***C2*** conformers are expected to be predominant in which the bulkier substituent (anisyl groups) is taking up the most staggered (equatorial) position (Table 4). Distinctive NMR and FT-IR spectral data are summarized in Table 4. The easily distinguishable strong peak at 3579 cm^{-1} in the ***C2*** conformer of *rac*-**5h** probably arises from intramolecular OH···π bonding between OH and the anisyl group which is not the case for the ***C2*** conformer of *rac*-**18**. [25xb] This OH···π bonding also increases the population of the ***C2*** conformer and thus accounts for the larger shielding for ^{13}C signals of the ***C2*** conformer of *rac*-**5h** which is in good accordance with literature.[25a] Assignments of the important ^{1}H NMR signals of the alicyclic protons were made on the basis of the measured coupling constants and chemical shift values as well as NOE-DIFF experiments. A larger coupling constant for H-1 in *rac*-**18** than *rac*-**5h** would be expected because the dihedral angle Φ for H_1-C_1-C_2-H_2 in *rac*-**18** must approximate 180°. However, the difference between the coupling constants for H-1 of *rac*-**18** and *rac*-**5h**, ^{3}J = 6.6 Hz and ^{3}J = 5.4 Hz respectively, was not large enough to distinguish the relative stereochemistry. NOESY and NOE-DIFF experiments revealed a strong correlation between the proton resonances appearing at 5.31 (H-1) and 3.05 (H-3a) of *rac*-**18**. Such a correlation was not observed between H-1 (δ_H 5.36) and H-3a (δ_H 3.30) or H-3e (δ_H 3.36) protons of *rac*-**5h**, as illustrated in Table 4. It is noteworthy that the compounds **5d**, *rac*-**11e**, *rac*-**11f**, **5i**, **5j**, **12d**, **12i**, and **12j**, having 2,4-bis(α,α-dimethylbenzyl)phenol (**7d**) as the building block, exhibit interesting characteristics in their NMR spectra. In these chiral compounds, methyl groups, which are adjacent to the methoxyl or phenolic hydroxyl groups, have different chemical shifts in the ^{1}H and ^{13}C NMR spectra, i.e. they were determined to be diastereotopic. This might be due to the hindered rotation about the C(aryl)-C(methyl) bond, which in turn causes two CH_3 groups of the 2,4-bis(α,α-dimethylbenzyl)phenol or 2,4-bis(α,α-dimethylbenzyl)anisole moieties to be diastereotopic.

Table 4. Conformers and spectral data of the *cis*-and *trans*-compounds *rac*-**5h** and *rac*-**18**.

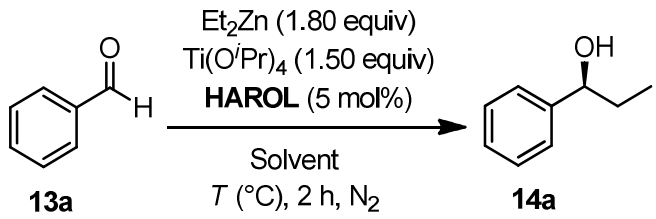


ν_{OH} (cm^{-1})	δ_C
3579	76.6 (C-1)
3599	44.2 (C-2)
3435	37.8 (C-3)

	δ_H (*J* in Hz) 1.68 (d, *J* = 5.1, 1H, OH) 3.30 (dd, *J* = 15.8, 7.8, 1H, H-3a) 3,36 (dd, *J* = 15.8, 7.8, 1H, H-3e) 3.86 (s, 3H, OCH_3) 4.17 (td, *J* = 7.9, 6.2, 1H, H-2) 5.36 (t, *J* = 5.5, 1H, H-1) 7.19 (d, *J* = 2.4, 1H, H-5')
 ***C1*** (*rac*-**18**) ⇌ ***C2*** (*rac*-**18**)	ν_{OH} (cm^{-1}) / δ_C 3460 — 83.7 (C-1) 3430 — 49.5 (C-2) 3394 — 38.9 (C-3) δ_H (*J* in Hz) 2.56 (t, *J* = 11.4, 1H, OH) 3.05 (dd, *J* = 15.8, 9,4, 1H, H-3a) 3,43 (dd, *J* = 15.9, 8.3, 1H, H-3e) 3.86 (s, 3H, OCH3) 3.91 (dd, *J* = 16.9, 8.2, 1H, H-2) 5.31 (t, *J* = 6.6, 1H, H-1) 7.19 (d, *J* = 2.4, 1H, H-5')

With ten chiral HAROLs (**12a–j**) in hand, we started to assess their catalytic activities and stereoselectivities in some asymmetric transformations. Analogous to ArBINMOLs as well as to numerous other diol and aminoalcohol ligands, we first employed them as chiral ligands in the addition of diethylzinc to benzaldehyde (**13a**), a benchmark reaction for testing the performance of new chiral ligands.[14,26,27] The initial setting for the Et_2Zn addition to benzaldehyde consisted of 1.80 equivs. of Et_2Zn, 1.50 equivs. of $Ti(O^iPr)_4$ and 5 mol% of a HAROL ligand compared to benzaldehyde in a solvent (Table 5). Our HAROLs were found to be highly active in this reaction, providing (*S*)-1-phenyl-1-propanol (**14a**) in nearly quantitative yield. Acyclic HAROLs carrying bulkier substituents appeared to be more enantioselective than those carrying smaller substituents, **12c** and **12e** vs. **12a** and **12b** (entries 3, 17, 1, 2). Of the solvents tested, hexane provided the optimum results (entries 4, 6, 7, 8). While the cyclic HAROL ligands **12h–i** with indane backbones exhibited superior enantioselectivity compared to their acyclic counterparts (entries 12 and 13), the cyclic HAROL ligand **12j** based on tetralin backbone gave the addition product **14a** in almost racemic form (entry 18). The reaction temperature was determined to be an important factor that predominantly affects the enantioselectivity (entries 13, 14, 15, 16). As the reaction temperature was decreased, enantioselectivity increased. However, the best compromise was to conduct reactions at –20 °C (entry 14). After all these screening reactions, the most enantioselective ligand appeared to be **12i** among the HAROLs examined and the optimum reaction conditions were identified (entry 14).[28]

Table 5. Optimization of Et_2Zn addition to benzaldehyde (**13a**) catalyzed by HAROLs.[a]



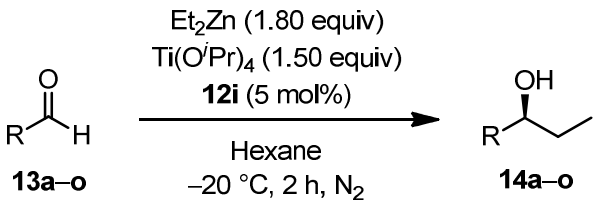
Entry	HAROL	Solvent	*T* (℃)	Yield (%)[b]	*ee* (%)[c]
1	**12a**	Toluene	0	95	10 (*S*)
2	**12b**	Toluene	0	95	30 (*S*)
3	**12c**	Toluene	0	95	50 (*S*)
4	**12c**	Hexane	0	95	58 (*S*)
5	**12c**	Hexane	–40	95	58 (*S*)
6	**12c**	Et_2O	0	95	54 (*S*)
7	**12c**	THF	0	70	50 (*S*)
8	**12c**	DCM	0	70	50 (*S*)
9	**12d**	Hexane	0	98	64 (*S*)
10	**12f**	Hexane	0	96	58 (*S*)
11	**12g**	Hexane	0	97	8 (*S*)
12	**12h**	Hexane	0	97	68 (*S*)
13	**12i**	Hexane	0	97	74 (*S*)
14	**12i**	Hexane	–20	97	83 (*S*)
15	**12i**	Hexane	–78	97	83 (*S*)
16	**12i**	Hexane	60	97	58 (*S*)
17	**12e**	Hexane	–20	97	80 (*S*)
18	**12j**	Hexane	–20	97	2 (*S*)

[a] *Reaction conditions:* **13a** (0.5 mmol, 1.00 equiv), Et_2Zn (1.80 equiv), $Ti(O^iPr)_4$ (1.50 equiv), HAROL ligand (5 mol%), solvent (2 mL), *T* (℃) for 2 h.
[b] Isolated yield of **14a**.
[c] Determined by GC, using a chiral column (CP-Chirasil-Dex-CB, 25 m, 0.25 mm ID).

In order to examine the general applicability of the HAROL-Ti catalytic system, we next subjected diverse aldehydes to the diethylzinc addition. The results using the HAROL **12i** in combination with $Ti(O^iPr)_4$ under the optimized conditions are shown in Table 6. While electron-withdrawing substituents at the 4-position of benzaldehyde did not have a significant influence on selectivity (entries 1-5), electron donating groups resulted in a decrease in enantiomeric excesses (entries 1, 6 and 7). In the case of sterically more demanding aldehydes, such as 2-methylbenzaldehyde (**13g**) and naphthalene-2-carbaldehyde (**13o**), somewhat lower enantiomeric excesses were observed (entries 8 and 15). Pyridine-2-carbaldehyde (**13i**) gave the addition product **14i** in high yields but almost racemic form (entry 9). The addition product of pyridine-4-carbaldehyde (**14j**) was obtained in modest *ee* (entry 10). Furfural (**13k**) could

also be reacted with Et_2Zn giving **14k** in somewhat diminished yield (65%) with 85% *ee* (entry 11). The next heteroaromatic aldehyde **13l** (thiophene-2-carbaldehyde) could be transformed into the corresponding alcohol **14l** in high yield and enantiomeric excess (90% *y*, 88% *ee*, entry 12). Aliphatic aldehydes such as *n*-heptanal (**13m**) and cyclohexanecarbaldehyde (**13n**) could be converted into the corresponding propanol derivatives **14m** and **14n** in high yields as well (entries 13 and 14). But, a lower enantiomeric excess for **14n** was measured.

Table 6. Asymmetric addition of Et_2Zn to aldehydes catalyzed by **12i**.[a]



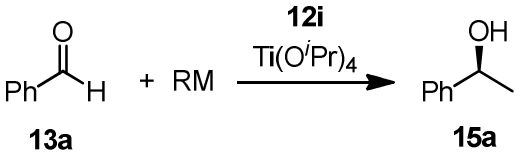
Entry	R	Product, Yield (%)[b]	*ee* (%)[c]
1	Ph	**14a**, 97	83 *(S)*
2	*p*-FC_6H_4	**14b**, 91	82 *(S)*
3	*p*-ClC_6H_4	**14c**, 85	83 *(S)*
4	*p*-BrC_6H_4	**14d**, 88	86 *(S)*
5	*p*-$CF_3C_6H_4$	**14e**, 80	86 *(S)*
6	*p*-$MeOC_6H_4$	**14f**, 90	78 *(S)*
7	*p*-MeC_6H_4	**14g**, 85	81 *(S)*
8	*o*-MeC_6H_4	**14h**, 93	70 *(S)*
9	2-pyridyl	**14i**, 81	2 *(S)*
10	4-pyridyl	**14j**, 30	40 *(S)*
11	2-furyl	**14k**, 65	85 *(S)*
12	2-thiophenyl	**14l**, 90	88 *(S)*
13	hexyl	**14m**, 86	88 *(S)*
14	cyclohexyl	**14n**, 85	58 *(S)*
15	2-naphthyl	**14o**, 96	76 *(S)*

[a] *Conditions:* **13** (0.5 mmol, 1.00 equiv), Et_2Zn (0.9 mmol, 1.80 equiv, 1.8 mL of 1.0 M Et_2Zn solution in hexane), **12i** (11.5 mg, 25 µmol, 5 mol%), $Ti(O^iPr)_4$ (0.75 mmol, 1.50 equiv), hexanes (2 mL), –20 °C, 2 h, N_2. The aldehydes **13c** and **13d** were added to the reaction mixture by dissolving them in Et_2O (2 mL).
[b] Isolated yield of the NMR-pure product.
[c] Enantiomeric excesses determined by HPLC or GC on a chiral column. The absolute configurations of the products (**14a–o**) were determined by comparing the sign of the rotation with literature data.

To further investigate the suitability of HAROLs for general use as ligands, the enantioselective addition of some other organometallics to benzaldehyde was examined (Table 7). The HAROL ligand **12i** which effected the diethylzinc addition to aldehydes with the highest level of enantioselectivity was employed in the addition of methyllithium (MeLi),

methylmagnesium bromide (MeMgBr) as well as trimethylaluminum (Me_3Al) to benzaldehyde (**13a**). Indeed, the additions of these common organometallic reagents to benzaldehyde took place smoothly in the presence of $Ti(O^iPr)_4$ and a catalytic amount of **12i**. However, the addition of MeLi proceeded with the highest level of enantioselectivity affording (*S*)-1-phenylethanol (**15a**) in 68% *ee* (entry 1), whereas (*S*)-1-phenylethanol was obtained in mediocre enantiomeric excesses via the addition of MeMgBr and Me_3Al, 46% and 24% *ee* (entries 2 and 3, respectively).[15-17]

Table 7. Asymmetric addition of methyl-organometallics (RM) to benzaldehyde (**13a**) catalyzed by **12i**.



13a **15a**

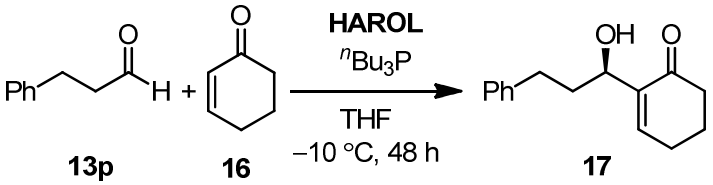
Enrty	RM	Yield (%)[a]	*ee* (%)[b]
1[c]	MeLi	70	68 *(S)*
2[d]	MeMgBr	95	46 *(S)*
3[e]	Me_3Al	90	24 *(S)*

[a] Isolated yield of the NMR-pure product.
[b] Enantiomeric excesses determined by HPLC or GC on a chiral column. The absolute configurations of the products (**15a**) were determined by comparing the sign of the optical rotation with literature data.
[c] **13a** (0.25 mmol, 1.00 equiv), MeLi (0.8 mmol, 3.20 equiv, 258 µL of 3.1 M MeLi in diethoxymethane), **12i** (23 mg, 50 µmol, 20 mol%), $Ti(O^iPr)_4$ (1.5 mmol, 6.00 equiv), THF (1.5 mL), –78 ℃, 2 h, N_2.
[d] **13a** (0.5 mmol, 1.00 equiv), MeMgBr (1.5 mmol, 3.00 equiv, 0.5 mL of 3.0 M MeMgBr in Et_2O), **12i** (11.5 mg, 25 µmol, 5 mol%), $Ti(O^iPr)_4$ (2.5 mmol, 5.00 equiv), Diglyme (2 mL), 0 ℃, 2 h, N_2.
[e] **13a** (0.5 mmol, 1.00 equiv), Me_3Al (0.75 mmol, 1.50 equiv, 375 µL of 2.0 M Me_3Al in hexane), **12i** (23 mg, 50 µmol, 10 mol%), $Ti(O^iPr)_4$ (2.0 mmol, 4.00 equiv), Et_2O (2 mL), 0 ℃, 2 h, N_2.

We reasoned that our HAROL-type 1,4-diols, carrying a phenolic and an alcohol hydroxyl (-OH) functionalities, could also be exploited as HBD organocatalysts due to their potential to form *inter*molecular hydrogen bonds with electrophiles such as aldehydes and ketones (Figure 1). In order to demonstrate the feasibility of this idea, we explored the Morita-Baylis-Hillman (MBH) reaction between 3-phenylpropanal (**13p**) and 2-cyclohexen-1-one (**16**) as the proof-of-concept reaction, in the presence of 10 mol% of some selected HAROLs as well as 2.00 equivs. of trialkylphosphines as Lewis base promoters (Table 8). All the HAROLs (**12c**, **12e**, **12i**) showed similar catalytic activity, giving the MBH product **17** in 52–43% isolated yields in the presence tributylphosphine (2.00 equiv) as the Lewis base promoter and THF as the solvent (entries 1–3). Among our HAROLs, **12i** turned out to be the best organocatalyst in terms of enantioselectivity, affording the MBH adduct **17** in 52% yield and with 40% *ee* (entry 3). Using triethylphosphine instead of tri-*n*-butylphosphine resulted in a decrease in enantioselectivity and activity (entry 4). This observation is contrary to that reported by McDougal and Schaus, in which they reported that Et_3P promoted this MBH reaction with higher yield and enantioselectivity than $^nBu_3P$ in the

presence of a BINOL-derived organocatalyst.[9a] Changing the solvent from THF to acetonitrile made some improvement in the catalytic activity of HAROL **12i** (67% y), however, this resulted in a dramatic decrease in enantioselectivity (16% *ee*, entry 5). It should be noted that other nucleophilic promoters such as tri-cyclohexylphosphine, tri-*tert*-butylphosphine, DABCO, DBU, and DMAP were found to be inactive in our catalytic system.

Table 8. Enantioselective Morita-Baylis-Hillman reaction catalyzed by HAROLs.[a]



Entry	HAROL	Yield (%)[b]	*ee* (%)[c]
1	**12c**	52	0
2	**12e**	43	14 *(R)*
3	**12i**	52	40 *(R)*
4[d]	**12i**	40	32 *(R)*
5[e]	**12i**	67	16 *(R)*

[a] *Conditions:* The reactions were carried out with 1.0 mmol (1.00 equiv) of **13p**, 2.00 equiv of **17**, 2.00 equiv of ^{n}Bu$_3$P, and 10 mol% HAROL (**12**) at –10 °C in THF (1 mL) for 48 h under N_2.
[b] Isolated yield of the NMR-pure product.
[c] Enantiomeric excesses determined by HPLC or GC on a chiral column. The absolute configuration of the MBH product **17** was determined by comparing the sign of the optical rotation with literature data.
[d] Et$_3$P (2.00 equiv) instead of ^{n}Bu$_3$P was employed.
[e] Acetonitrile as the solvent.

3. Conclusion

In summary, we have devised two efficient synthetic routes to chiral 2-(2-hydroxyaryl)alcohols (HAROLs), new 1,4-diols carrying a phenolic and an alcohol hydroxyl group: The first route is based on the regioselective ring-opening of enantiopure (*R*)-styrene oxide with *ortho*-lithioanisoles as the key transformation, whereas the second route comprises palladium-catalyzed α-arylation of ketones with *ortho*-bromoanisoles (Buchwald-Hartwig α-arylation) and the enantioselective reduction of the resulting ketones through Ru-ATH or CBS reduction, subsequently. Due to their modularity and complementarity, our synthetic routes allow for the facile generation of structurally diverse HAROLs in enantiopure form. Furthermore, the small library consisting of ten HAROLs was subjected to to screening as chiral ligands and HBD organocatalysts, one of which with an indane backbone was found to catalyze the 1,2-addition of some organometallic compounds (such as Et_2Zn, MeLi, MeMgBr, and Me_3Al) to aldehydes with high yields and enantioselectivities (up to 97% yield and 88% *ee*). The same

HAROL (**12i**) was also identified as a promising HBD organocatalyst for the enantioselective Morita-Baylis-Hillman reaction, promoted by trialkylphosphines. We are optimistic that HAROLs will find applications as catalysts in a broad range of asymmetric transformations. Consequently, optimization of the synthetic routes to HAROLs, enlargement of HAROL library in terms of structural diversity, as well as exploration of their use as catalysts are ongoing efforts in our laboratory. Those results will be reported in due course.

4. Experimental section

4.1. General

All air-sensitive reactions were performed under an inert atmosphere of dry nitrogen (N_2) using oven-dried glassware. All reagents and solvents were transferred using gas-tight syringe and cannula techniques under N_2. Reactions were monitored by thin layer chromatography (TLC) on aluminum sheets that were pre-coated with silica gel *SIL G/UV*$_{254}$ from MN GmbH & Co., in which the spots were visualized in UV-light (λ=254 nm) and/or by staining with phosphomolybdic acid solution in EtOH (10%, w/v). Chromatographic separations were performed using silica gel (MN-silicagel 60, 230-400 mesh). All melting points were determined in open glass capillary tube by means of a BÜCHI Melting Point B-540 apparatus and values are uncorrected. Infrared (FT-IR) spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H and ^{13}C NMR spectra were recorded on a 500 MHz or 600 MHz NMR spectrometer. Chemical shifts δ are reported in parts per million (ppm) relative to the residual protons in the NMR solvent ($CHCl_3$: δ 7.26) and carbon resonance of the solvent ($CDCl_3$: δ 77.00). NMR peak multiplicities were given as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectra were recorded on a gas chromatography with mass sensitive detector from Agilent Technologies 6890N Network GC System (EI, 70 eV) using Standard Method (column: HP-5MSI, 30 m, 0.25 mm ID, 0.25 µm film tickness; inlet: 300 °C (split modus); det: 300 °C; He, 1 mL/min (constant flow modus); oven: 40 °C (5 min), 5 °C/min, 280 °C (5 min)). High resolution electrospray ionization mass spectra (HR-ESI-MS) were obtained with MeOH on a Bruker micrOTOF-Q. The specific rotations ([α]) were measured on an Optical Activity Ltd. AA-65 polarimeter using 1 mL cell with a 1.0 dm path length and the sample concentrations are given in g/100 mL unit. Tetrahydrofuran (THF), diethyl ether (Et_2O), toluene, hexane, and *c*-hexane was freshly distilled under N_2 from sodium/benzophenone prior to use under nitrogen atmosphere. Diglyme, *N,N*-dimethylformamide (DMF), and anisole were distilled under reduced pressure from calcium hydride (CaH_2). Dichloromethane (DCM) and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) were dried by distillation over CaH_2 under N_2. Some reagents, such as Et_2Zn (1.0 M solution in hexane), MeLi (3.1 M solution in diethoxymethane), MeMgBr (3.0 M solution in Et_2O), Me_3Al (2.0 M solution in hexane), $BF_3{\cdot}OEt_2$, ^{n}BuLi (2.5 M or 1.7 M solution in hexane), Me_2SO_4, EtSH, ^{t}Bu$_3$P (1.0 M in toluene), $BH_3{\cdot}SMe_2$, ^{n}Bu$_3$P, Ph_3P, $Pd(OAc)_2$, the Noyori-Ikariya catalyst **13**, and the CBS catalyst **14** were purchased from commercial suppliers and used as received. All the aldehydes were filtered through a short plug of neutral

alumina before use. $Ti(O^iPr)_4$ was distilled under reduced pressure and stored under nitrogen. The formic acid-triethylamine azeotropic mixture (HCO_2H/Et_3N, 5:2) was prepared according to the literature procedure and its quality was checked by ^1H NMR spectroscopy.[29] 8-Phenyl-1-naphthol (**7f**) was prepared according to the literature procedure.[21] All experimental procedures for the synthesis of the anisoles **2b–e**, **9c–d** and the bromophenols **8c–d** are presented in the Supplementary Data part.

*4.2. (S)-(–)-2-(2-Methoxyphenyl)-1-phenylethanol (**5a**)*

An oven-dried 250 mL round-bottomed Schlenk flask, capped with a glass stopper and equipped with a magnetic stirring bar, was evacuated under heating with a blow-drier for 15 min. After the flask was cooled down to room temperature, dry nitrogen was back-filled and the glass stopper was replaced with a rubber septum, under a positive pressure of nitrogen. The flask was charged with anisole (**2a**) (3.26 mL 3.24 g, 30.0 mmol, 3.00 equiv) and TMEDA (0.70 g, 0.90 mL, 6.0 mmol, 0.60 equiv), which was succeeded by the addition of dry THF (60 mL) as the solvent. After the mixture was cooled in an ice-bath, 12 mL of a 2.50 M solution of ^{n}BuLi in hexanes (30.0 mmol, 3.00 equiv of ^{n}BuLi) were dropwise added to the mixture. The mixture was then stirred for 3 h while the temperature was allowed to rise to room temperature. After cooling the reaction mixture down to −78 °C in an acetone-dry ice bath, (*R*)-(+)-styrene oxide (**4a**) (1.20 g, 1.15 mL, 10.0 mmol, 1.00 equiv) and $BF_3{\cdot}OEt_2$ (3.60 g, 3.10 mL, 25.0 mmol, 2.50 equiv) were added sequentially. The reaction mixture was stirred at −78 °C for 1 h and quenched with saturated $NaHCO_3$ solution (60 mL). THF was removed by rotary evaporation under reduced pressure and the aqueous residue was extracted with Et_2O (3×100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. The residue was then purified by silica gel column chromatography eluting with hexanes/EtOAc (9:1) to afford **5a** (1.90 g, 8.3 mmol, 83%) as a colorless solid. Mp: 75–76 °C. TLC: R_f = 0.24 (silica gel; hexane/EtOAc, 9:1). $[\alpha]_D^{22}$ = −10 (c = 0.5, CH_2Cl_2). HPLC: Chiralcel OD-H; *n*-hexane/^{i}PrOH (90:10), 1.0 mL/min; 254 nm (UV–vis); t_R = 8.1 min (*ent*-**5a**), t_R = 9.7 min (**5a**). FTIR (KBr): ν_{max} (cm^{-1}) = 3292 (m), 3064 (m), 3028 (s), 2836 (m), 2057 (w), 1928 (w), 1893 (m), 1798 (w), 1603 (m), 1587 (m), 1500 (s), 1454 (s), 1292 (s), 1245 (s), 1180 (m), 1162 (s), 765 (m), 745 (s), 699 (s). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.51 (s, 1H), 2.98 (dd, *J* = 13.6, 8.8 Hz, 1H), 3.12 (dd, *J* = 13.6, 4.0 Hz, 1H), 3.85 (s, 3H), 4.96 (dd, *J* = 8.8, 4.0 Hz, 1H), 6.88 (dd, *J* = 10.5, 4.2 Hz, 2H), 7.08 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.20–7.28 (m, 2H), 7.35 (ddd, *J* = 15.1, 10.8, 4.6 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.1 (CH_2), 55.3 (CH_3), 74.2 (CH), 110.4 (CH), 120.7 (CH), 125.7 (CH), 126.6 (C), 127.2 (CH), 128.0 (CH), 128.2 (CH), 131.4 (CH), 144.5 (C), 157.6 (C). GCMS: t_R = 29.67 min, *m/z* (%) = 210 ([M-18]$^+$, 10), 194 ([M-34]$^+$, 1), 178 (2), 165 (6), 152 (3), 137 (1), 122 (100), 107 (29), 91 (24), 79 (22). HR MS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{15}H_{16}O_2Na$: 251.1043; found: 251.1055.

*4.3. (S)-(–)-2-(2-Methoxy-3-phenylphenyl)-1-phenylethanol (**5b**)*

An oven-dried 500 mL round-bottomed Schlenk flask, capped with a glass stopper and equipped with a magnetic stirring bar, was evacuated under heating with a blow-drier for 15 min. The flask was cooled down to room temperature, back-filled with dry nitrogen and the glass stopper was replaced with a rubber septum, under a positive pressure of nitrogen. The flask was charged with 2-phenylanisole (**2b**)

(9.21 g, 50.0 mmol, 5.00 equiv) and TMEDA (1.57 mL, 1.14 g, 10.0 mmol, 1.00 equiv), which was followed by the addition of dry Et_2O (150 mL) as the solvent. After the mixture was cooled in an ice-bath, 20 mL of 2.50 M *n*-butyllithium solution in hexanes (50.0 mmol, 5.00 equiv of ^{n}BuLi) were dropwise added with a syringe. The mixture was then stirred overnight (ca. 16 h) while the temperature was allowed to rise to room temperature. After cooling the reaction mixture down to −78 °C in an acetone-dry ice bath, absolute THF (43 mL) was added with a gas-tight syringe. (*R*)-(+)-Styrene oxide (**4a**) (1.20 g, 1.15 mL, 10.0 mmol, 1.00 equiv) and $BF_3{\cdot}OEt_2$ (7.10 g, 6.17 mL, 50.0 mmol, 5.00 equiv) were added to the reaction mixture, successively. After stirring the mixture at −78 °C for 1 h, the reaction was quenched by the addition of saturated $NaHCO_3$ solution (85 mL). After etheral solvents were removed by rotary evaporation under reduced pressure, the aqueous residue was extracted with Et_2O (3×100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. The residue was purified by silica gel column chromatography eluting with hexanes/EtOAc (9:1) to give 2.00 g (6.6 mmol, 66%) of the title compound (**5b**) as a colorless oil. TLC: R_f = 0.20 (silica gel; hexane/EtOAc, 9:1). $[\alpha]_D^{22}$ = −22 (c = 0.5, CH_2Cl_2). HPLC: Chiralcel OD-H; *n*-hexane/^{i}PrOH (98:2), 1.0 mL/min; 254 nm (UV−vis); t_R = 16.2 min (*ent*-**5b**), t_R = 19.8 min (**5b**). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.86 (s, 1H), 3.05 (dd, *J* = 13.8, 8.8 Hz, 1H), 3.14 (dd, *J* = 13.7, 3.9 Hz, 1H), 3.37 (s, 3H), 5.03 (dd, *J* = 8.8, 3.9 Hz, 1H), 7.06–7.16 (m, 2H), 7.21–7.30 (m, 2H), 7.36 (dd, *J* = 10.4, 4.5 Hz, 3H), 7.39–7.46 (m, 4H), 7.57–7.62 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.3 (CH_2), 60.4 (CH_3), 75.0 (CH), 124.3 (CH), 125.8 (CH), 127.2 (CH), 127.4 (CH), 128.4 (CH), 129.1 (CH), 130.1 (CH), 130.8 (CH), 131.8 (C), 134.9 (C), 138.7 (C), 144.6 (C), 156.0 (C). GCMS: t_R = 34.89 min, *m/z* (%) = 286 ([M-18]$^+$, 6), 270 ([M-34]$^+$, 1), 252 (1), 239 (1), 215 (1), 209 (4), 198 (100), 183 (22), 165 (11), 152 (11), 128 (3), 107 (19), 79 (13). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{21}H_{20}O_2Na$: 327.1356; found: 327.1373.

*4.4. (S)-(−)-2-(3,5-Di-tert-butyl-2-methoxyphenyl)-1-phenylethanol (**5c**)*

An oven-dried 500 mL round-bottomed Schlenk flask, capped with a glass stopper and equipped with a magnetic stirring bar, was evacuated under heating with a blow-drier for 15 min. The flask was cooled down to room temperature, back-filled with dry nitrogen and the glass stopper was replaced with a rubber septum, under a positive pressure of nitrogen. 2,4-Di-*tert*-butylanisole (**2c**) (7.70 g, 35.0 mmol, 5.00 equiv) and TMEDA (1.10 mL, 0.80 g, 7.0 mmol, 1.00 equiv) were added into the flask, which was followed by the addition of dry Et_2O (105 mL) as the solvent. After the mixture was cooled in an ice-bath, 14.0 mL of 2.50 M *n*-butyllithium solution in hexanes (35.0 mmol, 5.00 equiv of ^{n}BuLi) were dropwise added with a syringe. The mixture was then stirred overnight (ca. 16 h) while the temperature was allowed to rise to room temperature. After cooling the reaction mixture down to −78 °C in an acetone-dry ice bath, absolute THF (30 mL) was added. (*R*)-(+)-Styrene oxide (**4a**) (0.84 g, 0.80 mL, 7.0 mmol, 1.00 equiv) and $BF_3{\cdot}OEt_2$ (4.97 g, 4.32 mL, 35.0 mmol, 5.00 equiv) were added successively at −78 °C. After stirring the mixture at −78 °C for 1 h, the reaction was quenched by the addition of saturated $NaHCO_3$ solution (60 mL). After etheral solvents were removed by rotary evaporation under reduced pressure, the aqueous residue was extracted with Et_2O (3×100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification by flash column

chromatography (hexanes/EtOAc, 8:2) gave 1.62 g (4.75 mmol, 68%) of the title compound (**5c**) as a colorless solid. Mp: 87–88 °C. TLC: R_f = 0.51 (silica gel; hexane/EtOAc, 8:2). $[\alpha]_D^{22}$ = –20 (c = 0.5, CH_2Cl_2). FTIR (KBr): ν_{max} (cm^{-1}) = 3307 (s), 2961(s), 1601 (w), 1477 (s), 1454 (s), 1427 (m), 1389 (m), 1323 (w), 1271 (m), 1231 (s), 1203 (m), 1156 (w), 1116 (s), 1077 (w), 1034 (s), 1010 (s), 950 (m), 907 (w), 878 (m), 772 (w), 754 (m), 697 (s), 652 (w), 541 (w). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (s, 9H), 1.41 (s, 9H), 2.91 (s, 1H), 3.09 (d, J = 6.0 Hz, 2H), 3.83 (s, 3H), 4.98 (t, J = 6.3 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 7.21–7.26 (m, 2H), 7.29–7.35 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.3 (CH_3), 31.5 (CH_3), 34.4 (C), 35.3 (C), 42.1 (CH_2), 61.8 (CH_3), 74.9 (CH), 123.2 (CH), 125.8 (CH), 126.9 (CH), 127.3 (CH), 128.3 (CH), 130.9 (C), 142.1 (C), 144.5 (C), 146.1 (C), 156.0 (C). GCMS: t_R = 33.16 min, *m/z* (%) = 322 ([M-18]$^+$, 7), 307 ([M-33]$^+$, 10), 234 (65), 219 (100), 203 (5), 177 (10), 163 (9), 107 (10), 91 (6), 79 (7). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{23}H_{32}O_2Na$: 363.2295; found: 363.2295.

*4.5. (S)-(–)-2-(2-Methoxy-3,5-bis(2-phenylpropan-2-yl)phenyl)-1-phenylethanol (**5d**)*

An oven-dried 250 mL round-bottomed Schlenk flask, capped with a glass stopper and equipped with a magnetic stirring bar, was evacuated under heating with a blow-drier for 15 min. The flask was cooled down to room temperature, back-filled with dry nitrogen and the glass stopper was replaced with a rubber septum, under a positive pressure of nitrogen. The flask was charged with 2,4-bis(α,α-dimethylbenzyl)anisole (**2d**) (6.90 g, 20.0 mmol, 5.00 equiv) and TMEDA (0.63 mL, 0.46 g, 4.00 mmol, 1.00 equiv), which was succeeded by the addition of dry Et_2O (60 mL) as the solvent. After the mixture was cooled in an ice-bath, 8.0 mL of 2.50 M *n*-butyllithium solution in hexanes (20.0 mmol, 5.00 equiv of ^{n}BuLi) were dropwise added to the mixture, by means of a gas-tight syringe. The mixture was then stirred overnight (ca. 16 h) while the temperature was allowed to rise to room temperature. After the reaction flask was cooled down to −78 °C in a acetone-dry ice bath, absolute THF (17 mL) was added. (*R*)-(+)-Styrene oxide (**4a**) (457 µL, 481 mg, 4.0 mmol, 1.00 equiv) and $BF_3{\cdot}OEt_2$ (2.84 g, 2.47 mL, 20.0 mmol, 5.00 equiv) were added to the reaction mixture at −78 °C sequentially. After stirring the mixture at −78 °C for 1 h, the reaction was quenched with saturated $NaHCO_3$ solution (34 mL). After etheral solvents were removed by rotary evaporation under reduced pressure, the aqueous residue was extracted with Et_2O (3×100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. The crude product was purified by flash chromatography (hexanes/EtOAc, 9:1) to afford 1.10 g (2.4 mmol, 60%) of the title compound (**5d**) as a colorless solid. Mp: 82 °C. TLC: R_f = 0.35 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{28}$ = –18 (c = 0.5, $CHCl_3$). FTIR (KBr): ν_{max} (cm^{-1}) = 3467 (m), 3082 (m), 3054 (m), 3024 (m), 2970 (m), 2931 (m), 2870 (m), 1951 (s), 1876 (m), 1808 (m), 1750 (m), 1598 (s), 1578 (s), 1491 (m), 1470 (m), 1444 (m), 1378 (s), 1425 (s), 1361 (s), 1321 (s), 1231 (s), 1204 (s), 1150 (s), 1133 (s), 1112 (s), 1075 (s), 1025 (m), 1006 (m), 914 (s), 891 (s), 874 (s), 799 (s), 770 (m), 755 (m), 603 (s), 578 (s), 549 (s), 535 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.60 (s, 3H), 1.61 (s, 3H), 1.62 (s, 6H), 2.70 (d, J = 1.3 Hz, 3H), 2.94 (d, J = 5.4 Hz, 3H), 4.88 (t, J = 6.2 Hz, 1H), 7.12 (td, J = 7.1, 1.4 Hz, 1H), 7.31–7.15 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.1 (CH_3), 30.2 (CH_3), 30.9 (CH_3), 41.6 (C), 42.2 (CH_3), 42.6 (C), 59.6 (CH_3), 74.7 (CH), 124.4 (CH), 125.2 (CH), 125.5 (CH), 125.7 (CH), 126.1 (CH), 126.7 (CH), 127.1 (CH), 127.9 (CH), 127.9 (CH), 128.1 (CH), 128.7 (CH), 130.9 (C), 142.4 (C), 144.2 (C), 145.4 (C), 150.7 (C), 151.8 (C),

155.3 (C). GCMS: t_R = 41.65 min; m/z (%) = 462 ([M-2]$^+$, 3), 307 ([M-18]$^+$, 100), 431 (74), 358 (67), 343 (66), 265 (21), 239 (10), 119 (40), 91 (51). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{33}H_{36}O_2Na$: 487.2608; found: 487.2613.

*4.6. (S)-(–)-2-(1-Methoxy-8-phenylnaphthalen-2-yl)-1-phenylethanol (**5e**)*

An oven-dried 50 mL dried round-bottomed Schlenk flask was charged with 1-methoxy-8-napthalene (**2e**) (1.10 g, 4.5 mmol, 3.00 equiv), and the system was evacuated for 15 minutes and back-filled with nitrogen. TMEDA (135 µL, 0.9 mmol, 0.60 equiv) and THF (12 mL) were added by means of syringes. The solution was cooled in an ice-bath and 2.80 mL of 1.60 M *n*-butyllithium solution in hexanes (4.5 mmol, 3.00 equiv of ^{n}BuLi) were dropwise added to the mixture with a gas-tight syringe. The resulting solution was then stirred for 3 h while the temperature was allowed to rise to room temperature. After the reaction flask was cooled down to –78 °C in a acetone-dry ice bath, (*R*)-(+)-styrene oxide (**4a**) (170 µL, 180 mg, 1.5 mmol, 1.00 equiv) and $BF_3{\cdot}OEt_2$ (460 µL, 532 mg, 3.75 mmol, 2.50 equiv) were successively added to the reaction mixture. After stirring the mixture at –78 °C for 1 h, the reaction was quenched by the addition of saturated $NaHCO_3$ solution (6 mL). After THF was removed by rotary evaporation under reduced pressure, the aqueous residue was extracted with Et_2O (3×50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to give 280 mg (0.78 mmol, 53%) of the title compound (**5e**) as a colorless oil. TLC: R_f = 0.24 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{24}$ = –50 (c = 0.5, $CHCl_3$). HPLC: Chiralpak AS-H; *n*-hexane/^{i}PrOH (95:5), 1.0 mL/min; 254 nm (UV–vis); t_R = 9.6 min (*ent*-**5e**), t_R = 10.6 min (**5e**). FTIR (KBr): ν_{max} (cm^{-1}) = 3428 (br), 3025 (s), 1945 (w), 1808 (w), 1743 (w), 1599 (m), 1570 (s), 1493 (s), 1363 (s), 1244 (s), 1082 (s), 833 (s), 756 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.99 (s, 3H), 3.11 – 3.23 (m, 2H), 5.03 (dd, *J* = 7.6, 5.1 Hz, 1H), 7.18–7.40 (m, 11H), 7.41–7.49 (m, 3H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.81 (dd, *J* = 8.2, 1.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 40.8 (CH_2), 60.9 (CH_3), 75.1 (CH), 125.0 (d), 125.0 (d), 125.5 (C), 125.8 (CH), 126.2 (CH), 126.8 (CH), 127.3 (CH), 128.1 (CH), 128.2 (C), 128.2 (CH), 129.0 (CH), 129.5 (CH), 130.3 (CH), 135.5 (C), 138.0 (C), 143.6 (C), 144.3 (C), 154.7 (C). HRMS: *m/z* [M+Na]$^+$ calcd for $C_{25}H_{22}O_2Na$: 377.1512; found: 377.1536.

*4.7. General Procedure I (Buchwald-Hartwig arylation of ketones with ortho-bromoanisoles): 2-(3,5-Di-tert-butyl-2-methoxyphenyl)-1-phenylethanone (**11a**)*

An oven-dried 50 mL Schlenk tube was charged with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol, 2 mol%) and NaO^{t}Bu (1.10 g, 11.0 mmol, 2.20 equiv). The tube was then equipped with a magnetic stirring bar and capped with a glass stopper. After evacuating the tube for 15 minutes, the system was back-filled with dry N_2, the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. Anhydrous THF (5 mL) and 100 µL of 1.0 M tri-*tert*-butylphosphine solution in toluene (0.1 mmol, 2 mol% P^{t}Bu$_3$) were added sequentially by means of gas-tight syringes and the resulting heterogenous dark mixture was stirred for 30 minutes at ambient temperature. In a separate oven-dried 10 mL Schlenk tube, 1-bromo-3,5-di-*tert*-butyl-2-methoxybenzene (**9c**) (1.30 mL, 1.50 g, 5.0 mmol, 1.00 equiv) was dissolved in 5 mL of anhydrous THF under nitrogen and added dropwise to the reaction mixture via syringe. The mixture was stirred for

30 minutes. In another oven-dried 10 mL Schlenk tube, acetophenone (**10a**) (642 µL, 661 mg, 5.5 mmol, 1.10 equiv) was dissolved in anhydrous THF (5 mL) and introduced into the reaction mixture dropwise, using a syringe. The reaction mixture was stirred for 16 h at ambient temperatures under N_2 during which time the solution turned to dark green. It was then quenched with 1 M HCl solution (10 mL). After THF was removed by rotary evaporation under reduced pressure, the aqueous residue was extracted with Et_2O (3×30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification by flash column chromatography (hexanes/EtOAc, 98:2) gave 1.29 g (3.8 mmol, 76%) of the title compound (**11a**) as a colorless solid. Mp: 120-122 °C. TLC: R_f = 0.40 (silica gel; hexanes/EtOAc, 98:2). FTIR (KBr): ν_{max} (cm^{-1}) = 3435 (w), 2956 (s), 1685 (s), 1597 (w), 1581 (w), 1479 (m), 1414 (m), 1338 (m), 1320 (s), 1233 (s), 1212 (s), 1116 (m), 999 (s), 881 (w), 754 (m), 691 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (s, 9H), 1.39 (s, 9H), 3.70 (s, 3H), 4.33 (s, 2H), 7.05 (d, J = 2.5 Hz, 1H), 7.25 (d, J = 2.5 Hz, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.57–7.49 (m, 1H), 8.01 (dd, J = 8.4, 1.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.1 (CH_3), 31.5 (CH_3), 41.0 (CH_2), 61.9 (CH_3), 123.2 (CH), 126.6 (CH), 127.6 (C), 128.5 (CH), 128.5 (CH), 132.9 (CH), 136.7 (C), 142.0 (C), 145.8 (C), 155.6 (C), 198.4 (C=O). GCMS: t_R = 33.53 min, *m/z* (%) = 338 ($[M]^+$, 86), 323 ($[M-15]^+$, 100), 267 (13), 233 (19), 177 (20), 191 (8), 105 (98), 57 (36). HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{31}O_2$: 339.2319; found: 339.2319.

*4.8. 2-(3,5-Di-tert-butyl-2-methoxyphenyl)-1-(naphthalen-2-yl)ethanone (**11b**)*

Following the general procedure I as described above, $Pd(OAc)_2$ (22.5 mg, 0.1 mmol, 2 mol%), NaO^{t}Bu (1.10 g, 11.0 mmol, 2.20 equiv), 100 µL of 1.0 M tri-*tert*-butylphosphine solution in toluene (0.1 mmol, 2 mol% P^{t}Bu$_3$), 1-bromo-3,5-di-*tert*-butyl-2-methoxybenzene (**9c**) (1.30 mL, 1.50 g, 5.0 mmol, 1.00 equiv), and 2-acethylnapthalene (**10b**) (851 mg, 5.0 mmol, 1.00 equiv) were employed. After stirring the reaction mixture for 16 h at ambient temperatures under N_2, it was quenched with 1 M HCl solution (10 mL) and subsequently subjected to the usual work-up. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 8:2) afforded 1.50 g (3.75 mmol, 75%) of the title compound (**11b**) as a colorless solid. Mp: 127 °C. TLC: R_f = 0.20 (silica gel; hexanes/EtOAc, 8:2). FTIR (KBr): ν_{max} (cm^{-1}) = 3436 (w), 2954 (w), 2865 (s), 1691 (s), 1627 (s), 1597 (s), 1475 (s), 1429 (s), 1361 (s), 1333 (s), 1274 (s), 1229 (s), 1182 (s), 1120 (s), 1005 (s), 862 (s), 823 (s), 748 (s), 651 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (s, 9H), 1.42 (s, 9H), 3.77 (s, 3H), 4.46 (s, 2H), 7.13 (d, J = 2.5 Hz, 1H), 7.25 (d, J = 2.5 Hz, 1H), 7.53 (ddd, J = 8.1, 6.9, 1.3 Hz, 1H), 7.58 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.86 (dd, J = 8.3, 4.6 Hz, 2H), 7.92 (d, J = 8.1 Hz, 1H), 8.08 (dd, J = 8.6, 1.8 Hz, 1H), 8.56 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.0 (CH_3), 31.4 (CH_3), 34.4 (C), 35.3 (C), 41.1 (CH_2), 62.0 (CH_3), 123.2 (CH), 124.2 (CH), 126.4 (CH), 126.6 (CH), 127.7 (CH), 127.8 (C), 128.2 (CH), 128.3 (CH), 129.6 (CH), 130.4 (CH), 132.5 (C), 133.8 (C), 135.5 (C), 142.0 (C), 145.8 (C), 155.4 (C), 198.3 (C). GCMS: t_R = 37.22 min, *m/z* (%) = 388 ($[M]^+$, 23), 373 ($[M-15]^+$, 7), 155 (100), 127 (21), 57 (7), 28 (36). HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{33}O_2$: 389.2475; found: 389.2477.

*4.9. 1-(3,5-Di-tert-butyl-2-methoxyphenyl)-3,3-dimethylbutan-2-one (**11c**).*

Following the general procedure I as described above, $Pd(OAc)_2$ (22.5 mg, 0.1 mmol, 2 mol%), NaO^{t}Bu (1.10 g, 11.0 mmol, 2.20 equiv), 100 µL of 1.0 M tri-*tert*-butylphosphine solution in toluene (0.1 mmol, 2 mol% P^{t}Bu$_3$), 1-bromo-3,5-di-*tert*-butyl-2-methoxybenzene (**9c**) (1.30 mL, 1.50 g, 5.0 mmol, 1.00 equiv), and 3,3-dimethylbutan-2-one (**10c**) (625 µL, 501 mg, 5.0 mmol, 1.00 equiv) were employed. After stirring the reaction mixture for 16 h at ambient temperatures under N_2, it was quenched with 1 M HCl solution (10 mL) and subsequently subjected to the usual work-up. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 98:2) afforded 1.35 g (4.3 mmol, 86%) of the title compound (**11c**) as a colorless solid. Mp: 67 °C. TLC: R_f = 0.40 (silica gel; hexanes/EtOAc, 98:2). FTIR (KBr): ν_{max} (cm^{-1}) = 3403 (w), 3013 (s), 2950 (s), 1984 (w), 1708 (s), 1599 (w), 1475 (s), 1410 (s), 1358 (s), 1320 (s), 1273 (m), 1230 (s), 1158 (m), 1114 (s), 1064 (s), 996 (s), 924 (m), 878 (s), 809 (m), 704 (m), 652 (m), 547 (w). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (s, 9H), 1.29 (s, 9H), 1.39 (s, 9H), 3.65 (s, 3H), 3.89 (s, 2H), 6.92 (d, *J* = 2.5 Hz, 1H), 7.24 (d, *J* = 2.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.9 (q), 31.2 (q), 31.5 (q), 34.4 (s), 35.3 (s), 30.0 (t), 44.6 (s), 61.7 (t), 123.0 (d), 126.6 (d), 127.7 (s), 141.7 (s), 145.5 (s), 155.8 (s), 213.8 (s). GCMS: t_R = 29.49 min, *m/z* (%) = 318 ([M]$^+$, 100), 303 ([M-15]$^+$, 51), 233 (90), 219 (19), 203 (17), 191 (8), 177 (56), 161 (36), 105 (14), 57 (93). HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{21}H_{35}O_2$: 319.2632; found: 319.2627.

*4.10. 2-(3,5-Di-tert-butyl-2-methoxyphenyl)indan-1-one (rac-**11d**)*

Following the general procedure I as described above, $Pd(OAc)_2$ (22.5 mg, 0.1 mmol, 2 mol%), NaO^{t}Bu (1.10 g, 11.0 mmol, 2.20 equiv), 100 µL of 1.0 M tri-*tert*-butylphosphine solution in toluene (0.1 mmol, 2 mol% P^{t}Bu$_3$), 1-bromo-3,5-di-*tert*-butyl-2-methoxybenzene (**9c**) (1.30 mL, 1.50 g, 5.0 mmol, 1.00 equiv), and 1-indanone (**10d**) (661 mg, 5.0 mmol, 1.00 equiv) were employed. After stirring the reaction mixture for 16 h at ambient temperatures under N_2, it was quenched with 1 M HCl solution (10 mL) and subsequently subjected to the usual work-up. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 10:0.3) afforded 1.45 g (4.15 mmol, 83%) of the title compound (*rac*-**11d**) as a colorless solid. Mp: 198 °C. TLC: R_f = 0.28 (silica gel; hexanes/EtOAc, 10:0.3). FTIR (KBr): ν_{max} (cm^{-1}) = 3416 (w), 2952 (w), 2862 (s), 1714 (s), 1608 (s), 1475 (s), 1428 (s), 1359 (s), 1327 (s), 1236 (s), 1205 (s), 1158 (s), 1113 (s), 1036 (s), 994 (s), 876 (s), 755 (s), 654 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (s, 9H), 1.44 (s, 9H), 3.17 (dd, *J* = 17.3, 4.7 Hz, 1H), 3.74 (dd, *J* = 17.4, 8.3 Hz, 1H), 3.89 (s, 3H), 4.37 (dd, *J* = 8.4, 4.7 Hz, 1H), 6.73 (d, *J* = 2.5 Hz, 1H), 7.26 (d, *J* = 3.2 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.66 (td, *J* = 7.5, 1.2 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.3 (CH_3), 31.4 (CH_3), 34.5 (C), 35.4 (C), 37.6 (CH_2), 47.8 (CH), 63.4 (CH_3), 123.00 (CH), 123.5 (CH), 124.3 (CH), 126.4 (CH), 127.6 (CH), 133.6 (C), 134.8 (CH), 136.8 (C), 142.0 (C), 146.3 (C), 153.9 (C), 156.5 (C), 207.4 (C). GCMS: t_R = 34.48 min, *m/z* (%) = 350 ([M]$^+$, 75), 335 ([M-15]$^+$, 100), 279 (9), 160 (5), 57 (10), 28 (25). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{24}H_{30}O_2Na$: 373.2138; found: 373.2135.

*4.11. 2-(2-Methoxy-3,5-bis(2-phenylpropan-2-yl)phenyl)indan-1-one (rac-**11e**)*

Following the general procedure I as described above, $Pd(OAc)_2$ (22.5 mg, 0.1 mmol, 2 mol%), NaO^{t}Bu (1.10 g, 11.0 mmol, 2.20 equiv), 100 µL of 1.0 M tri-*tert*-butylphosphine solution in toluene (0.1 mmol, 2

mol% P^{t}Bu$_3$), 6-bromo-2,4-bis(2-phenylpropan-2-yl)anisole (**9d**) (2.10 g, 5.0 mmol, 1.00 equiv), and 1-indanone (**10d**) (727 mg, 5.5 mmol, 1.10 equiv) were employed. After stirring the reaction mixture for 16 h at ambient temperatures under N_2, it was quenched with 1 M HCl solution (10 mL) and subsequently subjected to the usual work-up. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) afforded 1.80 g (3.8 mmol, 76%) of the title compound (*rac*-**11e**) as a colorless solid. Mp: 59 °C. TLC: R_f = 0.33 (silica gel; hexanes/EtOAc, 9:1). FTIR (KBr): ν_{max} (cm^{-1}) = 3415 (s), 3055 (m), 3022 (m), 2966 (m), 2871 (m), 1944 (m), 1871 (m), 1803 (m), 1714 (s), 1606 (s), 1493 (m), 1465 (m), 1443 (m), 1428 (m), 1382 (s), 1361 (s), 1273 (s), 1233 (s), 1203 (s), 11561 (m), 1110 (m), 1030 (s), 1000(s), 767 (m), 754 (m), 700 (s), 658 (s), 609 (s), 575 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.56 (d, J = 2.2 Hz, 3H), 1.61 (dd, J = 4.8, 2.7 Hz, 6H), 1.65 (d, J = 2.3 Hz, 3H),), 2.75 (d, J = 2.7 Hz, 3H), 3.04 (d, J = 17.4 Hz, 1H), 3.62 (dd, J = 17.3, 8.3 Hz, 1H), 4.19–4.10 (m, 1H), 6.70 (t, J = 2.6 Hz, 1H), 7.12 (ddd, J = 8.2, 6.8, 1.4 Hz, 2H), 7.26–7.16 (m, 9H), 7.38 (t, J = 7.4 Hz, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.3 (q), 30.8 (q, 30.9 (q), 31.1 (q), 37.3 (t), 42.3 (s), 42.8 (s), 47.7 (d), 61.5 (q), 124.2 (d), 124.6 (d), 125.0 (d), 125.2 (d), 125.5 (d), 126.15 (d), 126.3 (d), 126.7 (d), 127.5 (d), 127.9 (d), 128.0 (d), 133.7 (s), 134.7 (d), 136.7 (s), 142.3 (s), 145.6 (s), 150.6 (s), 151.6 (s), 153.6 (s), 155.97 (s), 206.8 (s). GCMS: t_R = 43,55 min, m/z (%) = 326 ([M]$^+$, (100)), 459 (70), 281 (7), 265 (4), 220 (9), 207 (8), 119 (31), 91 (27), 28 (60). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{34}H_{34}O_2Na$: 497.2451; found: 497.2458.

*4.12. 2-(2-Methoxy-3,5-bis(2-phenylpropan-2-yl)phenyl)-3,4-dihydro-2H-naphthalen-1-one (rac-**11f**)*

Following the general procedure I as described above, $Pd(OAc)_2$ (22.5 mg, 0.1 mmol, 2 mol%), NaO^{t}Bu (1.10 g, 11.0 mmol, 2.20 equiv), 100 µL of 1.0 M tri-*tert*-butylphosphine solution in toluene (0.1 mmol, 2 mol% P^{t}Bu$_3$), 6-bromo-2,4-bis(2-phenylpropan-2-yl)anisole (**9d**) (2.10 g, 5.0 mmol, 1.00 equiv), and α-tetralone (**10e**) (731 µL, 804 mg, 5.5 mmol, 1.10 equiv) were employed. After stirring the reaction mixture for 16 h at ambient temperatures under N_2, it was quenched with 1 M HCl solution (10 mL) and subsequently subjected to the usual work-up. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) afforded 2.27 g (4.65 mmol, 93%) of the title compound (*rac*-**11f**) as a colorless solid. **Mp:** 126 °C. **TLC:** R_f = 0.56 (silica gel; hexanes/EtOAc, 9:1). FTIR (KBr): ν_{max} (cm^{-1}) = 3445 (w), 3056 (w), 3022 (w), 2965 (s), 1685(s), 1599 (s), 1469 (m), 1360 (w), 1221 (s), 1002 (s), 767 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.55 (s, 3H), 1.68 (d, J = 3.5 Hz, 9H), 2.23–2.15 (m, 1H), 2.34-2.23 (m, 1H), 2.63 (s, 3H), 2.96 (dt, J = 16.7, 3.6 Hz, 1H), 3.11 (ddd, J = 16.5, 11.9, 4.5 Hz, 1H), 4.04 (dd, J = 12.6, 4.5 Hz, 1H), 6.86 (d, J = 2.1 Hz, 1H), 7.10 (dd, J = 7.5, 5.1 Hz, 1H), 7.15 (td, J = 6.1, 2.7 Hz, 1H), 7.33–7.19 (m, 11H), 7.46 (t, J = 7.5 Hz, 1H), 8.01 (d, J = 7.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.9 (q), 29.7 (t), 31.0 (q), 31.6 (q), 31.9 (t), 42.3 (s), 42.9 (s), 48.8 (d), 60.8 (q), 124.6 (d), 125.2 (d), 125.5 (d), 126.0 (d), 126.2 (d), 126.6 (d), 126.8 (d), 127.6 (d), 127.9 (d), 128.0 (d), 128.8 (d), 133.1 (s), 133.2 (d), 133.7 (s), 141.9 (s), 144.0 (s), 145.1 (s), 150.9 (s), 151.7 (s), 155.3 (s), 198.9 (s). GCMS: t_R = 45.34 min, *m/z* (%) = 488 ([M]$^+$, (100)), 473 ([M-15]$^+$, (84)), 457 (7). HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{35}H_{37}O_2$: 489.2788; found: 489.2794.

*4.13. General Procedure II (Enantioselective reduction of ketones with the CBS catalyst **14**): (S)-(–)-2-(3,5-Di-tert-butyl-2-methoxyphenyl)-1-(naphthalen-2-yl)ethanol (**5f**)*

An oven-dried and nitrogen-flushed 25 mL Schlenk tube was charged with the (*R*)-(+)-2-Methyl-CBS-oxazaborolidine catalyst **14** (17.8 mg, 63 µmol, 5 mol%). The tube was equipped with a magnetic stirring bar and capped with a glass stopper. After evacuating the tube for 15 minutes, the system was back-filled with dry N_2, the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. Then anhydrous THF (1.5 mL) was added by means of a gas-tight syringe. The mixture was cooled to 0 °C in an ice-bath, $BH_3{\cdot}SMe_2$ (119 µL, 95 mg, 1.25 mmol, 1.00 equiv) was added, and it was stirred for 30 minutes at 0 °C. In a separate oven-dried 10 mL Schlenk tube, 2-(3,5-di-*tert*-butyl-2-methoxyphenyl)-1-(naphthalen-2-yl)ethan-1-one (**11b**) (486 mg, 1.25 mmol, 1.00 equiv) was dissolved in 1.5 mL of anhydrous THF under nitrogen. The solution of ketone (**11b**) in THF was then transferred into the 25 mL Schlenk tube containing the CBS catalyst **14** at 0 °C, via cannula technique and the reaction mixture were stirred for 30 minutes at 0 °C. Conversion of the ketone **11b** was followed by TLC and determined to be completed within 1 h at 0 °C. The reaction mixture was quenched by the dropwise addition of MeOH (1 mL). Solvents were removed by rotary evaporation under reduced pressure, the residue was treated with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with DCM (3×30 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) gave 470 mg (1.2 mmol, 96%) of the title compound (**5f**) as a colorless solid, in 97% *ee*. Mp: 118 °C. TLC: R_f = 0,35 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{28}$ = −22 (c = 0.5, $CHCl_3$). FTIR (KBr): ν_{max} (cm^{-1}) = 3340 (s), 3050 (s), 3247 (s), 2954 (m), 2865 (m), 1601(s), 1508 (s), 1478 (m), 1389 (s), 1360 (s), 1271 (s),1228 (s), 1124 (s), 1037 (m), 1013 (m) 903 (s), 882 (s), 857 (s), 820 (s), 752 (s), 705 (m),654 (m), 544 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 (s, 9H), 1.43 (s, 9H), 3.08 (d, J = 2.4 Hz, 1H), 3.23–3.12 (m, 2H), 3.87 (s, 3H), 5.18–5.13 (m, 1H), 6.90 (d, J = 2.5 Hz, 1H), 7.23 (d, J = 2.5 Hz, 1H), 7.48–7.42 (m, 2H), 7.50 (dd, J = 8.5, 1.7 Hz, 1H), 7.85–7.74 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.3 (CH_3), 31.4 (CH_3), 34.4 (C), 35.3 (C), 42.0 (CH_2), 61.8 (CH_3), 75.0 (CH), 123.3 (CH), 124.1 (CH), 124.4 (CH), 125.6 (CH), 125.9 (CH), 126.9 (CH), 127.6 (CH), 127.9 (CH), 128.0 (CH), 130.8 (C), 132.9 (C), 133.3 (C), 141.8 (C), 142.2 (C), 146.1 (C), 156.0 (C). GCMS: t_R = 37.22 min, *m/z* (%) = 372 ([M-18]$^+$, (100)), 357 (57), 234 (42), 219 (49), 155 (23), 141 (24), 128 (13). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{27}H_{34}O_2Na$: 413.2451; found: 413.2459.

*4.14 (S)-(–)-1-(3,5-Di-tert-butyl-2-methoxyphenyl)-3,3-dimethylbutan-2-ol (**5g**)*

Following the general procedure II as described above, an oven-dried and nitrogen-flushed 50 mL Schlenk tube was charged with the CBS catalyst **14** (87.3 mg, 0.32 mmol, 5 mol%). The tube was equipped with a magnetic stirring bar and capped with a glass stopper. After evacuating the tube for 15 minutes, the system was back-filled with dry N_2, the glass stopper was replaced with a rubber septum, under positive pressure of dry nitrogen. Then anhydrous THF (6 mL) was added by means of a gas-tight syringe. The mixture was cooled to 0 °C in an ice-bath, $BH_3{\cdot}SMe_2$ (600 µL, 479 mg, 6.3 mmol, 1.00 equiv) was added, and it was stirred for 30 minutes at 0 °C. In a separate oven-dried 10 mL Schlenk tube, 1-(3,5-di-tert-

butyl-2-methoxyphenyl)-3,3-dimethylbutan-2-one (**11c**) (2.0 g, 6.3 mmol, 1.00 equiv) was dissolved in 6 mL of anhydrous THF under nitrogen. The solution of ketone (**11c**) in THF was then transferred into the 50 mL Schlenk tube containing the CBS catalyst **14** at 0 °C, via cannula technique and the reaction mixture were stirred for 30 minutes at 0 °C. Conversion of the ketone **11c** was followed by TLC and determined to be completed within 1 h at 0 °C. The reaction mixture was quenched by the dropwise addition of MeOH (5 mL). Solvents were removed by rotary evaporation under reduced pressure, the residue was treated with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with DCM (3×30 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) yielded 1.90 g (5.94 mmol, 94%) of the title compound (**5g**) as a colorless solid, in 98% *ee*. Mp: 63 °C. TLC: R_f = 0.56 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{28}$ = −38 (c = 0.5, $CHCl_3$). HPLC: Chiralcel OD-H; *n*-hexane (100%), 1.0 mL/min; 254 nm (UV–vis); t_R = 6.7 min (*ent*-**5g**), t_R = 7.1 min (**5g**). FTIR (KBr): ν_{max} (cm^{-1}) = 3445 (m), 2954 (m), 2905 (m), 2867 (m), 2019 (m), 1770 (s), 1600 (s), 1477 (m), 1361 (s), 1229 (m), 1159 (s), 1115 (s), 1073 (s), 1013 (m), 880 (s), 845 (s), 700 (s), 654 (s), 588 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.02 (s, 9H), 1.30 (s, 9H), 1.40 (s, 9H), 2.69 (dd, *J* = 14.0, 10.5 Hz, 1H), 2.85 (dd, *J* = 14.0, 2.1 Hz, 1H), 3.43 (dd, *J* = 10.5, 2.1 Hz, 1H), 3.80 (s, 3H), 7.05 (d, *J* = 2.5 Hz, 1H), 7.23 (d, *J* = 2.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.8 (CH_3). 31.3 (CH_3), 31.5 (CH_3), 34.0 (C), 35.0 (C), 35.3 (C), 61.6 (CH), 80.4 (CH_3), 123.0 (CH), 126.3 (CH), 132.7 (C), 142.1 (C), 146.3 (C), 156.0 (C). GCMS: t_R = 29.71 min, *m/z* (%) = 320 ($[M]^+$, 7), 234 (38), 219(100), 178 (14), 163 (14), 151 (10), 57 (21). HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{21}H_{36}O_2Na$: 343.2613; found: 343.2617.

*4.15. General Procedure III (Enantioselective transfer hydrogenation of ketones with RuCl(p-cymene)[(S,S)-TsDPEN]): (1S,2R)-(−)-2-(3,5-Di-tert-butyl-2-methoxyphenyl)indan-1-ol (**5h**)*

An oven-dried 100 mL Schlenk flask equipped with a magnetic stir bar was charged with RuCl(*p*-cymene)[*(S,S)*-Ts-DPEN] (**13**) (76.4 mg, 0.12 mmol, 2 mol%). The flask was capped with a glass stopper, evacuated for 15 minutes, back-filled with N_2, and the glass stopper was replaced with a rubber septum under positive pressure of dry N_2. Then 6.6 mL of HCO_2H/TEA (5:2) azeotropic mixture was added to the reaction flask. In a separate oven-dried 50 mL Schlenk tube, 2-(3,5-di-*tert*-butyl-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-one (*rac*-**11d**) (2.10 g, 6.0 mmol, 1.00 equiv) was dissolved in 25 mL of anhydrous THF under N_2 and the solution was transferred into the 100 mL Schlenk flask by cannula technique. After stirring the reaction mixture for 16 h at 40 °C under N_2, THF was removed by rotary evaporation under reduced pressure. The residue was treated with water (20 mL) and extracted with DCM (3×30 mL). The combined organic pahes were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) afforded 560 mg (1.60 mmol, 27%) of the title compound (**5h**) as a colorless solid, in 98% *ee*. Mp: 155 °C. TLC: R_f = 0.55 (silica gel, hexanes/EtOAc, 9:1). $[\alpha]_D^{28}$ = −74 (c = 0.5, $CHCl_3$). GC: CP-Chirasil-Dex CB, 25 m, 0.25 mm ID, 0.25 µm film tickness; 190 °C inlet (split modus); 195 °C detector (FID); He, 2.0 mL/min (constant flow modus); 160 °C (4 min), 5 °C/min, 180 °C (52 min); t_R = 50.19 min (*ent*-**5h**), t_R = 51.87 min (**5h**). FTIR (KBr): ν_{max} (cm^{-1}) = 3434 (w), 2964 (m), 2950 (m), 1600 (m), 1473 (m), 1427 (s), 1360 (s), 1227 (s), 1112

(s), 1004 (s), 946 (s), 884 (s), 807 (s), 752 (m), 740 (m), 690 (s), 613 (s), 528 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (s, 9H), 1.46 (s, 9H), 1.68 (d, *J* = 5.1 Hz, 1H), 3.33-3.26 (dd, *J* = 15.8, 7.9 Hz, 1H), 3.39-3.33(dd, *J* = 15.8, 7.9 Hz, 1H), 3.86 (s, 3H), 4.17 (td, *J* = 7.9, 6.2 Hz, 1H), 5.36 (t, *J* = 5.5 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.39 – 7.28 (m, 4H), 7.51 (d, *J* = 6.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.3 (CH_3), 31.4 (CH_3), 34.5 (C), 35.4 (C), 37.8 (CH_2), 44.2 (CH), 62.4 (CH_3), 76.6 (CH), 123.2 (CH), 124.4 (CH), 124.6 (CH), 125.3 (CH), 126.9 (CH), 128.6 (CH), 132.1 (C), 142.0 (C), 143.3 (C), 143.9 (C), 145.7 (C), 156.2 (C). GCMS: t_R = 34.08 min, *m/z* (%) = 352 ([M]$^+$, 52), 334 ([M-18]$^+$, (65)), 319 (100), 305 (19), 281 (6), 263 (7), 233 (28), 221 (7), 205 (12), 177 (17), 161 (9), 131 (6), 115 (10), 105 (6), 91 (8), 57 (28), 41 (5). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{24}H_{32}O_2Na$: 375.2295; found: 375.2323.

*4.16. (1S,2R)-(–)-2-(2-Methoxy-3,5-bis(2-phenylpropan-2-yl)phenyl)indan-1-ol (**5i**)*

Following the general procedure III as described above, the catalyst **13** (28 mg, 44 µmol, 2 mol%), 2.42 mL of HCO_2H/TEA (5:2) azeotropic mixture, 2-(2-methoxy-3,5-bis(2-phenylpropan-2-yl)phenyl)-2,3-dihydro-1*H*-inden-1-one (*rac*-**11e**) (1.04 g, 2.2 mmol, 1.00 equiv) were employed. After stirring the reaction mixture for 16 h at 40 °C under N_2, it was subjected to the usual work-up. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) gave 524 mg (1.1 mmol, 50%) of the title compound (**5i**) as a colorless solid, in 96% *ee*. Mp: 54 °C. TLC: R_f = 0.35 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{28}$ = –70 (c = 0.5, $CHCl_3$). FTIR (KBr): ν_{max} (cm^{-1}) = 3437 (s), 3055 (m), 3023 (m), 2965 (m), 2871 (m), 1946 (m), 1870 (m), 1803 (m), 1599 (s), 1493 (s), 1466 (s), 1444 (s), 1426 (s), 1382 (s), 1361 (s), 1284 (m), 1232 (s), 1200 (s), 1109 (s), 1048 (s), 1029 (s), 1006 (s), 948 (s),888 (s), 767 (m), 750 (m), 700 (s), 606 (s), 5825 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.44 (t, *J* = 6.4 Hz, 1H), 1.62 (d, *J* = 7.5 Hz, 3H), 1.66 (s, 9H), 2.70 (d, *J* = 0.8 Hz, 3H), 3.21–3.09 (m, 2H), 3.88 (dd, *J* = 14.0, 7.8 Hz, 1H), 5.17 (t, *J* = 5.4 Hz, 1H), 7.03 (d, *J* = 2.2 Hz, 1H), 7.14 (dtd, *J* = 7.8, 7.1, 0.9 Hz, 2H), 7.28–7.19 (m, 12H), 7.33 (d, *J* = 2.3 Hz, 1H), 7.38 (d, *J* = 6.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.7 (CH_3), 30.8 (CH_3), 30.8 (CH_3), 37.2 (CH_2), 42.4 (C), 42.8 (C), 44.3 (CH), 60.3 (CH_3), 76.4 (CH), 124.3 (CH), 124.5 (CH), 125.2 (CH), 125.3 (CH), 125.6 (CH), 126.1 (CH), 126.4 (CH), 126.6 (CH), 126.9 (CH), 128.0 (CH), 128.5 (CH), 132.3 (C), 142.4 (C), 143.1 (C), 143.8 (C), 145.3 (C), 150.6 (C), 151.8 (C), 155.6 (C). GCMS: t_R = 42,81 min, *m/z* (%) = 476 ([M]$^+$, 33), 458 ([M-18]$^+$, (100)), 443 (73), 357 (6), 253 (9), 207 (9), 119 (61), 91 (44), 28 (73). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{34}H_{36}O_2Na$: 499.2608; found: 499.2634.

*4.17. (1S,2R)-(–)-2-(2-Methoxy-3,5-bis(2-phenylpropan-2-yl)phenyl)-3,4-dihydro-2H-naphthalen-1-ol (**5j**)*

Following the general procedure III as described above, the catalyst **13** (89 mg, 140 µmol, 2 mol%), 7.7 mL of HCO_2H/TEA (5:2) azeotropic mixture, 2-(2-methoxy-3,5-bis(2-phenylpropan-2-yl)phenyl)-3,4-dihydronaphthalen-1(2*H*)-one (*rac*-**11f**) (2.45 g, 7.0 mmol, 1.00 equiv) were employed. After stirring the reaction mixture for 16 h at 40 °C under N_2, it was subjected to the usual work-up. Purification of the crude product by flash column chromatography on silica gel (hexanes/DCM, 1:1) afforded 859 mg (1.75 mmol, 25%) of the title compound (**5j**) as a colorless solid, in 99% *ee*. Mp: 61 °C. TLC: R_f = 0.28 (silica gel; hexanes/DCM, 1:1). $[\alpha]_D^{28}$ = –64 (c = 0.5, $CHCl_3$). FTIR (KBr): ν_{max} (cm^{-1}) = 3437 (w), 2965 (m), 1598 (w), 1492 (w), 1466 (w), 1444 (w), 1426 (w), 1382 (w), 1361 (w), 1232 (w), 1202 (w), 1007 (w), 771 (s), 700

(s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.47 (d, *J* = 13.1 Hz, 1H), 1.59 (s, 3H), 1.74–1.68 (m, 10H), 2.26 (qd, *J* = 12.6, 5.5 Hz, 1H), 2.60 (s, 3H), 2.88–2.78 (m, 1H), 2.98–2.88 (m, 1H), 3.28 (dt, *J* = 12.7, 2.7 Hz, 1H), 4.69 (d, *J* = 2.7 Hz, 1H), 7.31-7.07 (m, 15H), 7.35 (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5 (CH_2), 29.3 (CH_3), 29.9 (CH_2), 30.9 (CH_3), 30.92 (CH_3), 31.3 (CH_3), 39.2 (CH), 42.4 (C), 42.9 (C), 60.4 (CH_3), 69.7 (CH), 124.0 (CH), 125.2 (CH), 125.6 (CH), 126.0 (CH), 126.2 (CH), 126.3 (CH), 126.6 (CH), 127.9 (CH), 127.9 (CH), 128.0 (CH), 128.9 (CH), 130.4 (CH), 135.5 (C), 136.5 (C), 137.8 (C), 142.3 (C), 145.2 (C), 150.8 (C), 151.9 (C), 155.0 C). GCMS: t_R = 45.47 min, *m/z* (%) = 490 ([M]$^+$, 32), 472 ([M-18]$^+$, (100)), 379 (17), 355 (5), 329 (8), 293 (6), 265 (4), 207 (6), 119 (65), 91 (38). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{35}H_{38}O_2Na$: 513.2764; found: 513.2744.

*4.18. General Procedure IV (Demethylation of anisoles): (S)-(–)-2-(2-Hydroxyphenyl)-1-phenylethanol (**12a**)*

An oven-dried 50 mL Schlenk tube, capped with a glass stopper and equipped with a magnetic stir bar, was evacuated for 15 minutes, back-filled with dry N_2, and the glass stopper was replaced with a rubber septum under positive pressure of dry N_2. Dry DMF (20 mL) and EtSH (888 µL, 746 mg, 12.0 mmol, 3.00 equiv) were added into the tube. To the cooled reaction mixture in an ice-bath was added NaO^{t}Bu (461 mg, 482 mmol, 1.20 equiv) at once and it was stirred at 0 °C for 30 minutes. Then, (*S*)-(–)-2-(2-methoxyphenyl)-1-phenylethan-1-ol (**5a**) (912 mg, 4.0 mmol, 1.00 equiv) was added into the Schlenk tube at 0 °C and the reaction tube was heated to 120 °C, and stirred at this temperature for 2-3 hours. Conversion of the starting material **12a** was followed by TLC. After cooling down to 0 °C, pH value of the reaction mixture was adjusted to 5-6, by the addition of 1N HCl. The organic components were extracted with Et_2O (3×75 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Purification of the residue by flash column chromatography on silica gel (hexanes/EtOAc,8:2) gave 700 mg (3.26 mmol, 82%) of the title compound (**12a**) as a colorless solid, in >99% *ee*. Mp: 116 °C. TLC: R_f = 0.40 (silica gel; hexanes/EtOAc, 8:2). $[\alpha]_D^{26}$ = –64 (c = 0.5, $CHCl_3$). HPLC: Chiralcel OD-H; *n*-hexane/^{i}PrOH (90:10), 1.0 mL/min; 254 nm (UV–vis); t_R = 11.6 min (*ent*-**12a**), t_R = 13.6 min (**12a**). FTIR (KBr): ν_{max} (cm^{-1}) = 3351 (s), 3033 (m),1614 (m) , 1584 (s), 1490 (s), 1423(s), 1243 (s), 1104 (s), 1045 (s), 1030 (s), 972 (s) , 813 (s) , 752 (s), 698 (s), 571(s), 534 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.92 (dd, *J* = 14.6, 2.5 Hz, 1H), 3.15 (dd, *J* = 14.6, 9.1 Hz, 1H), 5.01 (dd, *J* = 9.1, 2.5 Hz, 1H), 6.83 (td, *J* = 7.4, 1.2 Hz, 1H), 6.94 (ddd, *J* = 12.2, 7.8, 1.4 Hz, 2H), 7.19–7.12 (m, 1H), 7.40–7.28 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.7 (CH_2), 77.1 (CH), 117.2 (C), 120.5 (C), 125.4 (C), 125.6 (CH), 128.0 (CH), 128.5 (CH), 128.6 (CH), 131.5 (CH), 143.3 (C), 155.5 (C). GCMS: t_R = 30.37 min, *m/z* (%) = 214 ([M]$^+$, 5), 196 ([M-18]$^+$, (58)), 179 (8), 167 (13), 152 (7), 139 (2), 128 (2), 118 (3), 108 (100), 89 (5), 79 (46). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{14}H_{14}O_2Na$: 237.0886; found: 237.0891.

*4.19. (S)-(–)-2-(2-Hydroxy3-phenylphenyl)-1-phenylethanol (**12b**)*

According to the general procedure IV as described above, DMF (30 mL), EtSH (1.82 mL, 1.53 g, 24.6 mmol, 4.00 equiv), NaO^{t}Bu (887 mg, 9.23 mmol, 1.50 equiv), and (*S*)-(–)-2-(2-Methoxy-3-phenylphenyl)-1-phenylethanol (**5b**) (1.87 g, 6.15 mmol, 1.00 equiv) were employed. After stirring the reaction mixture

at 120 °C for 2-3 h under N_2, it was subjected to the usual work up. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) afforded 1.50 g (5.17 mmol, 75%) of the title compound (**12b**) as a colorless solid, in >99% *ee*. TLC: R_f = 0.43 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{26}$ = –60 (c = 0.5, $CHCl_3$). HPLC: Chiralcel OD-H; *n*-hexane/^{i}PrOH (85:15), 1.0 mL/min; 254 nm (UV–vis); t_R = 15.8 min (*ent*-**12b**), t_R = 26.7 min (**12b**). FTIR (KBr): ν_{max} (cm^{-1}) = 3357 (s), 3059 (s),3028 (s), 2802 (s) , 1944 (s), 1875 (s), 1805 (s), 1587 (m), 1494 (s), 1462 s) , 1435 (m), 1359 (s), 1321 (s), 1268 (m), 1224 (s), 1071 (s),1040 (s), 1007 (s), 877 (s), 831 (s), 791 (s), 761 (m), 699 (s), 601 (s), 555 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ= 2.59 (s, 1H), 3.06 (dd, *J* = 14.4, 2.8 Hz, 1H), 3.19 (dd, *J* = 14.4, 9.2 Hz, 1H), 5.09 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 7.03 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.21 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.36 (tt, *J* = 25.4, 6.9 Hz, 7H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.56 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ= 41.8 (CH_2), 76.5 (CH), 120.5 (CH), 125.6 (CH), 125.9 (C), 127.3 (CH), 127.9 (CH), 128.6 (CH), 128.6 (CH), 129.4 (CH), 129.5 (CH), 129.8 (C), 131.0 (CH), 138.3 (C), 143.7 (C), 152.1 (C). GCMS: t_R = 35.63 min, *m/z* (%) = 272 ([M-18]$^+$, (75)), 253 (5), 239 (5), 215 (3), 202 (2), 184 (100), 165 (18), 152 (9), 128 (6), 107 (21), 79 (16). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{20}H_{18}O_2Na$: 313.1199; found: 313.1190.

*4.20. (S)-(–)-2-(3,5-Di-tert-butyl-2-hydroxyphenyl)-1-phenylethanol (**12c**)*

Following the general procedure IV as described above, DMF (20 mL), EtSH (1.18 mL, 994 mg, 16.0 mmol, 4.00 equiv), NaO^{t}Bu (577 mg, 6.0 mmol, 1.50 equiv), and **5c** (1.36 g, 4.0 mmol, 1.00 equiv) were employed. After stirring the reaction mixture at 120 °C for 2-3 h under N_2, it was subjected to the usual work up. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) afforded 848 mg (2.6 mmol, 65%) of the title compound (**12c**) as a colorless solid, in >99% *ee*. Mp: 106 °C. TLC: R_f = 0.40 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{26}$ = –20 (c = 0.5, $CHCl_3$). HPLC: Chiralcel OD-H; *n*-hexane/^{i}PrOH (98:2), 1.0 mL/min; 254 nm (UV–vis); t_R = 12.3 min (*ent*-**12c**), t_R = 14.2 min (**12c**). FTIR (KBr): ν_{max} (cm^{-1}) = 3529 (s), 3449 (m), 3247 (s), 3067 (m), 3034 (m),1951 (s), 1766 (m), 1598(s), (w), 1480 (s), 1455 (s), 1418 (s), 1390 (s), 1361 (s), 1299 (m), 1269 (s), 1231 (s), 1203 (s), 1162 (w), 1123 (w), 1077 (w), 1041 (s), 1006 (m), 951 (w), 910 (w), 876 (m), 844 (w), 755 (s), 700(s), 579 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.26 (s, 9H), 1.45 (s, 9H), 2.63 (s, 1H), 2.85 (d, *J* = 14.6 Hz, 1H), 3.19 (dd, *J* = 14.6, 9.6 Hz, 1H), 5.04 (d, *J* = 9.5 Hz, 1H), 6.84 (d, *J* = 2.3 Hz, 1H), 7.24 (dd, *J* = 12.6, 7.9 Hz, 1H), 7.28–7.43 (m, 4H), 7.94 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ= 29.9 (CH_3), 31.7 (CH_3), 34.2 (C), 35.1 (C), 42.2 (CH_2), 77.8 (CH), 122.9 (CH), 125.6 (CH), 125.7 (C), 126.1 (CH), 128.1 (CH), 128.7 (CH), 137.2 (C), 142.0 (C), 143.6 (C), 152.2 (C). GCMS: t_R = 33.70 min; *m/z* (%) = 326 ([M]$^+$, 6), 308 ([M-18]$^+$, (37)), 293 (100), 277 (1), 237 (2), 220 (9), 205 (37), 189 (6), 178 (1), 163 (3), 149 (4), 139 (1), 128 (1), 117 (1), 107 (5), 91 (5), 79 (5), 57 (8). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{22}H_{30}O_2Na$: 349.2138; found: 349.2142.

*4.21. (S)-(–)-2-(2-Hydroxy-3,5-bis(2-phenylpropan-2-yl)phenyl)-1-phenylethanol (**12d**)*

Following the general procedure IV as described above, DMF (4 mL), EtSH (355 µL, 298 mg, 4.8 mmol, 6.00 equiv), NaO^{t}Bu (154 mg, 1.6 mmol, 2.00 equiv), and **5d** (370 mg, 0.8 mmol, 1.00 equiv) were employed. After stirring the reaction mixture at 120 °C for 2-3 h under N_2, it was subjected to the usual

work up. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) afforded 280 mg (0.62 mmol, 78%) of the title compound (**12d**) as a colorless solid, in >99% *ee*. Mp: 83 °C. TLC: R_f = 0.30 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{28}$ = –46 (c = 0.5, $CHCl_3$). HPLC: Chiralcel OD-H; *n*-hexane/^{i}PrOH (95:5), 1.0 mL/min; 254 nm (UV–vis); t_R = 11.4 min (**12d**), t_R = 37.5 min (*ent*-**12d**). FTIR (KBr): ν_{max} (cm^{-1}) = 3529 (s), 3449 (m), 3247 (s), 3067 (m), 3034 (m),1951 (s), 1766 (m), 1598(s), (w), 1480 (s), 1455 (s), 1418 (s), 1390 (s), 1361 (s), 1299 (m), 1269 (s), 1231 (s), 1203 (s), 1162 (w), 1123 (w), 1077 (w), 1041 (s), 1006 (m), 951 (w), 910 (w), 876 (m), 844 (w), 755 (s), 700(s), 579 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.61 (s, 3H), 1.62 (s, 6H), 1.64 (s, 3H), 2.53 (d, *J* = 2.5 Hz, 1H), 2.97–2.82 (m, 2H), 4.98–4.75 (m, 1H), 5.94 (dd, *J* = 3.7, 1.8 Hz, 1H), 6.68 (d, *J* = 2.3 Hz, 1H), 7.38–7.14 (m, 16H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.5 (CH_3), 30.0 (CH_3), 31.0 (CH_3), 31.1 (CH_3), 41.5 (CH_2), 42.1 (C), 42.5 (C), 75.8 (CH), 124.1 (CH), 125.4 (CH), 125.5 (C), 125.6 (CH), 125.8 (CH), 126.2 (CH), 126.7 (CH), 127.4 (CH), 127.9 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 135.5 (C), 141.8 (C), 143.7 (C), 149.7 (C), 150.7 (C), 151.1 (C). GCMS: t_R = 42.14 min, *m/z* (%) = 450 ([M]$^+$, 1), 432 ([M-18]$^+$, (64)), 417 (100), 344 (19), 329 (27), 265 (7), 165 (4), 119 (21), 91 (21), 28 (10). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{32}H_{34}O_2Na$: 473.2451; found: 473.2490.

*4.22. (S)-(–)-2-(1-Hydroxy-8-phenylnaphthalen-2-yl)-1-phenylethanol (**12e**)*

Following the general procedure IV as described above, DMF (5 mL), EtSH (592 µL, 497 mg, 8.0 mmol, 8.00 equiv), NaO^{t}Bu (288 mg, 3.0 mmol, 3.00 equiv), and **5e** (354 mg, 1.0 mmol, 1.00 equiv) were employed. After stirring the reaction mixture at 120 °C for 2-3 h under N_2, it was subjected to the usual work up. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 8:2) afforded 270 mg (0.8 mmol, 80%) of the title compound (**12e**) as a colorless oil, in >99% *ee*. TLC: R_f = 0.40 (silica gel; hexanes/EtOAc, 8:2). $[\alpha]_D^{24}$ = –42 (c = 0.5, $CHCl_3$). FTIR (KBr): ν_{max} (cm^{-1}) = 3502 (br), 3305 (br), 3055 (m), 1949 (w), 1887 (w), 1622 (m), 1571 (s), 1493 (s), 1340 (s), 1073 (s), 828 (m), 758 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.19–3.03 (m, 2H), 4.98 (dd, *J* = 8.0, 4.5 Hz, 1H), 6.33 (s, 1H), 7.27–7.15 (m, 3H), 7.37–7.27 (m, 5H), 7.44–7.38 (m,2H), 7.48 (s, 5H), 7.80 (dd, *J* = 8.2, 1.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.5 (CH_2), 75.3 (CH), 120.65 (CH), 120.73 (C), 121.7 (C), 124.5 (CH), 125.7 (CH), 127.4 (CH), 128.0 (CH), 128.28 (CH), 128.32 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.9 (CH), 129.4 (CH), 129.5 (CH), 129.9 (CH), 134.9 (C), 136.5 (C), 142.3 (C), 144.2 (C), 150.9 (C). GCMS: t_R = 41.07 min, *m/z* (%) = 340 ([M]$^+$, 6), 322 ([M-18]$^+$, (100)), 234 (69), 218 (43), 202 (14), 77 (9), 28 (7). HRMS: *m/z* [M+Na]$^+$ calcd for $C_{24}H_{20}O_2Na$: 363.1356; found: 363.1373.

*4.23. (S)-(–)-2-(3,5-Di-tert-butyl-2-hydroxyphenyl)-1-(naphthalen-2-yl)ethanol (**12f**)*

Following the general procedure IV as described above, DMF (5 mL), EtSH (457 µL, 384 mg, 6.2 mmol, 6.00 equiv), NaO^{t}Bu (198 mg, 2.1 mmol, 2.00 equiv), and **5f** (400 mg, 1.03 mmol, 1.00 equiv) were employed. After stirring the reaction mixture at 120 °C for 2-3 h under N_2, it was subjected to the usual work up. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) gave 292 mg (0.78 mmol, 76%) of the title compound (**12f**) as a white solid, in >97% *ee*. Mp: 137 °C. TLC: R_f = 0.49 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{28}$ = –44 (c = 0.5, $CHCl_3$). HPLC: Chiralcel OD-H; *n*-

hexane/^{i}PrOH (94:6), 1.0 mL/min; 254 nm (UV–vis); t_R = 13.2 min (**12f**), t_R = 19.6 min (*ent*-**12f**). FTIR (KBr): ν_{max} (cm^{-1}) = 3446 (s), 3419 (m), 3053 (m),2953 (m), 1601(s), 1507 (s), 1480 (m), 1455 (m), 1440 (m), 1361 (s), 1281 (m), 1229 (s), 1120 (s), 1045 (s), 950 (s), 889 (m), 862 (m), 817 (s), 746 (s), 663 (s), 650 (s), 566 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 0.6 Hz, 9H), 1.47 (s, 9H), 2.70 (s, 1H), 2.93 (dt, *J* = 14.7, 2.0 Hz, 1H), 3.31 (dd, *J* = 14.6, 9.7 Hz, 1H), 5.22 (dt, *J* = 9.6, 2.3 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 7.26 (d, *J* = 2.4 Hz, 1H), 7.57–7.45 (m, 3H), 7.90–7.79 (m, 4H), 7.97 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.9 (CH_3), 31.6 (CH_3), 34.2 (C), 35.1 (C), 42.2 (CH_2), 78.0 (C), 123.0 (CH), 123.7 (CH), 124.4 (CH), 125.7 (C), 126.0 (CH), 126.1 (CH), 126.4 (CH), 127.7 (CH), 128.0 (CH), 128.5 (CH), 133.2 (C), 133.3 (C), 137.2 (C), 141.0 (C), 142.1 (C), 152.2 (C). GCMS: t_R = 37.77 min, *m/z* (%) = 376 ([M]$^+$, 3), 358 ([M-18]$^+$, (73)), 343 (100), 220 (11), 205 (40), 189 (6), 157 (13), 129 (20), 57 (13). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{26}H_{32}O_2Na$: 399.2295; found: 399.2314.

*4.24. (S)-(–)-1-(3,5-Di-tert-butyl-2-hydroxyphenyl)-3,3-dimethylbutan-2-ol (**12g**)*

Following the general procedure IV as described above, DMF (12.5 mL), EtSH (11.1 mL, 932 mg, 15.0 mmol, 6.00 equiv), NaO^{t}Bu (481 mg, 5.0 mmol, 2.00 equiv), and **5g** (800 mg, 2.5 mmol, 1.00 equiv) were employed. After stirring the reaction mixture at 120 °C for 2-3 h under N_2, it was subjected to the usual work up. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) gave 745 mg (2.43 mmol, 97%) of the title compound (**12g**) as a white solid, in >98% *ee*. Mp: 124 °C. TLC: R_f = 0.56 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{28}$ = +20 (c = 0.5, $CHCl_3$). FTIR (KBr): ν_{max} (cm^{-1}) = 3398 (s), 3273 (s), 2962 (m), 2871 (m), 1601 (s), 1480 (m), 1429 (m), 1392 (s), 1363 (s), 1277 (m), 1232 (s), 1123 (s), 1066 (s), 1014 (m), 1005 (m), 868 (m), 799 (m), 723 (s), 650 (s), 539 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.02 (s, 9H), 1.30 (s, 9H), 1.42 (s, 9H), 2.33 (s, 1H), 2.60 (dd, *J* = 14.4, 1.0 Hz, 1H), 2.88 (dd, *J* = 14.3, 10.5 Hz, 1H), 3.56 (dd, *J* = 10.5, 1.3 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 8.02 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.5 (CH_3), 29.9 (CH_3), 31.7 (CH_3), 34.2 (CH_2), 35.0 (C), 35.2 (C), 83.9 (CH), 122.6 (CH), 125.4 (CH), 127.0 (C), 137.1 (C), 141.9 (C), 152.2 (C). GCMS: t_R = 30.53 min, *m/z* (%) = 306 ([M]$^+$, 33), 288 ([M-18]$^+$, (11)), 273 (100), 245 (6), 233 (6), 219 (28), 205 (72), 189 (7), 164 (12), 149 (12), 137 (6), 57 (34), 41 (9), 28 (5). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{20}H_{34}O_2Na$: 329.2451; found: 329.2442.

*4.25. (1S,2R)-(–)-2-(3,5-Di-tert-butyl-2-hydroxyphenyl)indan-1-ol (**12h**)*

Following the general procedure IV as described above, DMF (6 mL), EtSH (542 µL, 455 mg, 7.32 mmol, 6.00 equiv), NaO^{t}Bu (235 mg, 2.44 mmol, 2.00 equiv), and **5h** (430 mg, 1.22 mmol, 1.00 equiv) were employed. After stirring the reaction mixture at 120 °C for 2-3 h under N_2, it was subjected to the usual work up. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) gave 300 mg (0.89 mmol, 73%) of the title compound (**12h**) as a white solid, in >98% *ee*. Mp: 182 °C. TLC: R_f = 0.43 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{28}$ = –48 (c = 0.5, $CHCl_3$). HPLC: Chiralcel OD-H; *n*-hexane/^{i}PrOH (98:2); 1.0 mL/min; 254 nm (UV–vis); t_R = 6.7 min (**12h**), t_R = 8.3 min (*ent*-**12h**). FTIR (KBr): ν_{max} (cm^{-1}) = 3542 (s), 3248 (s), 2956 (m), 1607 (m), 1477 (m), 1461 (m), 1380 (m), 1363 (m),

1345 (m), 1302 (s), 1231 (m), 1163 (m), 1105 (s), 1046 (s), 1007 (s), 946 (s), 891 (s), 827 (s), 757 (s), 654 (s), 613 (s), 577(s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 (s, 9H), 1.43 (s, 9H), 3.06 (dd, *J* = 16.2, 8.0 Hz, 1H), 3.67 (td, *J* = 8.3, 5.9 Hz, 1H), 3.88 (dd, *J* = 16.2, 8.8 Hz, 1H), 5.43 (dd, *J* = 5.6, 4.4 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 7.28 (d, *J* = 2.2 Hz, 2H), 7.38–7.32 (m, 2H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.79 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.0 (CH_3), 31.6 (CH_3), 34.2 (C), 34.6 (CH_2), 35.1 (C), 51.0 (CH), 79.6 (CH), 123.4 (CH), 124.7 (CH), 125.1 (CH), 126.0 (C), 126.4 (CH), 126.9 (CH), 129.2 (CH), 138.0 (C), 142.2 (C), 143.1 (C), 143.9 (C), 152.5 (C). GCMS: t_R = 34.73 min, *m/z* (%) = 320 ([M-18]$^+$, (46)), 305 (100), 249 (4), 215 (2), 145 (2), 131 (2), 115 (4), 91 (3), 57 (6), 41 (2). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{23}H_{30}O_2Na$: 361.2138; found: 361.2103.

*4.26. (1S,2R)-(–)-2-(2-Hydroxy-3,5-bis(2-phenylpropan-2-yl)phenyl)indan-1-ol (**12i**)*

Following the general procedure IV as described above, DMF (2.5 mL), EtSH (288 µL, 249 mg, 4.0 mmol, 8.00 equiv), NaO^{t}Bu (144 mg, 1.5 mmol, 3.00 equiv), and **5i** (238 mg, 0.5 mmol, 1.00 equiv) were employed. After stirring the reaction mixture at 120 °C for 2-3 h under N_2, it was subjected to the usual work up. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) gave 208 mg (0.45 mmol, 90%) of the title compound (**12i**) as a white solid, in >96% *ee*. Mp: 61 °C. TLC: R_f = 0.33 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{28}$ = –66 (c = 0.5, $CHCl_3$). HPLC: Chiralpak AD-H; *n*-hexane/^{i}PrOH (99.4:0.6); 1.0 mL/min; 254 nm (UV–vis); t_R = 8.3 min (*ent*-**12i**), t_R = 9.8 min (**12i**). FTIR (KBr): ν_{max} (cm^{-1}) = 3500 (s), 3247 (s), 3056 (m), 2965 (m), 2929 (m), 1947 (m), 1870 (m), 1803 (m), 1738 (m), 1599 (s), 1492 (s), 1463 (s), 1443 (s), 1383 (s), 1362 (s), 1231 (s), 1201 (m), 1049 (s), 1030 (s), 1008 (s), 946 (s), 881 (s), 788 (s), 764 (s), 700 (s), 605 (s), 565 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.63 (d, *J* = 10.9 Hz, 6H), 1.69 (t, *J* = 7.8 Hz, 6H), 1.91–1.81 (m, 1H), 2.99 (dd, *J* = 15.8, 7.9 Hz, 1H), 3.43 (dd, *J* = 15.8, 8.7 Hz, 1H), 3.79 (td, *J* = 8.3, 6.2 Hz, 1H), 5.13 (d, *J* = 4.0 Hz, 1H), 5.20 (t, *J* = 5.4 Hz, 1H), 7.04 (t, *J* = 4.7 Hz, 1H), 7.40–7.14 (m, 16H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.5 (CH_3), 30.1 (CH_3), 31.0 (CH_3), 34.8 (CH_2), 42.0 (C), 42.6 (C), 46.9 (CH), 77.3 (CH), 124.0 (CH), 124.6 (CH), 125.1 (CH), 125.5 (CH), 125.9 (CH), 126.6 (C), 126.7 (CH), 126.7 (CH), 126.8 (CH), 127.2 (CH), 127.9 (CH), 128.5 (CH), 129.0 (CH), 135.2 (C), 142.2 (C), 143.2 (C), 143.7 (C), 148.7 (C), 150.3 (C), 150.9 (C). GCMS: t_R = 40.75 min, *m/z* (%) = 444 ([M-18]$^+$, (29)), 429 (27), 281 (6), 207 (13), 220 (9), 119 (7), 91 (7), 28 (100). HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{33}H_{34}O_2Na$: 485.2451; found: 485.2460.

*4.27. (1S,2R)-(–)-2-(2-Hydroxy-3,5-bis(2-phenylpropan-2-yl)phenyl)-3,4-dihydro-2H-naphthalen-1-ol (**12j**)*

Following the general procedure IV as described above, DMF (7.5 mL), EtSH (692 µL, 597 mg, 9.6 mmol, 8.00 equiv), NaO^{t}Bu (346 mg, 3.6 mmol, 3.00 equiv), and **5j** (588 mg, 1.2 mmol, 1.00 equiv) were employed. After stirring the reaction mixture at 120 °C for 2-3 h under N_2, it was subjected to the usual work up. Purification of the crude product by flash column chromatography on silica gel (hexanes/EtOAc, 9:1) gave 477 mg (1.0 mmol, 84%) of the title compound (**12j**) as a white solid, in >99% *ee*. Mp: 68 °C. TLC: R_f = 0.29 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{22}$ = –58 (c = 0.5, $CHCl_3$). HPLC: Chiralpak AD-H; *n*-hexane/^{i}PrOH (97:3); 1.0 mL/min; 254 nm (UV–vis); t_R = 5.9 min (**12j**), t_R = 9.1 min (*ent*-**12j**). FTIR (KBr):

ν_{max} (cm^{-1}) = 3504 (s), 2966 (s), 1599 (w), 1492 (s), 1464 (s), 1444 (s), 1383 (w), 1362 (w), 1201 (w), 1030 (w), 941 (w), 771 (s), 700 (s), 557 (w). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.62 (d, *J* = 6.5 Hz, 4H), 1.65 (s, 3H), 1.72 (s, 7H), 2.33 (qd, *J* = 12.8, 5.5 Hz, 1H), 2.85–2.75 (m, 1H), 2.96–2.87 (m, 1H), 3.29 (dt, *J* = 13.1, 2.7 Hz, 1H), 4.72 (s, 1H), 4.99 (s, 1H), 7.00 (d, *J* = 2.3 Hz, 1H), 7.37–7.05 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3 (CH_2), 29.4 (CH_3), 29.9 (CH_2), 30.2 (CH_3), 31.0 (CH_3), 31.0 (CH_3), 40.9 (C), 42.1 (C), 42.7 (C), 69.7 (CH), 123.4 (CH), 125.5 (CH), 125.9 (CH), 126.0 (CH), 126.2 (CH), 126.7 (CH), 126.9 (CH), 127.8 (CH), 127.9 (CH), 128.9 (CH), 129.1 (CH), 129.5 (C), 130.3 (CH), 134.67 (C), 136.7 (C), 137.7 (C), 142.0 (C), 148.6 (C), 149.7 (C), 151.1 (C). GCMS: t_R = 51.24 min, *m/z* (%) = 476 ($[M]^+$,71), 458 ($[M\text{-}18]^+$, (68)), 281 (7), 207 (14), 119 (22), 91 (19), 28 (100). HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{34}H_{36}O_2Na$: 499.2608; found: 499.2612.

*4.28. General Procedure V (Enantioselective 1,2-addition of diethylzinc to aldehydes catalyzed by HAROL **12i** in the presence of Ti(O^{i}Pr)$_4$): (S)-(–)-1-Phenylpropan-1-ol (**14a**)*

An oven-dried 10 mL Schlenk tube, equipped with a magnetic stir bar, was charged with the HAROL ligand **12i** (11.5 mg, 25 µmol, 5 mol%). The tube was capped with a glass stopper, evacuated for 15 minutes, back-filled with dry N_2, and the glass stopper was replaced with a rubber septum under positive pressure of N_2. **12i** was dissolved by the addition of anhydrous hexane (2 mL) and the solution was cooled to 0 °C. Ti(O^{i}Pr)$_4$ (222 µL, 213 mg, 0.75 mmol, 1.50 equiv) was added at 0°C, whereupon the solution turned light green and the mixture was stirred at 0 °C for 30 minutes. Then 0.90 mL of 1.0 M solution of Et_2Zn in hexanes (0.9 mmol, 1.80 equiv of Et_2Zn) were dropwise added to the mixture and it was stirred at 0 °C for further 30 minutes. After the reaction mixture was cooled down to –20 °C in an acetone-dry ice bath, benzaldehyde (**13a**) (51 µL, 53 mg, 0.5 mmol, 1.00 equiv) was added. After stirring the reaction mixture at –20 °C for 2 h under N_2, it was quenched with saturated aqueous NH_4Cl solution (2 mL), extracted with EtOAc (2×30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. After purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), the title compound (**14a**) (66 mg, 485 µmol, 97%) was obtained as a colorless oil, in 83% *ee*. TLC: R_f = 0.18 (silica gel; hexanes/EtOAc, 9:1). $[\alpha]_D^{22}$ = –28 (c = 0.5, $CHCl_3$). GC: CP-Chirasil-Dex CB, 25 m, 0.25 mm ID, 0.25 µm film tickness; 190 °C inlet (split modus); 195 °C detector (FID); He, 2.0 mL/min (constant flow modus); 80 °C (4 min), 10 °C/min, 110 °C (42 min), 10 °C/min, 180 °C (4 min) ; t_R = 21.48 min (*ent*-**14a**), t_R = 22.06 min (**14a**). FTIR (KBr): ν_{max} (cm^{-1}) = 3368 (s), 2965 (s), 2933 (s), 2876 (s), 1948 (w), 1809 (w), 1603 (w), 1493 (s), 1453 (s), 1331 (w), 1201 (w), 1096 (w), 1014 (w), 974 (w), 763 (w), 700 (s), 545 (w). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.4 Hz, 3H), 1.76–1.68 (m, 1H), 1.85–1.76 (m, 1H), 2.13 (s, 1H), 4.55 (t, *J* = 6.6 Hz, 1H), 7.29–7.23 (m, 1H), 7.36–7.29 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.1 (CH_3), 31.8 (CH_2), 75.9 (CH), 125.9 (CH), 127.4 (CH), 128.3 (CH), 144.6 (C). GCMS: t_R = 19.52 min, *m/z* (%) = 136 ($[M]^+$, 14), 117 (7), 107 (100), 91 (7), 79 (71), 51 (10).

*4.29. Enantioselective 1,2-addition of methyllithium (MeLi) to benzaldehyde (**13a**) catalyzed by HAROL **12i** in the presence of Ti(O^{i}Pr)$_4$: (S)- 1-phenylethan-1-ol (**15a**)*

An oven-dried 10 mL Schlenk tube, equipped with a magnetic stir bar, was charged with the HAROL ligand **12i** (23 mg, 50 μmol, 20 mol%). The tube was capped with a glass stopper, evacuated for 15 minutes, back-filled with dry N_2, and the glass stopper was replaced with a rubber septum under positive pressure of N_2. **12i** was dissolved by the addition of anhydrous THF (1.5 mL) and the solution was cooled to 0 °C. $Ti(O^iPr)_4$ (444 μL, 426 mg, 1.5 mmol, 6.00 equiv) was added at 0°C, whereupon the solution turned light green and the mixture was stirred at 0 °C for 30 minutes. Then 260 μL of 3.1 M MeLi solution in diethoxymethane (0.8 mmol, 3.20 equiv of MeLi) were dropwise added to the mixture and it was stirred at 0 °C for further 15 minutes. After the reaction mixture was cooled down to −78 °C in an ethyl acetate-liquid nitrogen bath, benzaldehyde (**13a**) (25.4 μL, 26.5 mg, 0.25 mmol, 1.00 equiv) was added. After stirring the reaction mixture at −70 °C for 2 h under N_2, it was quenched with saturated aqueous NH_4Cl solution (2 mL), extracted with EtOAc (2×30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. After purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), the title compound (**15a**) (21 mg, 175 μmol, 70%) was obtained as a colorless oil, in 68% *ee*. TLC: R_f = 0.15 (silica gel; hexanes/EtOAc, 9:1). GC: CP-Chirasil-Dex CB, 25 m, 0.25 mm ID, 0.25 μm film tickness; 190 °C inlet (split modus); 195 °C detector (FID); He, 2.0 mL/min (constant flow modus); 80 °C (4 min), 10 °C/min, 110 °C (42 min), 10 °C/min, 180 °C (4 min); t_R = 14.78 min (*ent*-**15a**), t_R = 15.80 min (**15a**). FTIR (KBr): ν_{max} (cm^{-1}) = 3368 (s), 2965 (s), 1604 (w), 1493 (s), 1454 (s), 1201 (w), 1014 (s), 975 (s), 763 (s), 700 (s), 545 (w). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.45 (d, J = 6.5 Hz, 3H), 2.33 (d, J = 17.2 Hz, 1H), 4.82 (q, J = 6.4 Hz, 1H), 7.27–7.20 (m, 1H), 7.36 – 7.28 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.2 (CH_3), 70.3 (CH), 125.4 (CH), 127.4 (CH), 128.5 (CH), 145.9 (C). GCMS: t_R = 27.35 min, *m/z* (%) = 122 ($[M]^+$, 37), 107 (100), 79 (82), 51 (18), 43 (14), 28 (14).

*4.30. Enantioselective 1,2-addition of methylmagnesium bromide (MeMgBr) to benzaldehyde (**13a**) catalyzed by HAROL **12i** in the presence of $Ti(O^iPr)_4$*

An oven-dried 10 mL Schlenk tube, equipped with a magnetic stir bar, was charged with the HAROL ligand **12i** (11.5 mg, 25 μmol, 5 mol%). The tube was capped with a glass stopper, evacuated for 15 minutes, back-filled with dry N_2, and the glass stopper was replaced with a rubber septum under positive pressure of N_2. **12i** was dissolved by the addition of anhydrous diglyme (2 mL) and the solution was cooled to 0 °C. $Ti(O^iPr)_4$ (740 μL, 711 mg, 2.5 mmol, 5.00 equiv) was added at 0°C, whereupon the solution turned light green and the mixture was stirred at 0 °C for 30 minutes. Then 0.5 mL of 3.0 M MeMgBr solution in Et_2O (1.5 mmol, 3.00 equiv of MeMgBr) were dropwise added to the mixture and it was stirred at 0 °C for further 15 minutes. After the reaction mixture was cooled down to 0 °C in an ice bath, benzaldehyde (**13a**) (51 μL, 53 mg, 0.5 mmol, 1.00 equiv) was added. After stirring the reaction mixture at 0 °C for 2 h under N_2, it was quenched with saturated aqueous NH_4Cl solution (2 mL), extracted with EtOAc (2×30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. After purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), (*S*)-1-phenylethan-1-ol (**15a**) (57 mg, 475 μmol, 95%) was obtained as a colorless oil, in 46% *ee*.

*4.31. Enantioselective 1,2-addition of trimethylaluminum (Me_3Al) to benzaldehyde (**13a**) catalyzed by HAROL **12i** in the presence of $Ti(O^iPr)_4$*

An oven-dried 10 mL Schlenk tube, equipped with a magnetic stir bar, was charged with the HAROL ligand **12i** (23 mg, 50 μmol, 10 mol%). The tube was capped with a glass stopper, evacuated for 15 minutes, back-filled with dry N_2, and the glass stopper was replaced with a rubber septum under positive pressure of N_2. **12i** was dissolved by the addition of anhydrous Et_2O (2 mL) and the solution was cooled to 0 °C. $Ti(O^iPr)_4$ (590 μL, 569 mg, 2.0 mmol, 4.00 equiv) was added at 0°C, whereupon the solution turned light green and the mixture was stirred at 0 °C for 30 minutes. Then 375 μL of 2.0 M Me_3Al solution in hexane (0.75 mmol, 1.50 equiv of Me_3Al) were dropwise added to the mixture and it was stirred at 0 °C for further 15 minutes. After the reaction mixture was cooled down to 0 °C in an ice bath, benzaldehyde (**13a**) (51 μL, 53 mg, 0.5 mmol, 1.00 equiv) was added. After stirring the reaction mixture at 0 °C for 2 h under N_2, it was quenched with saturated aqueous NH_4Cl solution (2 mL), extracted with EtOAc (2×30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. After purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), (*S*)-1-phenylethan-1-ol (**15a**) (54 mg, 450 μmol, 90%) was obtained as a colorless oil, in 24% *ee*.

*4.32. HAROL-catalyzed MBH reaction between 3-phenylpropanal (**13p**) and 2-cyclohexen-1-one (**16**)*

An oven-dried 10 mL Schlenk tube, equipped with a magnetic stir bar, was charged with a HAROL **12** (50 μmol, 10 mol%). The tube was capped with a glass stopper, evacuated for 15 minutes, back-filled with dry N_2, and the glass stopper was replaced with a rubber septum under positive pressure of N_2. The catalyst was dissolved in anhydrous THF (1 mL) and 2-cyclohexen-1-one (**16**) (97 μL, 1.0 mmol, 2.00 equiv) was added at room temperature. The resulting solution was cooled to −78 °C. $^nBu_3P$ (250 μL, 1.0 mmol, 2.00 equiv) and 3-phenylpropanal (**13p**) (65 μL, 0.5 mmol, 1.00 equiv) were added successively at −78 °C. The reaction tube was then placen in a −10 °C bath and stirred for 48 h. The reaction mixture was subjected to flash column chromatography eluting with hexanes/EtOAc (8:2) to give the MBH product **17** ((*R*)-2-(1-Hydroxy-3-phenyl-propyl)-cyclohex-2-en-1-one) as a colorless oil, in 40% *ee*. TLC: R_f = 0.16 (silica gel; hexanes/EtOAc, 8:2). HPLC: Chiralcel OD-H, *n*-hexane/^{i}PrOH (90:10), 1.0 mL/min; 254 nm (UV–vis) t_R = 11.4 min (*ent*-**17**), t_R = 14.1 min (**17**). Absolute configuration was assigned by comparison of the retention times with those reported in the literature.[9a]

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Appendix A. Supplementary data

Procedures for the synthesis of anisoles **2b–e**, **9c–d** and the bromophenols **8c–d**. Synthesis of the racemic compounds. Details of the catalytic studies. ^{1}H and ^{13}C NMR spectra of all synthesized compounds, gas and HPLC chromatograms.

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