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Catalytic enantioselective arylation of aryl aldehydes by chiral aminophenol ligands

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ABSTRACT

The catalytic enantioselective arylation of aryl aldehydes using boronic acids as the source of transferable aryl groups is described; the reaction is found to proceed in good yields and in good to high enantioselectivities (up to 99% ee) in the presence of a chiral aminophenol ligand.

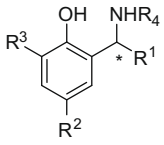
1. Introduction

Enantiopure diarylmethanols are the basis of economically and therapeutically important medicines such as (*R*)-neobenodine, (*R*)-orphenadrine, and (*S*)-carbinoxamine.[1] Since the pioneering work of Fu,[2] several reports concerning the preparation of chiral diarylmethanols by arylzinc addition to aldehydes have been published.[3] One interesting approach to the synthesis of such compounds has been recently introduced by Bolm et al.[4] It consists of using arylboronic acids as the source of the transferable aryl groups. This new methodology offers interesting advantages over the use of Ph_2Zn itself, or over the most widely used Ph_2Zn–Et_2Zn mixture, because (1) it allows for an easy preparation of several substituted arylzinc reagents and therefore for the synthesis of a wide range of diarylmethanols; (2) phenylboronic acid offers an inexpensive alternative to the expensive Ph_2Zn. The most interesting feature of this methodology is that both enantiomers of a given diarylmethanol can be easily prepared in excellent yields and high enantiomeric excess with the same chiral ligand, just by the appropriate choice of the reaction partners: arylboronic acid and aldehyde. However, because ligands that effectively catalyze the asymmetric arylation of aldehydes with high ee values are relatively rare,[5] the search for efficient chiral ligands to realize high enantioselectivity still remains an important challenge in this area.

In connection with our current interests in the asymmetric addition of organozinc reagents to aldehydes,[6] we herein report the behavior of these chiral aminophenols as ligands in the enantioselective arylation of aryl aldehydes.

2. Results and discussion

Chiral aminophenol ligands **1**–**5** and **7** (Fig. 1) were prepared following the procedure recently reported.[6a,b] Ligand **6** was synthesized from the electrophilic aromatic substitution reaction of Br_2 to **1**.



1: R^1 = ^{t}Bu, R^2 = ^{t}Bu, R^3 = H, R^4 = H
2: R^1 = ^{i}Pr, R^2 = ^{t}Bu, R^3 = H, R^4 = H
3: R^1 = ^{t}Bu, R^2 = ^{t}Bu, R^3 = ^{t}Bu, R^4 = H
4: R^1 = ^{i}Pr, R^2 = ^{t}Bu, R^3 = ^{t}Bu, R^4 = H
5: R^1 = Me, R^2 = Me, R^3 = ^{t}Bu, R^4 = H
6: R^1 = ^{t}Bu, R^2 = ^{t}Bu, R^3 = Br, R^4 = H
7: R^1 = ^{t}Bu, R^2 = ^{t}Bu, R^3 = ^{t}Bu, R^4 = Me

Figure 1.

We initiated our studies by choosing *p*-tolualdehyde as a model substrate to examine the efficiency of the asymmetric arylation in the presence of a catalytic amount (10 mol %) of these aminophenol ligands using phenylboronic acid as an aryl resource. The results are summarized in Table 1. In all entries, a small amount of ethylation product was also formed. The results of **1**–**7** demonstrated the steric and electronic effects of a variety of corresponding substituents on the chiral carbon atom and 4,6-positions of phenol. Higher yields and enantiomeric excesses were achieved by using the chiral aminophenols **3**–**4** with a bulky *tert*-butyl group at the 6-position of phenol (Table 1, entries 1–4). Decreasing the substituent size on the chiral carbon from bulky *tert*-butyl **3** to the smallest methyl group **5** resulted in a decrease in both yield and ee (Table 1, entries 3–5). Replacement of the electron-donating *tert*-butyl group **3** with an electron-withdrawing bromo group **6** resulted in critically diminished catalytic activity (Table 1, entries 3 and 6). Methylation of the amino group **7** provided the product in a low yield (8%) with only 5% ee, while some N-substituted aminoalcohols or aminophenols are effective in the asymmetric addition of alkynylzinc reagents or diethylzinc to aldehydes.[7,8]

In order to optimize the reaction conditions, the effects of catalyst loading, solvent, temperature, and amount of $PhB(OH)_2$–Et_2Zn were investigated in some detail with **3** that was identified as the most effective ligand (Table 2). The phenylation of *p*-tolualdehyde

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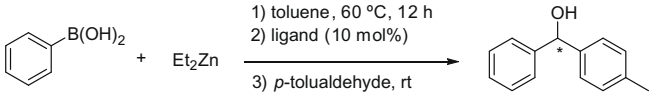
Table 1
Catalytic phenylation of *p*-tolualdehyde with phenylboronic acid in the presence of 10 mol % chiral aminophenol ligands **1**–**7**[a]

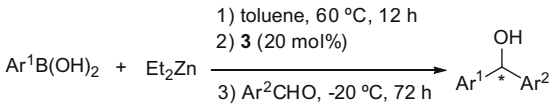


Entry	Ligand	Reaction conditions	Yield[b] (%)	ee[c,d] (%)
1	(*S*)-**1**	Toluene, rt, 28 h	80	6 (*S*)
2	(*S*)-**2**	Toluene, rt, 28 h	78	6 (*S*)
3	**(*S*)-3**	**Toluene, rt, 8 h**	**91**	**78 (*R*)**
4	(*S*)-**4**	Toluene, rt, 8 h	90	48 (*R*)
5	(−)-**5**	Toluene, rt, 20 h	88	54 (*S*)
6	(*R*)-**6**	Toluene, rt, 18 h	89	10 (*S*)
7	(*R*)-**7**	Toluene, rt, 48 h	8	5 (*S*)

[a] Reactions were performed on a 0.25-mmol scale with $PhB(OH)_2$ (2 equiv), Et_2Zn (6 equiv) (first at 60 °C for 12 h, then at rt).
[b] Isolated yield.
[c] Based on HPLC analysis using OB-H column.
[d] Absolute configuration was determined by comparison of the HPLC elution order with the literature data.[5p]

in the presence of 20 mol % of **3** gave the corresponding product in a high yield and a high ee (Table 2, entry 2). We found that the reaction was strongly influenced by solvent (Table 2, entries 2 and 4–6). Toluene gave the best result with 93% yield and 83% ee (Table 2, entry 2). However, low ee values were obtained in toluene/CH_2Cl_2 or toluene/hexane, especially in toluene/THF (5% ee) (Table 2, entries 4–6). Therefore, toluene was selected as the reaction solvent in the following reactions. Decreasing or increasing the amount of phenylboronic acid resulted in the formation of products with significantly lower enantiomeric excesses (Table 2, entries 7 and 8). We then examined the effect of the $PhB(OH)_2$–Et_2Zn ratio on the reaction, and found that decreasing the ratio of $PhB(OH)_2$–Et_2Zn from 3:1 to 2:1 resulted in a decrease in the enantioselectivity (Table 2, entry 2 vs entry 9). A further decrease in the amount of $PhB(OH)_2$–Et_2Zn ratio to 1:1 gave no phenylation product (Table 2, entry 10). Optimization of the reaction temperature indicated that carrying out the reaction at −20 °C favored a higher ee (Table 2, entries 11–14). Thus, entry 14 was identified as the optimized reaction conditions because of the highest enantioselectivity.

Table 3
Catalytic arylation of aromatic aldehydes with aryl boronic acid by the chiral ligand **3**[a]

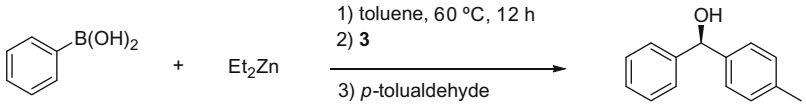


Entry	Ar^1	Ar^2	Yield[b] (%)	ee[c,d] (%)
1	Ph	*p*-BrPh	78	91 (*R*)
2	Ph	*p*-ClPh	80	90 (*R*)
3	Ph	*p*-MePh	83	92 (*R*)
4	Ph	*p*-C_6H_5Ph	84	75 (*R*)
5	Ph	*p*-MeOPh	21	50 (*R*)
6	Ph	*m*-MePh	45[e]	85 (*R*)
7	Ph	*o*-ClPh	65	80 (*R*)
8	Ph	*o*-BrPh	82	89 (*R*)
9	Ph	*o*-MePh	80	>99 (*R*)
10	Ph	2-Naphthyl	88	91 (*R*)
11	*p*-MePh	Ph	82	86 (*S*)
12	*o*-MePh	Ph	77	88 (*S*)
13	*o*-ClPh	Ph	68	73 (*S*)
14	*p*-ClPh	Ph	90	95 (*S*)
15	*p*-ClPh	*p*-BrPh	92	99 (*R*)
16	*p*-MePh	*o*-MePh	87	*95* (*R*)
17	*o*-MePh	*p*-MePh	84	*88* (*S*)
18	*p*-MePh	*p*-ClPh	88	90 (*R*)
19	*p*-ClPh	*p*-MePh	86	93 (*S*)

[a] Reactions were performed on a 0.25-mmol scale with $PhB(OH)_2$ (2 equiv), Et_2Zn (6 equiv) (first at 60 °C for 12 h, then at −20 °C).
[b] Isolated yield.
[c] Based on HPLC analysis.
[d] Absolute configuration was determined by comparison of the HPLC elution order with the literature data.[3c,5f,g,m,n,p,q]
[e] About 30% of the corresponding ethyl addition product was formed.

With the above optimal results, ligand **3** was further used in the asymmetric phenylation of other aromatic aldehydes, a series of substrates with different steric and electronic properties (Table 3, entries 1–10). Fortunately, **3** gave good enantioselectivities (90–92% ee) for *p*-substituted aryl aldehydes except for *p*-phenylbenzaldehyde (75% ee) and *p*-methoxybenzaldehyde (50% ee). The ee decreases in the order of Me > Ph > MeO for the substrates with electron-donating groups in the *para*-position. These results suggest that the substrate with stronger electron-donating group in

Table 2
Catalytic phenylation of *p*-tolualdehyde with phenylboronic acid[a]



Entry	Ligand **3** (equiv)	$PhB(OH)_2$ (equiv)/Et_2Zn (equiv)	Reaction conditions	Yield[b] (%)	ee[c,d] (%)
1	0.1	2/6	Toluene, rt, 8 h	91	78 (*R*)
2	0.2	2/6	Toluene, rt, 8 h	93	83 (*R*)
3	0.5	2/6	Toluene, rt, 8 h	92	84 (*R*)
4	0.2	2/6	Toluene/CH_2Cl_2, rt, 28 h	79	58 (*R*)
5	0.2	2/6	Toluene/THF, rt, 72 h	10	5 (*R*)
6	0.2	2/6	Toluene/hexane, rt, 30 h	68	60 (*R*)
7	0.2	1/3	Toluene, rt, 72 h	16	66 (*R*)
8	0.2	2.5/7.5	Toluene, rt, 24 h	88	72 (*R*)
9	0.2	2/4	Toluene, rt, 72 h	56	53 (*R*)
10	0.2	2/2	Toluene, rt, 72 h	—	—
11	0.2	2/6	Toluene, 10 °C, 32 h	86	85 (*R*)
12	0.2	2/6	Toluene, 0 °C, 36 h	85	85 (*R*)
13	0.2	2/6	Toluene, −5 °C, 36 h	85	88 (*R*)
14	**0.2**	**2/6**	**Toluene, −20 °C, 72 h**	**83**	**92 (*R*)**

[a] Reactions were performed on a 0.25-mmol scale.
[b] Isolated yield.
[c] Based on HPLC analysis using OB-H column.
[d] Absolute configuration was determined by comparison of the HPLC elution order with the literature data.[5p]

the *para*-position of aryl aldehydes affords lower enantioselectivities. On the other hand, only 20% chemical yield was obtained for *p*-methoxybenzaldehyde. This aldehyde remained unreacted after the reaction time, so that the reaction is apparently retarded by this functional group but the effect is not clear at present, which is different from the literature.[4,5a–n,p] The presence of groups at the *ortho*-position shows some differences in enantioselection. For example, *o*-tolualdehyde undergoes smooth aryl addition, delivering the corresponding diarylmethanol in over 99% ee, while the *o*-chloro and *o*-bromo derivatives resulted in much lower enantioselectivities (entries 7–9). These results suggest that the enantioselectivity of phenylzinc species to *ortho*-substituted aldehydes is affected not only by steric effect, but also by the electronic effect. In the next step, we investigated the aryl transfer to benzaldehyde with substituted phenylboronic acid (Table 3, entries 11–14). In order to examine if different aryl groups could be transferred to aldehydes with the same stereoselectivity, the aryl transfer reaction of some substituted arylboronic acids with benzaldehyde was studied; good to high yields and enantiomeric excesses were obtained (entries 11–14). For example, the aryl transfer reaction from *p*-chlorophenylboronic acid to benzaldehyde occurred with 90% yield and 95% ee (entry 14). The aryl transfer reaction of substituted phenylboronic acid (*p*-chlorophenylboronic acid) with substituted benzaldehyde (*p*-bromobenzaldehyde) also afforded the corresponding product with enantioselectivities of up to 99% (Table 3, entry 15).

So far, the substrate scope of the aryl transfer reaction seems to be rather limited,[5] that is, phenyl-transfer to aromatic aldehydes (substituted benzaldehydes) or aryl-transfer to benzaldehyde has usually been investigated, affording arylphenylmethanols. To the best of our knowledge, only two examples have been reported regarding the synthesis of diarylmethanols with two differently substituted aryl groups by organozinc reagents.[5d,m,n] In order to further examine the generality of this methodology and the applicability of the approach to more functionalized diarylmethanols, a series of reverse combinations of the reaction of arylaldehydes with arylboronic acid were tested, and the results are summarized in Table 3 (Table 3, entries 16–19). As seen in Table 3, just by the appropriate choice of the reaction partners, both enantiomers of a given diarylmethanol can be easily obtained in good yields with high enantioselectivities by means of the same ligand **3** (entries 16–19). On the other hand, the enantioselectivity of the reactions of *p*-chlorophenylboronic acid with substituted benzaldehydes is subject to an electronic effect. The substrate with an electron-withdrawing group (*p*-bromobenzaldehyde) afforded higher enantioselectivity than that with an electron-donating group (*p*-tolualdehyde) (Table 3, entries 14, 15, and 19).

The (*R*)-configuration for the arylphenyl addition products, the same as the addition of diethylzinc to arylaldehydes and the addition of phenylacetylene to arylaldehydes catalyzed by **3**,[6a,b] was noted in all the examples studied (Table 2; Table 3, entries 1–10). Comparison of the absolute configuration of the addition products for the phenylation of arylaldehydes with that obtained in ethylation and phenylethynylation of arylaldehydes enabled us to ascertain that the present phenyl transfer process was mechanistically similar to ethyl or phenylethynyl transfer process, that is, the *Re* face of arylaldehydes was attacked by a phenyl group, an ethyl group, and a phenylethynyl group, respectively (Fig. 2).[6a,b]

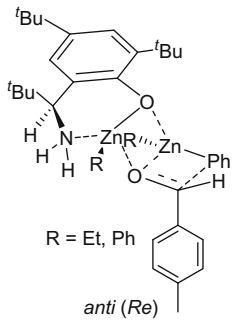


Figure 2.

3. Conclusions

In conclusion, an efficient and catalytic asymmetric synthesis of diarylmethanols by the aminophenol **3** has been demonstrated. This method provides a direct and convenient way to synthesize functionalized diarylmethanols with good to high enantioselectivities from the combination of readily available arylboronic acids and aryl aldehydes.

4. Experimental

The ^{1}H NMR spectra were recorded on Bruker AC300 or DPX400 MHz in Molecular Analysis and Life Science Center (Saitama University). The chemical shifts were reported in ppm downfield from Me_4Si in $CDCl_3$ solution, and the coupling constants were given in Hz. IR spectra were recorded on JASCO FT/IR 400. Enantiomeric excess determination was carried out using a set of JASCO LC 900 series with chiral columns. Optical rotations were measured with a JASCO DIP-370 polarimeter. Melting points were determined with a Mitamura Riken Kogyo MEL-TEMP instrument, and are reported uncorrected. All reagents that are commercially available were purchased at the highest quality and were purified by distillation when necessary. Hexane and toluene were distilled and stored over sodium wire before use.

4.1. (*R*)-2-(1-Amino-2,2-dimethylpropyl)-6-bromo-4-*tert*-butylphenol 6

To a solution of (*R*)-**1** (149.0 mg, 0.632 mmol) in glacial acetic acid (10 ml) was added Br_2 (50 μl) at 10–20 °C, and the mixture was stirred for 12 h. At 0 °C, an aqueous Na_2CO_3 solution was added to bring the solution to pH 8–9, and the mixture was extracted with ethyl acetate (5 ml × 3). The organic layer was dried with anhydrous Na_2SO_4, and the solvent was removed. The crude product was purified by silica gel TLC (hexane/ethyl acetate = 2:1) to give (*R*)-**6** (103.0 mg, 0.328 mmol, 51.6%) as a white solid. (*R*)-**6**, $[\alpha]_D^{20} = -14.1$ (*c* 1.0, MeOH). Mp: 137.8–139.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.41 (d, 1H, *J* = 2.4 Hz, ArH), 6.84 (d, 1H, *J* = 2.4 Hz, ArH), 3.85 (s, 1H, $(CH_3)_3CCHAr$), 1.26 (s, 9H, $(CH_3)_3CAr$), 0.97 (s, 9H, $(CH_3)_3CCHAr$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5, 141.6, 128.7, 127.2, 124.2, 110.9, 66.7, 36.2, 33.9, 31.4, 26.7. IR (KBr) 3482, 3014, 2964, 1644, 1595, 1407, 1323, 1270, 1140, 808, 776 cm^{-1}. Anal. Calcd for $C_{15}H_{24}BrNO$: C, 57.33; H, 7.70; N, 4.46. Found: C, 57.56; H, 7.81; N, 4.42.

4.2. Catalytic enantioselective arylation of aromatic aldehydes

Diethylzinc (1.5 mmol, 1.0 M in hexane) was added to a solution of arylboronic acid (0.5 mmol) in toluene (1.5 ml) under nitrogen atmosphere. After stirring for 12 h at 60 °C, the mixture was cooled to room temperature, and chiral ligand **3** (20 mol %) was added. After stirring for additional 30 min, the mixture was cooled to −20 °C, and aldehyde (0.25 mmol) was subsequently added under nitrogen atmosphere. After 72 h at −20 °C, the reaction was quenched with 1 N HCl aq. The mixture was extracted twice with ethyl acetate. The combined organic layer was washed with brine,

dried with anhydrous Na_2SO_4, filtered, and the solvent was removed. Purification of the residue by silica gel TLC afforded the pure diarylmethanol. Enantiomeric excess of the product was determined by chiral HPLC on a Chiralcel OB-H, OJ, AD-H, or OD-H column.

4.2.1. (*R*)-(*p*-Tolyl)phenylmethanol[5p]

83% isolated yield. 92% ee determined by HPLC analysis (Chiralcel OB-H column, 10% IPA in hexane, 0.5 ml/min, 254 nm UV detector). Retention time: t = 28.51 min ((*S*)-isomer: t = 47.31 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.23 (m, 7H), 7.12–7.11 (m, 2H), 5.36 (s, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6, 139.4, 139.3, 137.1, 129.1, 128.3, 127.3, 127.2, 127.1, 79.7, 21.2.

4.2.2. (*R*)-(*p*-Chlorophenyl)phenylmethanol[5q]

80% isolated yield. 90% ee determined by HPLC analysis (Chiralcel AD-H column, 10% IPA in hexane, 0.5 ml/min, 254 nm UV detector). Retention time: t = 16.82 min ((*S*)-isomer: t = 18.40 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.20 (m, 9H), 5.80 (s, 1H), 2.37 (s, 1H).

4.2.3. (*R*)-(*p*-Methoxyphenyl)phenylmethanol[5f]

21% isolated yield. 50% ee determined by HPLC analysis (Chiralcel OJ column, 10% IPA in hexane, 1.0 ml/min, 254 nm UV detector). Retention time: t = 39.03 min ((*S*)-isomer: t = 46.10 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.26 (m, 7H), 6.88–6.85 (m, 2H), 5.81 (s, 1H), 3.79 (s, 1H), 2.20 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 144.0, 136.2, 128.5, 127.9, 127.4, 127.2, 126.4, 113.9, 113.8, 75.7, 55.3.

4.2.4. (*R*)-(*p*-Bromophenyl)phenylmethanol[5g]

78% isolated yield. 91% ee determined by HPLC analysis (Chiralcel OB-H column, 10% IPA in hexane, 1.0 ml/min, 254 nm UV detector). Retention time: t = 20.21 min ((*S*)-isomer: t = 41.94 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.44 (m, 2H), 7.35–7.25 (m, 7H), 5.79 (s, 1H), 2.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 142.7, 131.6, 131.5, 128.7, 128.2, 127.9, 126.5, 121.4, 75.7.

4.2.5. (*R*)-(*m*-Tolyl)phenylmethanol[5g]

45% isolated yield. 85% ee determined by HPLC analysis (Chiralcel OJ column, 10% IPA in hexane, 1.0 ml/min, 254 nm UV detector). Retention time: t = 20.72 min ((*S*)-isomer: t = 30.37 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.20 (m, 9H), 5.81 (s, 1H), 2.33 (s, 3H), 2.18 (s, 1H).

4.2.6. (*R*)-(*o*-Chlorophenyl)phenylmethanol[5p]

65% isolated yield. 80% ee determined by HPLC analysis (Chiralcel OB-H column, 10% IPA in hexane, 0.5 ml/min, 254 nm UV detector). Retention time: t = 29.71 min ((*S*)-isomer: t = 42.99 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.16 (m, 9H), 6.23 (s, 1H), 2.45 (s, 1H).

4.2.7. (*R*)-(*o*-Bromophenyl)phenylmethanol[5g]

82% isolated yield. 89% ee determined by HPLC analysis (Chiralcel OD-H column, 10% IPA in hexane, 0.5 ml/min, 254 nm UV detector). Retention time: t = 18.89 min ((*S*)-isomer: t = 24.22 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.48 (m, 2H), 7.40–7.23 (m, 6H), 7.16–7.10 (m, 1H), 6.17 (s, 1H), 2.62 (s, 1H).

4.2.8. (*R*)-(*o*-Tolyl)phenylmethanol[5g]

80% isolated yield. 99% ee determined by HPLC analysis (Chiralcel OB-H column, 10% IPA in hexane, 0.5 ml/min, 254 nm UV detector). Retention time: t = 36.31 min ((*S*)-isomer: t = 54.21 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.50 (m, 1H), 7.33–7.13 (m, 8H), 5.99 (s, 1H), 2.24 (s, 3H), 2.21 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9, 141.4, 135.4, 130.5, 128.5, 127.6, 127.5, 127.1, 126.3, 126.1, 73.4, 19.4.

4.2.9. (*R*)-Naphthalen-2-yl-phenyl-methanol[5g]

88% isolated yield. 91% ee determined by HPLC analysis (Chiralcel OD-H column, 10% IPA in hexane, 0.5 ml/min, 254 nm UV detector). Retention time: t = 44.23 min ((*S*)-isomer: t = 37.27 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80–7.69 (m, 4H), 7.41–7.32 (m, 5H), 7.27–7.16 (m, 3H), 5.90 (s, 1H), 2.37 (s, 1H).

4.2.10. (*R*)-(4-Biphenyl)phenylmethanol[3c]

84% isolated yield. 75% ee determined by HPLC analysis (Chiralcel OB-H column, 10% IPA in hexane, 1.0 ml/min, 254 nm UV detector). Retention time: t = 30.49 min ((*S*)-isomer: t = 10.49 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.46 (m, 4H), 7.37–7.14 (m, 10H), 5.80 (s, 1H), 2.27 (s, 1H).

4.2.11. (*R*)-(2-Tolyl)-(4′-tolyl)methanol[5m,n]

87% isolated yield. 95% ee determined by HPLC analysis (Chiralcel OD-H column, 1% IPA in hexane, 1.0 ml/min, 254 nm UV detector). Retention time: t = 47.95 min ((*S*)-isomer: t = 53.69 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54–7.51 (m, 1H), 7.24–7.10 (m, 7H), 5.96 (s, 1H), 2.32 (s, 3H), 2.22 (s, 3H), 2.12 (s, 1H).

4.2.12. (*R*)-(4-Chlorophenyl)-(4′-tolyl)methanol[5m,n]

88% isolated yield. 90% ee determined by HPLC analysis (Chiralcel OD-H column, 2% IPA in hexane, 1.0 ml/min, 254 nm UV detector). Retention time: t = 80.10 min ((*S*)-isomer: t = 63.56 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.20 (m, 7H), 7.15–7.13 (m, 1H), 5.78 (s, 1H), 2.32 (s, 3H), 2.20 (s, 1H).

4.2.13. (*R*)-(4-Bromophenyl)-(4′-chlorophenyl)methanol

92% isolated yield. 99% ee determined by HPLC analysis (Chiralcel AD-H column, 2% IPA in hexane, 0.5 ml/min, 254 nm UV detector). Retention time: t = 68.96 min ((*S*)-isomer: t = 70.63 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.37 (m, 2H), 7.24–7.12 (m, 6H), 5.68 (s, 1H), 2.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3, 141.7, 133.6, 131.7, 131.5, 128.7, 128.2, 127.9, 127.7, 121.7, 74.9.

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