The Development of the Asymmetric Morita–Baylis–Hillman Reaction Catalyzed by Chiral Brønsted Acids

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Abstract: This report describes the development of a chiral Brønsted acid-catalyzed asymmetric Morita–Baylis–Hillman (MBH) reaction of cyclohexenone with aldehydes. During the course of our studies on chiral Lewis acid-promoted MBH reactions, we discovered that chiral binaphthol-derived Brønsted acids serve as promoters of the asymmetric MBH reaction. We propose that the phosphonium enolate of cyclohexenone is stabilized *via* hydrogen-bonding with the binaphthol-derived Brønsted acid, creating a chiral nucleophile. A practical and efficient set of conditions was developed using stoichiometric PEt_3 as the nucleophilic promoter and catalytic amounts of a binaphthol-derived Brønsted acid to effect the reaction of cyclohexenone with various aliphatic and aromatic aldehydes in good yields and enantiomeric excesses (up to 96% ee).

Keywords: asymmetric catalysis; Brønsted acid; Morita–Baylis–Hillman reaction; organic catalysis; phosphanes

Introduction

The Baylis-Hillman reaction is the reaction of electron-deficient alkenes with aldehydes, catalyzed by nucleophiles such as 1,4-diazabicyclo[2.2.2]octane (DABCO).[1] The original reaction communicated by A. B. Baylis and M. E. D. Hillman in a 1972 German patent described the addition of ethyl acrylate to acetaldehyde, promoted by DABCO. The reaction results in the formation of a carbon-carbon bond at the alpha position of an α,β-unsaturated carbonyl compound with the carbonyl carbon of the aldehyde, followed by regeneration of the nucleophile catalyst. In principle, the reaction is catalytic in the nucleophilic promoter.[2] Although the original nucleophilic amine-catalyzed process received the most attention, a trialkylphosphine-catalyzed reaction was being developed earlier, as illustrated by two communications. A nucleophilic phosphine-mediated coupling between an electrophilic alkene and an aldehyde was described by Oda and co-workers in 1964.[3] They reported the combination of triphenylphosphine and acrylonitrile for *in situ* formation of an ylide that would undergo a Wittig reaction with benzaldehyde. Although the reaction resulted in the formation of the corresponding olefin, the mechanism required the formation of the zwitterionic intermediate from the conjugate addition of triphenylphosphine with the acrylate or acrylonitrile. The development of a phosphine-catalyzed process that yielded the corresponding allylic alcohol was subsequently described by Morita and co-workers.[4] In this communication, Morita described the addition of acrylonitrile and other α,β-unsaturated acrylates to benzaldehydes catalyzed by tricyclohexylphosphine.

The Baylis–Hillman reaction has been limited in its utility in organic synthesis primarily because it suffers from slow reaction rates. Typical reaction times for the DABCO or trialkylphosphine-catalyzed process require days at room temperature, depending on the unsaturated carbonyl compound, to achieve completion of the reaction.[5] As a result, the reaction is often heated in order to increase the rate of reaction. Identification of a set of mild conditions that promote the reaction in a reasonable amount of time has led to the development of a practical asymmetric solution to the Baylis–Hillman reaction. In 1997, Leahy reported the tertiary amine-catalyzed asymmetric Baylis–Hillman reaction of chiral amide acrylates with aldehydes.[6] In this example, the optimal chiral auxiliary was determined to be Oppolzer's sultam.[7] Under the reaction conditions, the auxiliary was cleaved to yield the cyclic dioxanone as the final product. More recently, Chen used another camphor-derived chiral auxiliary in a diastereoselective DABCO-promoted Baylis–Hillman reaction that does not result in the cleavage of the auxiliary.[8] It is interesting to note that in Chen's experiments, either diastereomer of the β-hydroxy-α-methylene carbonyl product can be ob-

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tained in high optical purity by applying the appropriate reaction conditions. These examples illustrate the development of an asymmetric Baylis–Hillman reaction under conditions that take advantage of the rate acceleration at lower temperatures observed by Leahy.

Another way in which researchers have attempted to accelerate the Baylis–Hillman reaction is through the use of Lewis acids. This approach is potentially problematic in facilitating the reaction since the reaction conditions call for a Lewis basic promoter such as DABCO. The end result would potentially be a Lewis acid/Lewis base reaction without a significant increase in the observed rate. Nevertheless, this approach has been successfully employed with a significant increase in the reaction rate. Aggarwal completed a systematic study of ligands, Lewis acids, and conditions that successfully increased the rate of the DABCO-promoted reaction.[9] The Lewis acids that were employed in this example were lanthanide triflates. The end result was a reaction that used a catalytic amount of $La(OTf)_3$ and triethanolamine to promote the addition of ethyl acrylate to benzaldehyde with a 40-fold increase in rate over the parent reaction. This result was later developed into an asymmetric catalytic Baylis–Hillman reaction by Chen and co-workers.[10] Chen found that the ethylenediimine ligand derived from (+)-ketopinic acid was a good chiral ligand for the $La(OTf)_3$-catalyzed Baylis–Hillman reaction. This catalytic system was determined to be highly dependent on the nature of the acrylate and aldehyde, and the highest enantioselectivities were obtained from electron-rich aldehydes such as 4-methoxybenzaldehyde. However, the reaction developed by Chen is one of the first examples of an asymmetric Lewis acid-promoted Baylis–Hillman reaction.

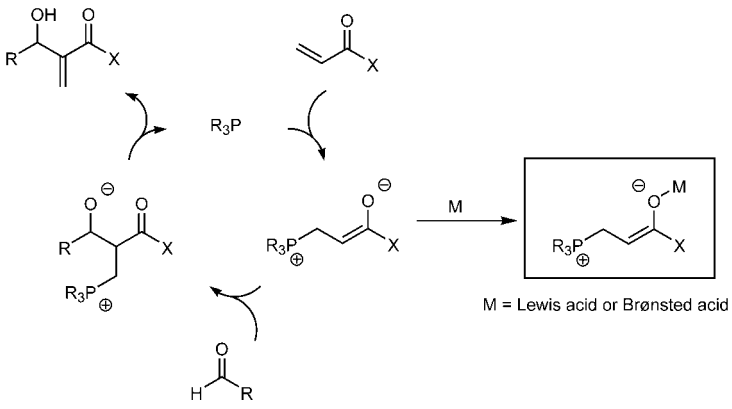
The necessary balance of the catalyst and the acrylate employed in an asymmetric Baylis–Hillman reaction is illustrated by the following example. Hatakeyama and co-workers developed a reaction using a quinidine-derived chiral nucleophilic amine catalyst with an electron-deficient acrylate, 1,1,1,3,3,3-hexafluoroisopropyl acrylate.[11] The reported reaction conditions were general enough for most aldehyde substrates. The Hatakeyama catalyst for the Baylis–Hillman reaction was one of the first asymmetric catalytic reactions of this type.[12] The reaction developed by Hatakeyama has been employed in the synthesis of the natural product (−)-mycestericin E.[13]

Development of an asymmetric Baylis–Hillman reaction has focused mainly on the tertiary amine-catalyzed process. Furthermore, substrates for an asymmetric Baylis–Hillman reaction have mainly been acrylate esters. However, some recent developments have facilitated the identification of an asymmetric catalytic Baylis–Hillman reaction that employs unsaturated aldehydes and ketones as the substrate for the reaction. Most notably, work by Miller and co-workers has identified a proline-peptide co-catalyst system that promotes the Baylis–Hillman reaction of methyl vinyl ketone and aldehydes.[14] While this result stands out as a significant advance in this area, little progress has been made towards the development of a suitably general catalytic asymmetric Morita–Baylis–Hillman reaction, a worthwhile goal because the products of MBH reactions are highly functionalized allylic alcohols that in enantioenriched form could be valuable building blocks for synthesis. We focused our investigations on the development of an asymmetric MBH reaction involving α,β-unsaturated enones with aldehydes (Scheme 1). Our initial approach was to identify a mild Lewis acid catalyst that would promote the MBH reaction of enones with aldehydes.

Results and Discussion

Lewis Acid-Catalyzed MBH Reactions

In our first series of experiments, we investigated the feasibility of promoting the MBH reaction of cyclohexenone with aldehydes using chiral Lewis acid complexes. A variety of Lewis acid metal isopropoxides (3 mol %) mixed with chiral diols were screened for catalysis in the addition of cyclohexenone to 3-phenylpropionaldehyde and 25 mol % PEt_3 in THF at room temperature. After 18 h, MBH product formation occurred in the presence of 3 mol % of most metal alkoxides investigated and 7.5 mol % (*R*)-BINOL **1** (Table 1). However, our use of just (*R*)-BINOL in the MBH reaction of cyclohexenone and 3-phenylpropionaldehyde resulted in the formation of product in 16% ee (entry 1, Table 1). Phenols, as well as other hydrogen-bond donators,[15] have been shown to enhance the rate of MBH reactions in which amine[16] and phosphine nucleophilic promoters[17] have been used, but not with any enantioselectivity. The reported calcium-BINOL complex[17] (entry 2, Ta-

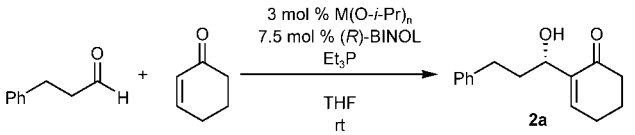


Scheme 1. Proposed catalytic cycle of the Morita–Baylis–Hillman reaction in which the reaction is promoted by a catalyst.

ble 1) did give product **2a** in higher enantioselectivity than the use of just (*R*)-BINOL, but with slightly reduced yield. Dysprosium(III), ytterbium(III), and zirconium(IV) isopropoxides all gave product in 16% ee (entries 3–5). Nd(O-*i*-Pr)$_3$ afforded **2a** in 25% ee (entry 6) and Y(O-*i*-Pr)$_3$ gave the best enantioselectivity observed (31% ee, entry 7). The reduced rates of these catalysts may be a result of the reduced amount of catalytic Lewis base, PEt_3, available for Michael addition to cyclohexenone through a Lewis acid/Lewis base interaction. Using enantioselectivity as the determining factor, we chose Y(O-*i*-Pr)$_3$ for our development of a Lewis acid-mediated asymmetric MBH reaction. Although enantioselectivity guided our future studies, the metal alkoxide-catalyzed process generally gave reduced yields in comparison to the Brønsted acid-catalyzed reaction. This suggests that differing mechanisms drive the metal alkoxide- and (*R*)-BINOL-promoted reactions.

Next, the effects of solvent and temperature on enantioselectivity and reactivity were studied. The MBH product from reactions performed in Et_2O, toluene, *p*-dioxane, and TBME was isolated in reduced enantioselectivity, whereas CH_2Cl_2 and $CHCl_3$ yielded product in comparable enantioselectivity, but gave complex reaction mixtures compared to reactions performed in THF. At elevated temperatures (up to 60 °C), the product was formed in slightly higher yield, but in reduced enantioselectivity. At lower temperatures (as low as −40 °C), **2a** was produced with slightly reduced enantioselectivity and only in trace amounts. The highest enantioselectivity achieved with the chiral yttrium-BINOL complex was at −10 °C, albeit in low yield (entry 1, Table 2).

Table 1. Asymmetric Morita–Baylis–Hillman reactions catalyzed by Lewis acid-BINOL complexes.[a]

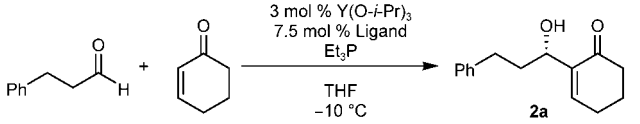


Entry	M(O-*i*-Pr)$_n$	Yield [%][b]	% ee[c]
1	–	56	16
2	Ca(O-*i*-Pr)$_2$	42	21
3	Dy(O-*i*-Pr)$_3$	55	16
4	Yb(O-*i*-Pr)$_3$	30	16
5	Zr(O-*i*-Pr)$_4$	22	16
6	Nd(O-*i*-Pr)$_3$	23	25
7	Y(O-*i*-Pr)$_3$	26	31

[a] Reactions were performed with 0.5 mmol of 3-phenylpropionaldehyde, 0.5 mmol of cyclohexenone, 25 mol % PEt_3, 7.5 mol % (*R*)-BINOL, and 3 mol % Lewis acid in THF (0.5 M) at room temperature for 18 h under Ar, followed by flash chromatography on silica gel.
[b] Yield of isolated product.
[c] Determined by chiral HPLC analysis.

We next turned our attention to the use of various ligands for Y(O-*i*-Pr)$_3$ to improve the enantioselectivity of the reaction. When (*R*)-BIPHEN-H$_2$ **3** was used as the ligand, racemic product was formed in only 10% yield (entry 2, Table 2). The use of (*R*)-6,6′-dibromo-BINOL **4** afforded product in low yield and correspondingly low enantioselectivity as well (entry 3). Improvements in enantioselectivity and yield were observed with the use of saturated BINOL derivatives[18] (entries 4 and 5) and (*R*)-3,3′-dibromo-H$_8$-BINOL **5b** (entry 5). The use of an additional ligand, 10.5 mol % (*R*)-3,3′-dibromo-H$_8$-BINOL **5b**, led to the best enantiose-

Table 2. Yttrium(III)-catalyzed Morita–Baylis–Hillman reactions.[a]



Entry	Ligand	Yield [%][b]	% ee[c]
1	**1**	10	33
2	**3**	10	<1
3	**4**	15	17
4	**5a**	30	45
5	**5b**	35	74
6	**5b**[d]	45	78
7	**5b**[d, e]	33	53
8	**5b**[d, f]	22	69

[a] Reactions were run with 1 mmol of 3-phenylpropionaldehyde, 1 mmol of cyclohexenone, 25 mol % PEt_3, 7.5 mol % ligand, and 3 mol % Y(O-*i*-Pr)$_3$ in THF (1 M) at −10 °C for 18 h under Ar, followed by flash chromatography on silica gel.
[b] Yield of isolated product.
[c] Determined by chiral HPLC analysis.
[d] 10.5 mol % ligand.
[e] 25 mol % PMe_3.
[f] 25 mol % P(*n*-Bu)$_3$.

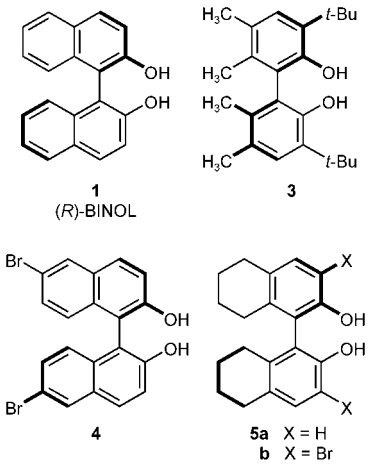


Figure 1. Ligands.

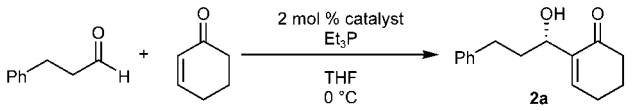
lectivities achieved with the Y(III)-mediated MBH reaction of cyclohexenone with 3-phenylpropionaldehyde (entry 6). Finally, employing other trialkylphosphines to promote the reaction led to reduced yields and enantioselectivities [PMe_3 and $P(n\text{-}Bu)_3$, entries 7 and 8], whereas PCy_3 and triarylphosphines did not promote the reaction.

Brønsted Acid-Catalyzed Asymmetric MBH Reactions[19]

During the course of our investigations the optimal catalyst mixture using 3 mol % $Y(O\text{-}i\text{-}Pr)_3$ required the use of 10.5 mol % ligand. (*R*)-BINOL is capable of catalyzing the MBH reaction without the use of metals (entry 1, Table 1). A control experiment was designed to determine whether **5b** was a competent asymmetric catalyst for the reaction. The reaction of cyclohexenone with 3-phenylpropionaldehyde using 0.5 equivalents of PEt_3 in THF at 0 °C yielded only 5% product after 48 h. However, the addition of only 2 mol % **5b** resulted in the production of **2a** in higher yield and enantioselectivity than was obtained under the optimized Lewis acid-mediated reaction conditions (compare entry 4, Table 3 and entry 6, Table 2). It was now envisioned that, instead of using a Lewis acid to stabilize the phosphonium zwitterionic enolate, we could produce chiral enolate complexes with the addition of chiral Brønsted acids (Scheme 1). The Brønsted acid-trialkylphosphine system was capable of selectively promoting the asymmetric MBH reaction of cyclohexenone with 3-phenylpropionaldehyde. In turn, we focused our attention to these Brønsted acid-catalyzed reactions.

Many of the enantioselectivity trends observed in the Y(III)-mediated reactions were also observed in the Brønsted acid-catalyzed asymmetric MBH reactions (Table 3). Saturation of the BINOL derivatives and substitution at the 3,3′-positions (entries 3–5 and 9–13) led to higher enantioselectivities. The highest levels of enantioselectivity were achieved with (*R*)-3,3′-diaryl-H_8-BINOL derivatives, with the exception of the 3,3′-dimesityl-catalyst **8e**,[20] which afforded the product in low enantioselectivity, 31% ee, and low yield (entry 12). It was postulated that the mesityl *ortho*-methyl groups restrict rotation about the biaryl bond of the 3-substituent and the binaphthalene core which must be a requirement for high yield and enantioselectivity. The *para*-substituted (*R*)-3,3′-(4-biphenyl)-H_8-BINOL **8d** (entry 13) did not give any improvement over phenyl-substituted catalyst **8a**.[21] Optimal results were obtained with 3,3′-(3,5-disubstituted aryl)-H_8-BINOL derivatives. In particular, the highest enantioselectivity was achieved with *meta*-substituted aryl-derivative (*R*)-3,3′-(3,5-dimethylphenyl)-H_8-BINOL **8b** (entry 11). Highest yields were obtained with (*R*)-3,3′-[3,5-bis(trifluoromethyl)-phenyl]-H_8-BINOL **8c** (entry 12). We reasoned that

Table 3. Asymmetric Morita–Baylis–Hillman reactions catalyzed by binaphthol-derived Brønsted acids.[a]



Entry	Catalyst	Yield [%][b]	% ee[c]
1	–	5	–
2	**1**	74	32
3	**5a**	73	48
4	**5b**	73	79
5	**5c**	36	74
6	**6a**	43	3
7	**6b**	15	3
8	**7**	13	5
9	**8a**	69	86
10	**8b**	70	88
11	**8c**	84	86
12	**8d**	68	86
13	**8e**	9	31

[a] Reactions were run with 1 mmol of 3-phenylpropionaldehyde, 1 mmol of cyclohexenone, 0.5 mmol of PEt_3, and 2 mol % catalyst in THF (1 M) at 0 °C for 36 h under Ar, followed by flash chromatography on silica gel.
[b] Yield of isolated product.
[c] Determined by chiral HPLC analysis.

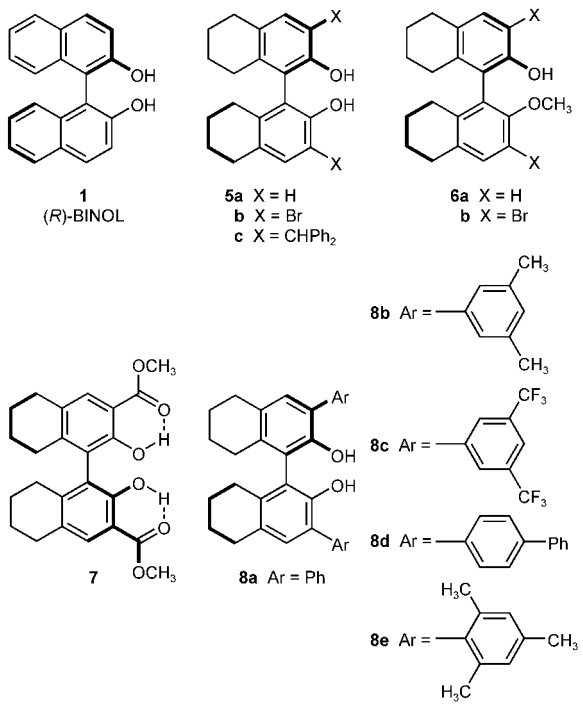
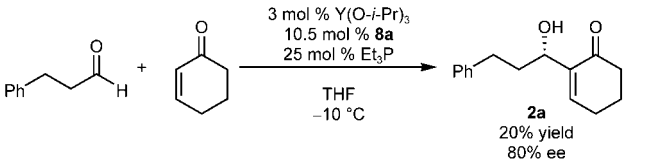


Figure 2. Binaphthol-derived Brønsted acids.

free rotation about the 3,3′-biaryl bond was necessary for catalysis and that the 3,5-methyl groups provide the proper steric environment, whereas the *para*-substitution of **8d** does not provide any steric interaction with

the site of catalysis. Interestingly, when Brønsted acid **8a** was evaluated as a chiral ligand under the reaction conditions for the Y(III)-mediated reactions, **2a** was isolated in 20% yield and only in 80% ee [Eq. (1)].

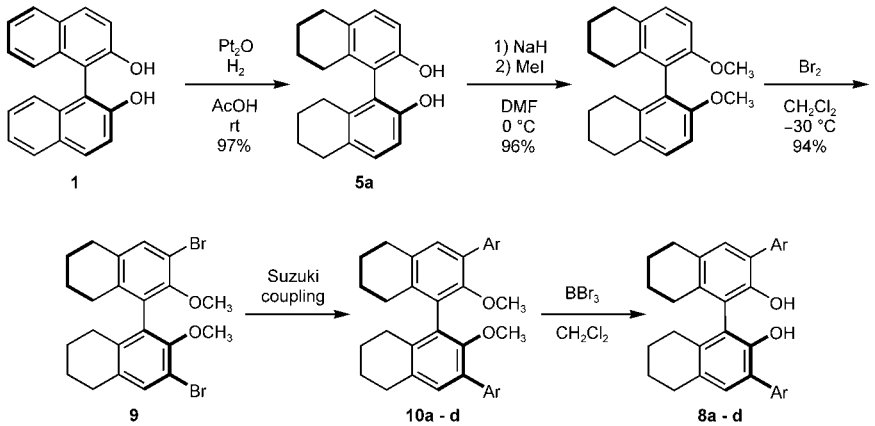


(1)

The importance of the hydrogen bonding capability of the binaphthol-derived catalysts was tested by synthesizing derivatives that would disrupt the hydrogen donor capability of the catalyst. The use of mono-methylated H_8-BINOL catalyst **6a** in the reaction resulted in near racemic product (entry 6, Table 3). Substitution at the 3,3′-positions of the mono-methylated catalyst did not improve enantioselectivity (entry 7). When 3,3′-dicarboxylic acid dimethyl ester-H_8-BINOL **7** was used, racemic product was isolated in only 10% yield. We reasoned that the propensity of **7** to form an intramolecular hydrogen bond between the phenolic hydrogen and the methyl ester groups reduces the hydrogen donor ability of **7**. These results indicate that the dual hydrogen bonding capability of BINOL-derived Brønsted acids is necessary for achieving catalysis and enantioselectivity.

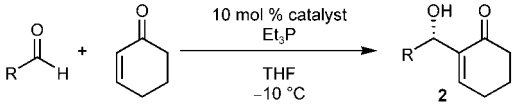
The 3,3′-disubstituted BINOL-derived Brønsted acids can be readily synthesized *via* a five-step sequence from commercially available (*R*)-BINOL **1**. The catalytic hydrogenation of optically pure (*R*)-BINOL was performed in 97% yield with Adam's catalyst in acetic acid under a balloon-pressure hydrogen atmosphere in only 36 h (Scheme 2).[22] Protection of **5a** was accomplished by methylation of the phenols through NaH deprotonation and alkylation with MeI at 0 °C in DMF (96% yield). The addition of bromine at −30 °C gave the 3,3′-dibromo cross-coupling partner **9** in 94% yield.[20] Using Suzuki reaction conditions as reported by Fu[23] or Snieckus[24] yielded the corresponding (*R*)-3,3′-diaryl-H_8-BINOMe compounds **10a–d**. Deprotection of the methyl ethers with boron tribromide at 0 °C gave catalysts **8a, b,d**. Demethylation of **10c** with boron tribromide was performed at −78 °C to −20 °C in order to avoid bromination of the highly activated 3,5-(bis-trifluoromethyl)phenyl group[25] yielding catalyst **8c**.

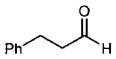
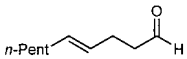
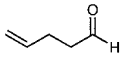
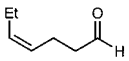
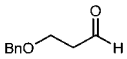
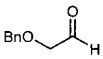
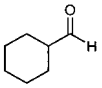
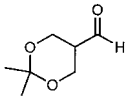
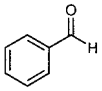
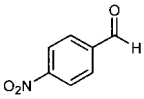
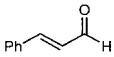
Finally, we sought to identify a set of general reaction conditions for the Brønsted acid-catalyzed asymmetric MBH reaction. Optimum enantioselectivity was achieved at −10 °C with higher conversions using 2 equivalents of cyclohexenone and PEt_3. Increased catalyst loading also improved conversion and enantioselectivity with the addition of 10 mol % **8b** or **8c** (Table 4). The reaction of 3-phenylpropanal with cyclohexenone using catalyst **8c** yielded the product in 90% ee (entry a). The asymmetric MBH reactions of cyclohexenone with aliphatic aldehydes afforded product in high yields and in high enantioselectivities (entries b – d, Table 4). The reaction of 3-benzyloxypropanal (entry e) resulted in good yield and 82% ee. However, the reaction of benzyloxyacetaldehyde resulted in low isolated yield and low enantioselectivity (entry f). The reaction of cyclohexanecarboxaldehyde using catalyst **8b** afforded the product in 96% ee (entry g). When catalyst **8c** was utilized in the MBH reaction with this aldehyde, the product was reproducibly obtained in 83% ee. This result illustrates how the identities of the catalyst, the aldehyde, and the enone are important for obtaining the product in high enantioselectivites. 2,2-Dimethyl-[1,3]dioxane-5-carbaldehyde (entry i) as the substrate for the reaction gave similar results as cyclohexanecarboxaldehyde, affording the corresponding product in 70% isolated yield and 92% ee using catalyst **8b**. When benzaldehyde was subjected to the asymmetric MBH reaction, the product could only be obtained at 40% yield and 67% ee. This particular substrate continues to be a challenge for this Brønsted acid-catalyzed reaction. Aromatic and unsaturated substrates of this type exhibit similar results, e.g.,



Scheme 2. Synthesis of binaphthol-derived Brønsted acids.

Table 4. Brønsted acid-catalyzed asymmetric Morita–Baylis–Hillman reactions.[a]

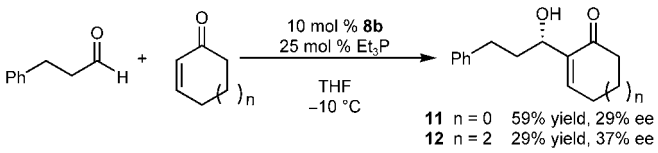


Entry	Aldehyde	Catalyst	Yield [%][b]	% ee[c]
a		**8c**	**2a** (88)	90
b		**8b**	**2b** (86)	91
c		**8b**	**2c** (80)	90
d		**8b**	**2d** (72)	96
e		**8c**[d]	**2e** (74)	82
f		**8b**	**2f** (56)	55
g		**8b**	**2 g** (71)	96
h		**8b**[d]	**2 h** (82)	95
i		**8c**	**2i** (70)	92
j		**8b**	**2j** (40)	67
k		**8b**	**2k** (30)	34
l		**8b**	**2 l** (39)	81

[a] Reactions were run with 1 mmol of aldehyde, 2 mmol of cyclohexenone, 2 mmol of PEt_3, and 10 mol % catalyst in THF (1 M) at $-10\,^{\circ}C$ for 48 h under Ar, followed by flash chromatography on silica gel.
[b] Yield of isolated product.
[c] Determined by chiral HPLC analysis.
[d] 20 mol % catalyst.

p-nitrobenzaldehyde (entry k) which afforded the product in both low yield and enantioselectivity (30% yield, 34% ee).

We investigated other cyclic enones in the asymmetric MBH reaction [Eq. (2)]. When cyclopentenone was employed as the nucleophile, product **11** was isolated in 59% yield and only 29% ee. Similarly, the reaction of cycloheptenone with 3-phenylpropanal afforded the product in 29% yield and 37% ee. These results highlight how reactivity and enantioselectivity is highly dependent on the reacting partners.



(2)

Conclusion

Through our investigations of the metal alkoxide-promoted Morita–Baylis–Hillman reaction we discovered an asymmetric Brønsted acid-catalyzed reaction. The reaction was developed into a highly enantioselective procedure for the addition of cyclohexenone to aldehydes promoted by PEt_3 and a catalytic amount of the BINOL-derived Brønsted acid. The use of small organic catalysts to promote asymmetric reactions is an emerging field within studies of asymmetric catalysis.[26] This asymmetric Brønsted acid-catalyzed MBH reaction is a unique addition to the area of organocatalysis in that an organic promoter and organic catalyst are necessary for the reaction to proceed. We anticipate that continued investigations into the reaction and the mechanism by which it proceeds will provide valuable information about the factors that govern catalysis and enantioselectivity.

Experimental Section

General Remarks

^1H NMR spectra were recorded on a 400 MHz spectrometer with $CDCl_3$ as the solvent unless otherwise noted. ^{13}C NMR spectra were recorded on a 100 MHz or 75.0 MHz spectrometer with $CDCl_3$ as the solvent unless otherwise noted. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, and integration. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. High-resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory using a Finnegan MAT-90 spectrometer. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and are recorded as $[\alpha]_D^{T[^\circ C]}$ (concentration in grams/100 mL solvent). Chiral HPLC analysis was performed using an Agilent 1100 series HPLC with a diode array detector and either a Chiralcel® OD (Chiral Technologies Inc., 24 cm × 4.6 mm I. D.) or an (*R*,*R*)-Whelk-O 1 (Regis® Technologies Inc., 25 cm × 4.6 mm I. D.) column. All reactions were performed under Ar in oven-dried glassware with magnetic stirring unless otherwise noted. Degassed HPLC grade THF and CH_2Cl_2 were purified by passage through an activated alumina column before use. 2-Cyclohexen-1-one was purchased from Alfa Aesar and fractionally distilled before use. All aldehydes were fractionally distilled before use. Triethylphosphine was purchased from Aldrich and used as received. Spectral data

for compounds **2a**, **d**, **e**, **g – j**, **l**, **6a**, **b**, **8b**, **c**, **10a – c** have been reported.[19] Compounds **5c** and **8e** were synthesized according to the literature procedure.[20] The absolute configurations of products **2a** and **2j** were determined by comparison to known products.[19] Other absolute configurations were assigned through analogy.

General Procedure for Lewis Acid-Mediated Morita–Baylis–Hillman Reactions

An oven-dried 10 mL flask was charged with (*R*)-3,3′-dibromo-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl-2,2′-diol (**5b**; 47.5 mg, 0.105 mmol) under an argon atmosphere. THF (1.0 mL) and yttrium(III -isopropoxide in toluene (20% w/w) (8.0 mg, 40 μL, 0.030 mmol) were added, and the solution was stirred at room temperature for 2 h. The catalyst solution was cooled to −78 °C. 2-Cyclohexen-1-one (95 mg, 1.0 mmol), triethylphosphine (30 mg, 0.25 mmol), and 3-phenylpropionaldehyde (130 mg, 1.00 mmol) were added successively at −78 °C. The flask was placed in a −10 °C bath and stirred for 18 h. The reaction mixture was subjected directly to flash chromatography on silica gel, and eluted with hexanes and ethyl acetate (3:1 → 1:1) to afford (*S*)-2-(1-hydroxy-3-phenylpropyl)-cyclohex-2-enone as a colorless oil.

Procedure for Brønsted Acid-Catalyzed Morita–Baylis–Hillman Reactions

(S)-2-(1-Hydroxy-3-phenylpropyl)-cyclohex-2-enone **(2a):** An oven-dried 10 mL flask was charged with (*R*)-3,3′-bis-(3,5-bis-trifluoromethylphenyl)-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl-2,2′-diol (**8c**; 72 mg, 0.10 mmol) under an argon atmosphere. The catalyst was dissolved in THF (1.0 mL) and the solution was cooled to −78 °C. 2-Cyclohexen-1-one (190 mg, 2.0 mmol), triethylphosphine (240 mg, 2.0 mmol), and 3-phenylpropionaldehyde (134 mg, 1.00 mmol) were added successively at −78 °C. The flask was placed in a −10 °C bath and the mixture stirred for 48 h. The reaction mixture then was subjected directly to flash chromatography on silica gel, and eluted with hexanes and ethyl acetate (3:1 → 1:1) to afford (*S*)-2-(1-hydroxy-3-phenylpropyl)-cyclohex-2-enone as a colorless oil, which was determined to be 90% ee by chiral HPLC analysis [Chiralcel® OD, 9:1 hexanes:*i*-PrOH, 1 mL/min, t_r(major) = 9.1 min, t_r(minor) = 11.9 min]; yield: 202 mg (0.88 mmol, 88%; $[\alpha]_D^{21}$: −37.4° (*c* 1.05, $CHCl_3$); characterization and spectroscopic data was in agreement with lit. values.[27]

(S)-2-[(E)-1-Hydroxydec-4-enyl]-cyclohex-2-enone **(2b):** Isolated as a colorless oil, which was determined to be 91% ee by chiral HPLC analysis [Chiralcel® OD, 99:1 hexanes: *i*-PrOH, 1 mL/min, t_r(major) = 13.1 min, t_r(minor) = 11.5 min]; yield: 215.0 mg (0.86 mmol, 86%); $[\alpha]_D^{21}$: −21.3° (*c* 0.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (t, *J* = 4.0 Hz, 1H), 5.39–5.45 (m, 2H), 4.28 (t, *J* = 6.6 Hz, 1H), 2.82 (br s, 1H), 2.29–2.43 (m, 4H), 1.92–2.15 (m, 6H), 1.59–1.74 (m, 2H), 1.23–1.39 (m, 6H), 0.83–0.87 (m, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ = 220.3, 145.7, 140.7, 130.9, 129.2, 70.5, 38.5, 35.9, 32.4, 31.2, 29.0, 28.9, 25.5, 22.4, 13.9; IR (neat): ν = 3440, 2924, 1653,1463, 1420, 1242, 1164, 1129, 966, 908 cm^{-1}; HRMS: calcd. for $C_{16}H_{26}O_2$: 250.1933; found: 250.1934.

(S)-2-(1-Hydroxypent-4-enyl)-cyclohex-2-enone **(2c):** Isolated as a colorless oil, which was determined to be 90% ee by chiral HPLC analysis of the 4-bromobenzoate ester [Chiralcel® OD, 99.8:0.2 hexanes:*i*-PrOH, 1 mL/min, t_r(major) = 41.8 min, t_r(minor) = 38.5 min]; yield: 143.1 mg (0.80 mmol, 80%); $[\alpha]_D^{21}$: −36.6° (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (t, *J* = 4.0 Hz, 1 H), 5.80 (m, 1H), 5.01 (d, *J* =16.7 Hz, 1H), 4.95 (d, *J* = 10.2 Hz, 1H), 4.29 (t, *J* = 6.7 Hz, 1H), 2.97 (br s, 1H)2.41 (m, 4H), 2.15 (m, 2H), 1.99 (m, 2H), 1.71 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ = 200.4, 145.9, 140.6, 138.1, 114.7, 70.6, 38.5, 35.2, 30.0, 25.5, 22.4; IR (neat): ν = 3432, 2925, 2891, 2869, 1668, 1453,1429, 1415, 1383, 1320, 1269, 1249, 1172, 1136, 1082, 1063, 1025, 998, 976, 912 cm^{-1}; HRMS: calcd. for $C_{11}H_{16}O_2$: 180.1150; found: 180.1137.

(S)-2-(2-Benzyloxy-1-hydroxyethyl)-cyclohex-2-enone **(2f):** Isolated as a colorless oil, which was determined to be 55% ee by chiral HPLC analysis [Chiralcel® OD, 9:1 hexanes: *i*-PrOH, 1 mL/min, t_r(major) = 13.3 min, t_r(minor) = 14.8 min]; yield: 136.9 mg (0.56 mmol, 56%); $[\alpha]_D^{21}$: −14.3° (*c* 1.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.35 (m, 5H), 7.07 (t, *J* = 3.6 Hz, 1H) 4.54 (dd, *J* = 12.0 Hz, 2H), 3.64 (dd, *J* = 3.6 Hz, 1H), 3.33 (dd, *J* = 7.4 Hz, 1H), 2.94 (d, *J* = 4.4 Hz, 1H), 2.39–2.42 (m, 4H), 1.94–1.99 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ = 99.1, 147.1, 137.8, 137.5, 128.2, 127.6, 77.2, 73.5, 72.9, 68.0, 38.2, 25.5, 22.3; IR (neat): ν = 3402, 2926, 1718, 1668, 1496, 1454, 1370, 1172, 1104 cm^{-1}; HRMS: calcd. for $(M+H)^+$ $C_{15}H_{19}O_3$: 247.1334; found: 247.1353.

(S)-2-[Hydroxy-(4-nitrophenyl)-methyl]-cyclohex-2-enone **(2k):** Isolated as a yellow oil, which was determined to be 34% ee by chiral HPLC analysis [(*R*,*R*)-Whelk-O 1, 9:1 hexanes:*i*-PrOH, 1 mL/min, t_r(major) = 29.3 min, t_r(minor) = 36.6 min]; yield: 73.3 mg (0.30 mmol, 30%; $[\alpha]_D^{21}$: −10.2° (*c* 1.01, $CHCl_3$); characterization and spectroscopic data was in agreement with lit. values.[28]

(S)-2-(1-Hydroxy-3-phenylpropyl)-cyclopent-2-enone **(11):** Isolated as a colorless oil, which was determined to be 29% ee by chiral HPLC analysis [Chiralcel® OD, 95:5 hexanes: *i*-PrOH, 1 mL/min, t_r(major) = 24.1 min, t_r(minor) = 28.6 min]; yield: 126.6 mg (0.59 mmol, 59%); $[\alpha]_D^{21}$: −7.3° (*c* 1.11, $CHCl_3$); characterization and spectroscopic data was in agreement with lit. values.[29]

(S)-2-(1-Hydroxy-3-phenylpropyl)-cyclohept-2-enone **(12):** Isolated as a colorless oil, which was determined to be 37% ee by chiral HPLC analysis [Chiralcel® OD, 9:1 hexane-s:*i*-PrOH, 1 mL / min, t_r(major) = 8.0 min, t_r(minor) = 11.1 min]; yield: 66.1 mg (0.29 mmol, 29%); $[\alpha]_D^{21}$: −4.1° (*c* 0.98, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.34 (m, 5H), 6.68 (t, *J* = 6.2 Hz, 1H), 4.30 (dd, *J* = 6.4 Hz, 1H), 3.24 (d, *J* = 7.6 Hz, 1H), 2.81–2.83 (m, 1H), 2.67–2.69 (m, 1H), 2.62 (t, *J* = 5.8 Hz, 2H), 2.46 (t, *J* = 5.4 Hz, 2H), 2.01–2.04 (m, 1H), 1.91–1.95 (m, 1H), 1.79–1.84 (m, 4H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ = 207.0, 144.2, 143.6, 141.9, 128.5, 128.4, 125.9, 74.2, 43.1, 38.0, 32.4, 27.5, 24.8, 21.4; IR (neat): ν = 3026, 2932, 2864, 1733, 1663, 1496, 1454, 1155, 1076; HRMS: calcd. for $C_{16}H_{20}O_2$: 244.1463; found: 244.1489.

Preparation of BINOL-Derived Brønsted Acids

(S)-2,2′-Dihydroxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl-3,3′-dicarboxylic acid dimethyl ester **(7):** Acetic acid (12 mL) and THF (5 mL) were added to a 25 mL flask

charged with (*S*)-2,2′-dihydroxy-[1,1′]binaphthalenyl-3,3′-dicarboxylic acid dimethyl ester[30] (180 mg, 0.44 mmol) and Adam's catalyst ($PtO_2 \cdot H_2O$, 18.1 mg, 0.074 mmol). The atmosphere of the flask was purged under vacuum and flushed with H_2 three times. The reaction was stirred under a balloon pressure H_2 atmosphere for 24 h. The reaction mixture was filtered through a bed of Celite, diluted with $CHCl_3$ (20 mL), and washed with excess water. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution (10 mL), and dried over Na_2SO_4. Concentration of the organic layer afforded (*S*)-2,2′-dihydroxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl-3,3′-dicarboxylic acid dimethyl ester as a pale yellow powder; yield: 174 mg (0.42 mmol, 95%); $[\alpha]_D^{21}$: $-36.6°$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 10.64$ (s, 2H), 7.61 (s, 2H), 3.90 (s, 6H), 2.68–2.84 (m, 4H), 2.38–2.48 (m, 2H), 2.10–2.20 (m, 2H), 1.58–1.80 (m, 8H); ^{13}C NMR (75.0 MHz, $CDCl_3$): $\delta = 170.9$, 156.2, 144.8, 129.5, 128.3, 123.8, 109.9, 51.9, 29.0, 27.3, 22.6, 22.5; IR (thin film): $\nu = 3019$, 2400, 1670, 1521, 1440, 1316, 1216, 1046, 929, 755, 670 cm^{-1}; HRMS: calcd. for $(M+H)^+$ $C_{24}H_{26}O_6$: 411.1808; found: 411.1789.

***(R)-5,6,7,8,5′,6′,7′,8′-Octahydro-[1,1′]binaphthalenyl-2,2′-diol* (5a):** Acetic acid (145 mL) was added to a 500 mL flask charged with (*R*)-BINOL (5.18 g, 18.1 mmol) and Adam's catalyst ($PtO_2 \cdot H_2O$, 0.52 g, 2.1 mmol). The atmosphere of the flask was purged under vacuum and flushed with H_2 three times. The reaction was stirred under a balloon pressure H_2 atmosphere for 36 h. The reaction mixture was filtered through a bed of Celite, diluted with $CHCl_3$ (250 mL), and washed with excess water. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution (500 mL), and dried over Na_2SO_4. Concentration of the organic layer yielded (*R*)-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl-2,2′-diol as a white solid; yield: 5.18 g (17.6 mmol, 97%). Characterization and spectroscopic data was in agreement with lit. values.[22]

***(R)-2,2′-Dimethoxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl* (13):** A solution of (*R*)-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl-2,2′-diol (1.47 g, 5.00 mmol) in DMF (16 mL) was added dropwise *via* cannula to a 100 mL flask charged with NaH (60% w/w in oil, 840 mg, 35.0 mmol) in DMF (14 mL) at 0 °C. The mixture was stirred at 0 °C for 40 min. Methyl iodide (2.84 g, 20.0 mmol) was added dropwise *via* syringe at 0 °C and the mixture was stirred at 0 °C for 20 min. The solution was removed from the ice bath and allowed to warm to room temperature over 1.5 h. The mixture was placed in a 0 °C bath, and the reaction was quenched with the careful addition of water. The white precipitate was filtered, dissolved in $CHCl_3$ (30 mL), and washed with excess water. The organic layer was dried over Na_2SO_4. Concentration of the organic layer afforded (*R*)-2,2′-dimethoxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl as a white powder; yield: 1.55 g (4.80 mmol, 96%). Characterization and spectroscopic data was in agreement with lit. values.[20]

***(R)-3,3′-Dibromo-2,2′-dimethoxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl* (9):** Bromine (3.00 g, 18.7 mmol) was added dropwise to a 250 mL flask charged with (*R*)-2,2′-dimethoxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl (2.7 g, 8.3 mmol) in CH_2Cl_2 (85 mL) at -30 °C. The solution was stirred at -30 °C for 25 min. 70 mL of a saturated aqueous $NaHSO_3$ solution were added, and the mixture was allowed to warm to room temperature over 1 h. The reaction mixture was diluted with CH_2Cl_2 and water. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution, and dried over Na_2SO_4. Concentration of the organic layer afforded (*R*)-3,3′-dibromo-2,2′-dimethoxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl as colorless crystals; yield: 3.8 g (7.9 mmol, 94%). Characterization and spectroscopic data was in agreement with lit. values.[20]

Representative Procedures for the Suzuki Coupling of 9 to Yield Compounds 10a – d

***Procedure 1:* (R)-3,3′-Bis-biphenyl-4-yl-2,2′-dimethoxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl (10d)**: Tris(dibenzylideneacetone)dipalladium (46 mg, 0.05 mmol), tricyclohexylphosphine (42 mg, 0.15 mmol), 4-biphenylboronic acid (590 mg, 3.0 mmol), potassium fluoride (360 mg, 6.2 mmol), and (*R*)-3,3′-dibromo-2,2′-dimethoxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl (480 mg, 1.0 mmol) were added to a 10 mL flask under an argon atmosphere. THF (2 mL) was added to the reaction flask, and the reaction mixture was refluxed at 75 °C for 18 h. Upon cooling to room temperature, the reaction mixture was diluted and filtered through a pad of silica gel with EtOAc, and the washings were concentrated. The residue was subjected to flash chromatography on silica gel and eluted with hexane and toluene (1:1) to afford (*R*)-3,3′-bis-biphenyl-4-yl-2,2′-dimethoxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl as colorless crystals; yield: 510 mg (0.81 mmol, 81%); $[\alpha]_D^{21}$: $-223.0°$ (*c* 0.98, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.60–7.75$ (m, 12H), 7.40–7.50 (m, 4H), 7.30–7.38 (m, 2H), 7.21 (s, 2H), 3.28 (s, 2H), 2.84 (t, $J = 6.0$ Hz, 4H), 2.50–2.60 (m, 2H), 2.20–2.30 (m, 2H), 1.66–1.83 (m, 8H); ^{13}C NMR (75.0 MHz, $CDCl_3$): $\delta = 152.8$, 140.8, 139.3, 138.4, 135.9, 132.7, 131.4, 131.1, 130.7, 129.3, 128.7, 127.1, 126.9, 126.8, 60.4, 29.4, 27.6, 23.1; IR (thin film). $\nu = 3009$, 2934, 2858, 2837, 1488, 1461, 1387, 1289, 1254, 1240, 1217, 1075, 1034, 1020, 842, 760, 698, 666 cm^{-1}; HRMS: calcd. for $(M+H)^+$ $C_{46}H_{43}O_2$: 627.3263; found: 627.3202.

***Procedure 2:* (R)-3,3′-Bis-(3,5-dimethylphenyl)-2,2′-dimethoxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl (10b):** Glyme (5 mL) was added to a flask charged with $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) and (*R*)-3,3′-dibromo-2,2′-dimethoxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl (480 mg, 1.0 mmol) under an argon atmosphere. The mixture was stirred 10 min at room temperature. The boronic acid (450 mg, 3.0 mmol) was added to the flasks a solution in EtOH (5 mL). 2.0 mL of a 2.0 M aqueous Na_2CO_3 solution (4.0 mmol) were added. The mixture was refluxed at 90 °C for 18 h. The reaction mixture was allowed to cool to room temperature, and filtered through a bed of Celite with EtOAc washings. The EtOAc washings were washed with a saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated. The residue was subjected to flash chromatography on silica gel and eluted with hexane and benzene (1:1) to afford (*R*)-3,3′-bis-(3,5-dimethylphenyl)-2,2′-dimethoxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl as a white foam; yield: 520 mg (0.97 mmol, 97%).

Representative Procedures for the Demethylation of 10a – e to Yield Compounds 8a – e

***(R)-3,3′-Bis-biphenyl-4-yl-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl-2,2′-diol* (8d):** BBr_3 (530 mg,

2.10 mmol) at 0 °C was added to a 200 mL flask charged with (*R*)-3,3′-bis-biphenyl-4-yl-2,2′-dimethoxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl (370 mg., 0.60 mmol) in CH_2Cl_2 (16 mL) under an argon atmosphere. The solution was stirred at 0 °C for 1 h, allowed to warm to room temperature and stirred for an additional 1 h. The reaction solution was then cooled to 0 °C and the reaction was quenched with the careful addition of water. The biphasic mixture was diluted with CH_2Cl_2 and water. The organic layer was dried over Na_2SO_4. After concentration of the organic layer, the residue was subjected to flash chromatography on silica gel and eluted with hexanes and toluene (1:1 → 1:9) to afford (*R*)-3,3′-bis-biphenyl-4-yl-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl-2,2′-diol as colorless crystals; yield: 320 mg (0.54 mmol, 90%); $[\alpha]_D^{21}$: −205.1° (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.75 (m, 12H), 7.40–7.50 (m, 4H), 7.30–7.38 (m, 2H), 7.21 (s, 2H), 4.95 (s, 2H), 2.81 (t, *J* = 6.0 Hz, 4H), 2.37–2.50 (m, 2H), 2.22–2.31 (m, 2H), 1.69–1.82 (m, 8H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ = 148.2, 140.8, 139.9, 136.8, 136.7, 131.7, 130.3, 129.6, 128.7, 127.2, 127.0, 125.5, 120.0, 29.2, 27.2, 23.0 cm^{-1}; IR (thin film): ν = 3514, 3027, 2929, 2856, 1599, 1488, 1456, 1435, 1394, 1233, 1132, 1074, 756 cm^{-1}; HRMS: calcd. for $(M+H)^+$ $C_{44}H_{39}O_2$: 599.2950; found: 599.2860.

***(R)-3,3′-Bis-(3,5-bis-trifluoromethylphenyl)-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl-2,2′-diol* (8c) and (R)-3,3′-bis-(3,5-bis-trifluoromethylphenyl)-2′-methoxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl-2-ol (14):** BBr_3 (2.89 g, 11.5 mmol) was added in three portions over 11 h at −78 °C to a 100 mL flask charged with (*R*)-3,3′-bis-(3,5-bis-trifluoromethylphenyl)-2,2′-dimethoxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl (889 mg., 1.19 mmol) in CH_2Cl_2 (30 mL) under an argon atmosphere at −78 °C. The solution was then allowed to warm to −20 °C over an additional 2 h. The reaction was quenched with the addition of a saturated aqueous $NaHCO_3$ solution, and allowed to warm to room temperature. The biphasic mixture was diluted with CH_2Cl_2 and water. The organic layer was dried over $NaSO_4$. After concentration of the organic layer, the resulting residue was subjected to flash chromatography on silica gel and eluted with hexanes and chloroform (95:5) to afford (*R*)-3,3′-bis-(3,5-bis-trifluoromethylphenyl)-2′-methoxy-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl-2-ol as a white foam (yield: 210 mg, 0.30 mmol, 25%) and (*R*)-3,3′-bis-(3,5-bis-trifluoromethyl-phenyl)-5,6,7,8,5′,6′,7′,8′-octahydro-[1,1′]binaphthalenyl-2,2′-diol as white crystals (yield: 471 mg, 0.65 mmol, 55%).

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