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Enantioselective Arylations Catalyzed by Carbohydrate-Based Chiral Amino Alcohols

Ana Dionéia Wouters,[a] Gustavo H. G. Trossini,[a] Hélio A. Stefani,[a] and Diogo S. Lüdtke*[a]

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The application of carbohydrate-derived amino alcohols in the asymmetric arylation of aldehydes by using arylboronic acids as the source of transferable aryl groups is described. The best ligand is derived from the readily available sugar D-xylose and it mediates the addition of a range of arylboronic acids to various aromatic aldehydes in excellent yields and high enantiomeric excesses.

Introduction

The boron-to-zinc exchange reaction has recently received much attention as a tool for the generation of reactive arylzinc species.[1] It stands out as one of the most interesting methods for the generation of transferable aryl groups, as a number of arylboron compounds are commercially available or easily prepared. Among the various organoboron compounds, arylboronic acids have received special attention; their reaction with Et_2Zn produces an [ArZnEt] intermediate, which, in the presence of a chiral ligand, can selectively transfer the aryl group to a range of aryl aldehydes, allowing the synthesis of a number of substituted diarylmethanols.[2] The use of arylboron reagents as precursors for the reactive organozinc intermediates overcomes a number of difficulties encountered in the reaction with the expensive and very reactive Ph_2Zn[3] or the more convenient mixture of Ph_2Zn/Et_2Zn. The latter method produces the mixed PhZnEt, which is less reactive than diphenylzinc itself, accounting for a more selective aryl transfer process.[4] These two protocols, however, have a serious drawback. The scope of the aryl group to be transferred is limited to the phenyl ring, because only diphenylzinc is a commercially available diarylzinc reagent. Another important feature of this methodology is that both enantiomers of a given product can be prepared by using the same chiral ligand simply by appropriate choice of the arylboronic acid and the aldehyde reaction partners.

Enantioenriched diarylmethanols are present in a number of biologically and pharmacologically active compounds (Figure 1).[5] For example it can be found in the structure of (*R*)-orphenadrine, (*R*)-neobenodine,[6] and (*S*)-cetirizine,[7] which display antihistaminic and anticholinergic activity. In addition to their direct applications, the chiral diarymethanol nucleus can serve as a precursor for diarylmethane derivatives by S_N2 substitution at the C–O bond, without loss of enantiomeric purity.[8] Compounds possessing a chiral diarylmethane nucleus are found to behave as antimuscarinics,[9] antidepressants,[10] and endothelin antagonists.[11]

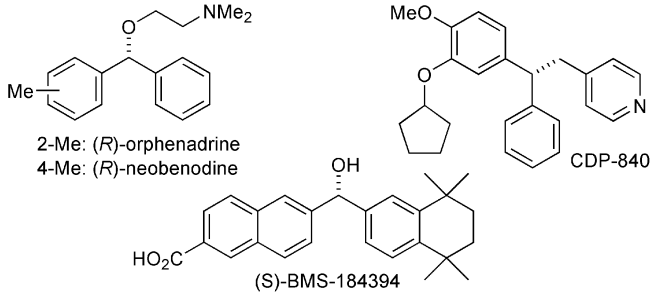


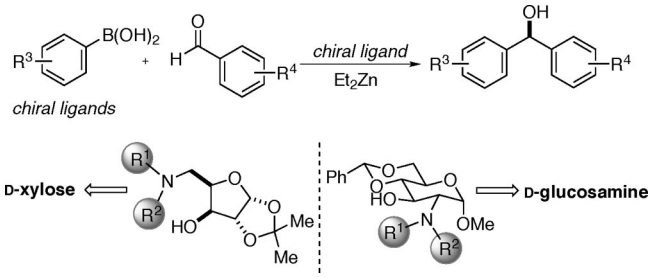
Figure 1. Structures of bioactive diarylmethanol derivatives.

Within the classes of compounds studied to catalyze the aryl transfer reaction to aldehydes, chiral amino alcohols and amino-alcohol-type ligands are among the most widely studied.[12] Other ligands with different scaffolds such as amino thiols and thioacetates,[13] sulfonamides,[14] and binol derivatives[15] have also found application in such transformations.

Carbohydrates are widespread in nature as enantiomerically pure compounds, which have interesting stereochemical diversity and have served as a chiral pool for the preparation of chiral auxiliaries, ligands, and catalysts.[16] In the context of our research program towards the use of readily available carbohydrates as the starting material in organic synthesis,[17] we describe herein the application of amino

[a] Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, USP,
CEP 05508-900, São Paulo, São Paulo, Brazil
Fax: +55-11-3815-4418
E-mail: dsludtke@usp.br

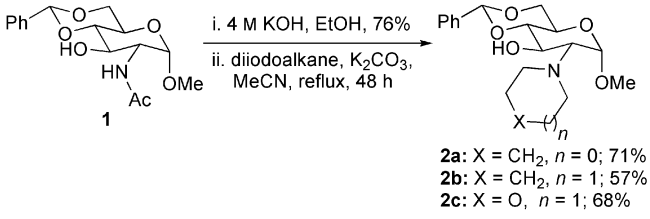
alcohols derived from D-xylose and D-glucosamine as chiral ligands for the asymmetric arylation of aldehydes (Scheme 1). Precedent for the ability of carbohydrate-derived amino alcohols to mediate organozinc additions was found in the literature in the work of Cho[18] and Davis[19] who, respectively, developed xylose- and glucosamine-based ligands for the enantioselective addition of Et_2Zn to aldehydes. To the best of our knowledge, this is the first time that sugar-based compounds were employed as chiral ligands in the asymmetric aryl transfer reaction.



Scheme 1. Carbohydrate-derived ligands for the enantioselective arylation of aldehydes.

Results and Discussion

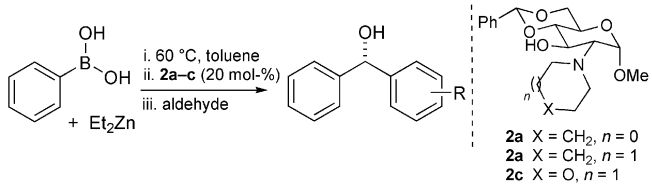
First, we focused our efforts on the application of D-glucosamine-derived ligands, as an amino group is already found in the starting sugar. Thus, the required amino alcohols were straightforwardly prepared by deprotection of the *N*-Ac group in **1**, followed by reaction with a diiodoalkane in the presence of K_2CO_3 in boiling acetonitrile to afford the corresponding aza-ring derivatives **2a**–**c** in good yields (Scheme 2).



Scheme 2. Synthesis of D-glucosamine-derived ligands.

These chiral carbohydrate derivatives were then tested as ligands in the asymmetric phenyl transfer reaction to *p*-tolylaldehyde by using phenylboronic acid as the phenyl source. Unfortunately, disappointing results were achieved with the use of 20 mol-% of ligands **2a**–**c** (Table 1). Pyrrolidine and piperidine derivatives **2a** and **2b** afforded the phenyl(*p*-tolyl)methanol in good yields, however, with very low *ee* values (<20%*ee*; Table 1, Entries 1 and 2). Ligand **2c**, which possesses a morpholine ring, afforded slightly better, albeit still unsatisfactory, enantiomeric excess values (36%*ee*; Table 1, Entry 3). In view of the poor results obtained in the phenyl transfer reaction to *p*-tolylaldehyde, we also tested the reaction with three other aromatic aldehydes, and again the enantioselectivity of the arylation reaction was low, and the corresponding diarylmethanols were isolated with *ee* values of 30–35% (Table 1, Entries 4–6).

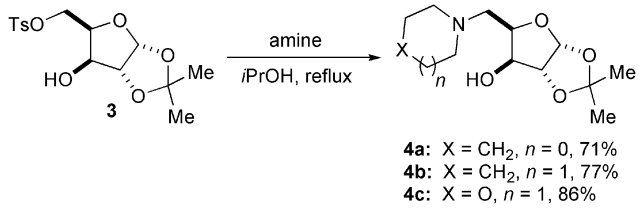
Table 1. Glucosamine-derived ligands in the arylation of aldehydes.



Entry	R	Ligand	Temp [°C]	Yield [%]	*ee* [%][a]
1	*p*-Me	**2a**	0	75	<20
2	*p*-Me	**2b**	0	73	<20
3	*p*-Me	**2c**	0	78	36
4	*p*-OMe	**2c**	0	92	31
5	*o*-Cl	**2c**	0	87	30
6	*o*-Br	**2c**	0	89	35

[a] Enantiomeric excess values determined by HPLC with a chiral stationary phase. Absolute configuration determined by comparison with literature data.

Disappointed by the results obtained in the arylations mediated by the ligands from the glucosamine series, we turned our attention to amino alcohols **4a**–**c** based on the xylose scaffold (Scheme 3). These ligands were readily prepared in a simple procedure, by reaction of tosylate **3** with an appropriate secondary amine and isopropanol as the solvent.

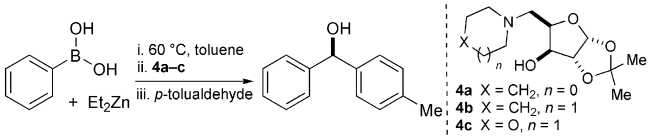


Scheme 3. Synthesis of D-xylose-derived ligands.

With these γ-amino alcohols in hands, we screened their behavior as chiral ligands in the phenylation of *p*-tolylaldehyde. The screening reactions were carried out at 0 °C, with a catalytic loading of 20 mol-%, and by using toluene as the solvent. Analysis of the results depicted in Table 2 reveals that all ligands afforded the desired product in high yields, and the best result in terms of enantioselectivity was obtained with morpholine ligand **4c**, which delivered (*R*)-phenyl(*p*-tolyl)methanol in 93% yield and an excellent *ee* of 96% (Table 2, Entry 3). Further studies were carried out with this ligand. The temperature has an important influence on the selectivity of the arylation reaction, because when the reaction was conducted at room temperature, a sharp decrease in the *ee* values was observed (Table 2, compare Entries 3 and 6). The use of DiMPEG (dimethoxypo-

lyethylene glycol), a commonly used additive for the improvement of selectivity in asymmetric organozinc additions, also proved to be detrimental to the reaction outcome, as it led to sluggish reactions and to erosion in both the yields and *ee* values (Table 2, Entries 4 and 5). To further examine the effect of the temperature, we lowered the temperature even more to –20 °C. Under these conditions, unfortunately, no further improvement was achieved, and the product was obtained in a decreased yield and *ee* (Table 2, Entry 7). Finally, we confirmed that 20 mol-% of the ligand was necessary to achieve high enantioselectivity, and lowering the ligand loading to 10 and 15 mol-% resulted in lower *ee* values (Table 2, Entries 8 and 9).

Table 2. Asymmetric arylation of *p*-tolualdehyde in the presence of xylose-derived ligands **4a**–**c**.

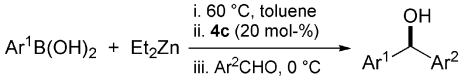


Entry	Ligand (mol-%)	Temp [°C]	Yield [%]	*ee* [%][a]
1	**4a** (20)	0	92	60
2	**4b** (20)	0	94	79
3	**4c** (20)	0	93	96
4[b]	**4c** (20)	25	75	53
5[c]	**4c** (20)	25	51	35
6	**4c** (20)	25	96	78
7	**4c** (20)	–20	90	86
8	**4c** (10)	0	80	66
9	**4c** (15)	0	78	72

[a] Enantiomeric excess values determined by HPLC with a chiral stationary phase, Chiralcel OD-H column, λ = 254 nm, hexanes/*i*PrOH (90:10), 0.5 mL min^{-1}. Absolute configuration determined by comparison with literature data. [b] DiMPEG (20 mol-%) MW 2000 was used as an additive. [c] DiMPEG (10 mol-%) MW 2000 was used as an additive.

With ligand **4c** identified as the most effective, we examined the scope of the arylation reaction with a varied set of aldehydes containing diverse steric and electronic properties (Table 3). The reaction tolerates a broad range of substituents, and as a general trend, the reactions performed with aldehydes possessing electron-withdrawing groups gave higher yields and *ee* values relative to the values obtained with the strong electron-donating methoxy group. For example, the product of phenylation of 4-bromobenzaldehyde was formed in 95% yield with 88%*ee*, whereas the same reaction with 4-anisaldehyde resulted in the corresponding product in comparative yields, but with a decreased *ee* value of 80%. Particularly relevant is that the arylation reaction tolerates *ortho* substitution, as the level of enantioselectivity obtained was similar to that obtained with *para*-substituted derivatives. For instance, high *ee* values were obtained with *ortho*-tolylaldehyde (90%*ee*; Table 3, Entry 2) and 2-chloro- and 2-bromobenzaldehyde (87%*ee*; Table 3, Entries 6 and 8). As regards the tolerance of our catalytic system to variations at the boronic acid counterpart, we first examined the arylation of benzaldehyde with *p*-tolylboronic acid and 4-chlorophenylboronic acid and excellent yields and good enantiomeric excesses were obtained (Table 3, Entries 10 and 11).

Table 3. Asymmetric arylation of aldehydes.

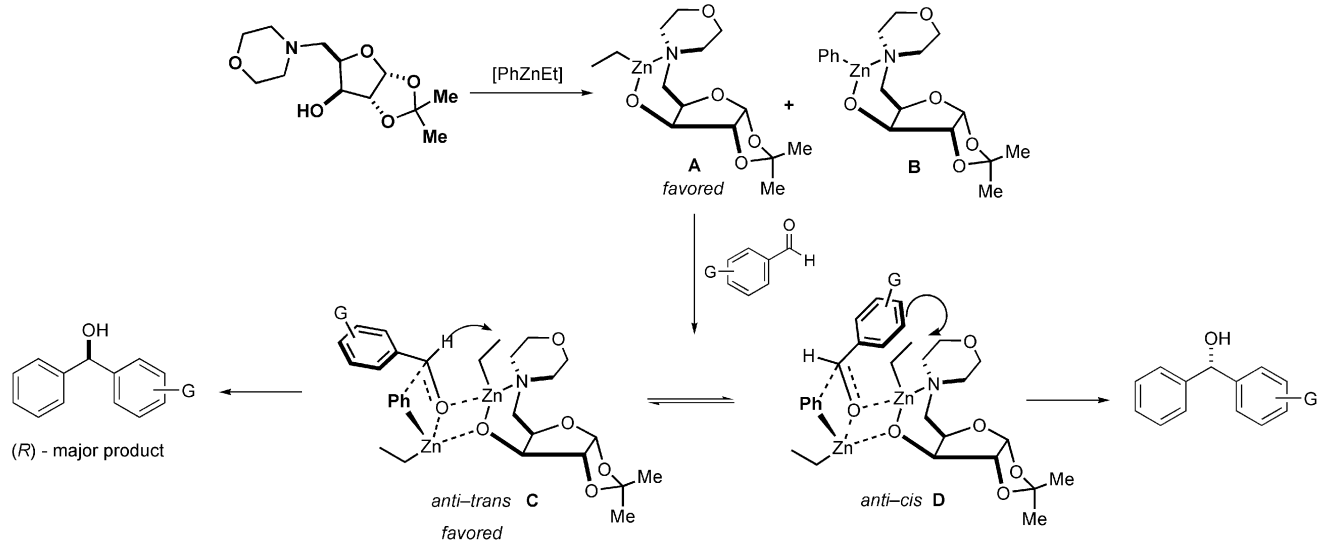


Entry	Ar^1	Ar^2	Yield [%]	*ee* [%][a]
1	phenyl	4-methylphenyl	97	96
2	phenyl	2-methylphenyl	96	90
3	phenyl	4-methoxyphenyl	94	80
4	phenyl	2-methoxyphenyl	96	78
5	phenyl	4-chlorophenyl	96	83
6	phenyl	2-chlorophenyl	91	87
7	phenyl	4-bromophenyl	95	88
8	phenyl	2-bromophenyl	91	87
9	phenyl	cyclohexyl	84	67
10	4-methylphenyl	phenyl	95	84
11	4-chlorophenyl	phenyl	94	82
12	4-methylphenyl	4-chlorophenyl	91	83
13	4-chlorophenyl	4-methylphenyl	92	88
14	4-biphenyl	4-methylphenyl	92	86

[a] Enantiomeric excess values determined by HPLC with a chiral stationary phase. Absolute configuration determined by comparison with literature data.

Moreover, the synthesis of diarylmethanols substituted at both aromatic rings with high enantioselectivity is also possible by varying the substitution pattern of the arylboronic acid and the aldehyde at the same time. For example, the reaction between *p*-tolylboronic acid with 4-chlorobenzaldehyde smoothly produced the corresponding (*R*)-diarylmethanol in excellent yield and 84%*ee*. The opposite combination of substituents, that is, 4-chlorobenzaldehyde and *p*-tolylaldehyde, resulted in the opposite (*S*) enantiomer of the above-mentioned diarylmethanol, with a similar level of enantioselection (Table 3, compare Entries 12 and 13). Finally, a diarylmethanol containing halogen groups at both rings and a biphenyl derivative were also prepared in high yields with good *ee* values. In addition to the reaction with aryl aldehydes, the arylation of cyclohexanecarboxaldehyde was also performed and the arylated product was achieved in 84% yield with moderate enantioselectivity (67%*ee*; Table 3, Entry 9).

The mechanism of the reaction is believed to proceed as depicted in Scheme 4. First, reaction of amino alcohol **4c** with the PhZnEt reagent results in the formation of zinc complex **A**, which is the actual catalyst for the enantioselective aryl transfer reaction. Formation of ethyl-substituted chiral zinc complex **A** is favored over phenyl-substituted complex **B**, as proposed by Pericàs.[4c,12i,20] Following this, the aldehyde reacts with the catalyst, resulting in a tricyclic transition state (TS), as originally proposed by Noyori.[21] Transition-state structure **C**, with an *anti–trans* conformation is preferred over *anti–cis* structure **D**, because it avoids axial positioning of the aldehyde Ar group, thus minimizing any steric interactions with the ethyl group attached to the zinc atom. Accordingly, aryl transfer to the *Re* face of the



Scheme 4. Proposed reaction pathway.

aldehyde results in the formation of the (*R*)-diarylmethanol as the major product. This is in agreement with the results observed experimentally.

To obtain more evidence of the validity of the proposed mechanism, some theoretical calculations were performed by using a semiempirical PM3 method. Due to the large size of the structures involved, the PM3 method was chosen instead of the more time-consuming methods (DFT, MP2). Results for transition-state calculation with the use of the PM3 method usually predict efficiently the reaction outcome in enantioselective processes.[22] Transition-state structures were calculated by using ligand **4c** for the phenyl-transfer reaction to 4-tolylaldehyde. The most important diastereomeric TSs according to the pioneering work or Noyori,[23] namely, *anti–trans*, *anti–cis*, *syn–cis*, and *syn–trans*, were considered, and the four most stable TSs were located with their relative energies and are depicted in Figure 2. The *anti–trans* and *syn–trans* structures would lead to the (*R*) product, whereas the *anti–cis* and *syn–cis* systems would lead to the (*S*) enantiomer. Among these, the *anti–trans* structure was found to be the most stable TS structure, followed by the *anti–cis*. The *syn–trans* and *syn–cis* TSs are higher in energy and should not contribute substantially to product formation. Thus, in this case, the selectivity of the reaction should be mainly determined by the energy gap between the two *anti* arrangements. To our delight, the calculated TSs are in accordance with our proposed model, and the energy difference for the *anti–trans*/*anti–cis* TS was found to be 6.3 kcal mol^{-1}, leading to the prediction of (*R*)-(4-tolyl)phenylmethanol as the main product. In addition, the distance between the aryl group in the aldehyde and the spectator ethyl group was found to be 4.24 and 3.93 Å for the *anti–trans* and *anti–cis* TS, respectively. The calculated distances indicate that the axial positioning of the 4-tolyl group indeed results in a more severe steric interaction with the ethyl group, accounting for the higher energy of the TS.

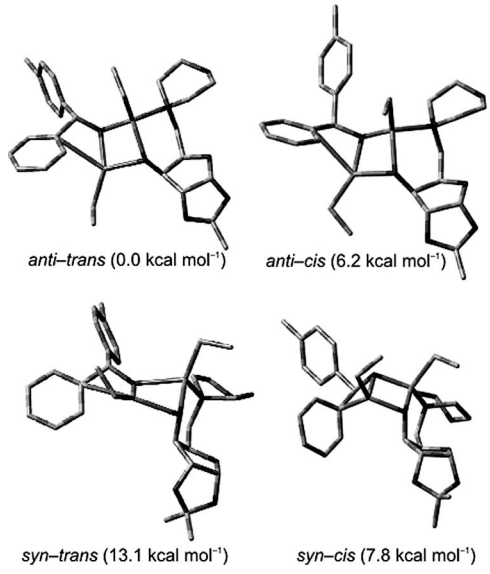


Figure 2. PM3 transition-state structures of ligand **4c**.

These calculations are in agreement with the experimentally observed selectivity. Thus, it was shown that the theoretical calculations performed in the PM3 model correctly predict the stereochemical outcome observed for the arylation of aromatic aldehydes with the use of xylose-derived ligand **4c**.

Conclusions

In summary we have described the application of chiral amino alcohols with a sugar backbone as ligands in the asymmetric arylation of aldehydes by using arylboronic acids as the source of the transferable aryl group. The most efficient ligand identified by the present study was a deriva-

tive from D-xylose, which possesses a furanoside backbone and a morpholino group. Yields of the arylation reaction in the presence of ligand **4c** were generally high, and the diarylmethanol products were obtained with *ee* values of up to 96%.

Experimental Section

General Considerations: All reactions were performed under an argon atmosphere with dried glassware. The solvents used for reactions under inert atmosphere were dried, and the reagents were purified according to standard procedures,[24] unless otherwise noted. The progress of the reactions was monitored by thin-layer chromatography (TLC) by using silica gel GF_{254} (0.25 mm thickness). For visualization, TLC plates were either placed under ultraviolet light or stained with phosphomolybdic acid, followed by heating. Column chromatography was performed by using silica gel (230–400 mesh) by following the methods described by Still.[25] ^1H and ^{13}C NMR spectra were obtained with a Bruker spectrometer at 300 and 75 MHz, respectively. Chemical shifts are reported in ppm referenced to the solvent peak of residual $CHCl_3$ or tetramethylsilane (TMS) as reference. Analysis of enantiomeric excess was performed by using HPLC equipped with columns with a chiral stationary phase. All measurements were performed at a column temperature of 20 °C by using a UV detector at 254 nm, except where noted otherwise. Theoretical calculations were performed in Gaussian 03W v.6 software. Optimization of the bond angles and distances was made by molecular mechanics. Transition-state calculations were performed by using the semiempirical PM3 method, and the results were visualized in GaussView 3.09 software.

Typical Experimental Procedure for the Enantioselective Arylation: To a solution of arylboronic acid (1.2 mmol) in toluene (2 mL) was added diethylzinc (1 M in toluene, 3.5 mL, 3.5 mmol) at room temperature. The reaction was stirred at 60 °C for 1 h and then cooled to room temperature. A solution of the ligand (20 mol-%) in toluene (1 mL) was added to the reaction, and the system was stirred for 20 min at this temperature. The reaction was then cooled to 0 °C, and the aldehyde (0.5 mmol) was added. The reaction mixture was stirred, and it was kept at this temperature for 6 h. The reaction was quenched by the addition of water and extracted with CH_2Cl_2 (3×20 mL). The organic layers were combined and dried with magnesium sulfate. Evaporation of the solvent under reduced pressure and purification with flash chromatography (hexane/ethyl acetate, 4:1) gave the desired diarylmethanol. Enantiomeric excess were determined by HPLC analysis with a chiral stationary phase.

(2-Tolyl)phenylmethanol: Yield: 105 mg (96%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.2 (s, 3 H, CH_3), 5.9 (d, J = 1.8 Hz, 1 H, CH), 7.1–7.4 (m, 9 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3, 73.3, 126, 126.2, 127, 127.5, 128.4, 130.5, 135.3, 141.4, 142.8 ppm. HPLC (Chiralpak AD-H, 2% *i*PrOH/hexane, 0.5 mL min^{-1}): t_R = 16.8 (*R*), 18.6 (*S*) min.

(4-Tolyl)phenylmethanol: Yield: (*R*)-product, 106 mg (97%); (*S*)-product, 104 mg (95%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.3 (s, 3 H, CH_3), 5.7 (s, 1 H, CH), 7.1–7.3 (m, 9 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21, 76, 126.4, 126.5, 127.3, 128.3, 129.1, 137.1, 140.9, 143.9 ppm. HPLC (Chiralcel OD-H, 10% *i*PrOH/hexane, 0.5 mL min^{-1}): t_R = 40.3 (*S*), 42.6 (*R*) min.

(2-Methoxyphenyl)phenylmethanol: Yield: 103 mg (96%). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.7 (s, 3 H, OCH_3), 6.0 (d, J = 3.9 Hz, 1 H, CH), 6.8–6.9 (m, 2 H, Ar), 7.2–7.3 (m, 7 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.2, 71.7, 110.6, 120.6, 126.4, 126.9, 127.6, 127.9, 128.4, 131.9, 143.2, 156.5 ppm. HPLC (Chiralcel OD-H, 2% *i*PrOH/hexane, 0.5 mL min^{-1}): t_R = 60.7 (*R*), 73.7 (*S*) min.

(4-Methoxyphenyl)phenylmethanol: Yield: 101 mg (94%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.3 (s, 1 H, OH), 3.7 (s, 3 H, OCH_3), 5.7 (s, 1 H, CH), 6.8 (m, 2 H, Ar), 7.2–7.3 (m, 7 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.2, 75.7, 113.8, 126.3, 127.3, 127.8, 128.3, 136.1, 144, 158.9 ppm. HPLC (Chiralcel OD-H, 10% *i*PrOH/hexane, 0.5 mL min^{-1}): t_R = 20.2 (*S*), 21.1 (*R*) min.

(2-Chlorophenyl)phenylmethanol: Yield: 99 mg (91%). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.2 (s, 1 H, CH), 7.1–7.3 (m, 8 H, Ar), 7.5 (d, J = 7.2 Hz, 1 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 72.6, 126.8, 127, 127.3, 128, 128.4, 128.6, 129.4, 132.4, 140.9, 142.2 ppm. HPLC (Chiralcel OD-H, 10% *i*PrOH/hexane, 0.5 mL min^{-1}): t_R = 14.7 (*R*), 16.5 (*S*) min.

(4-Chlorophenyl)phenylmethanol: Yield: (*R*)-product, 105 mg (96%); (*S*)-product, 103 mg (94%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.4 (s, 1 H, OH), 5.74 (s, 1 H, CH), 7.22–7.33 (m, 9 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 75.5, 126.4, 127.7, 127.8, 128.51, 128.55, 133.1, 142.1, 143.3 ppm. HPLC (Chiralpak AD-H, 10% *i*PrOH/hexane, 1.0 mL min^{-1}): t_R = 8.4 (*R*), 9.1 (*S*) min.

(2-Bromophenyl)phenylmethanol: Yield: 120 mg (91%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.8 (s, 1 H, OH), 6.1 (s, 1 H, CH), 7.0–7.5 (m, 9 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 74.6, 122.7, 126.9, 127.6, 128.3, 128.4, 129, 130.1, 132.7, 142.1, 142.4 ppm. HPLC (Chiralcel OD-H, 10% *i*PrOH/hexane, 0.8 mL min^{-1}): t_R = 10.4 (*R*), 11.9 (*S*) min.

(4-Bromophenyl)phenylmethanol: Yield: 125 mg (95%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.4 (s, 1 H, OH), 5.7 (s, 1 H, CH), 7.2–7.4 (m, 9 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 75.6, 121.3, 126.4, 127.8, 128.1, 128.6, 131.4, 142.7, 143.3 ppm. HPLC (Chiralcel OB-H, 10% *i*PrOH/hexane, 0.5 mL min^{-1}): t_R = 22.6 (*R*), 30.2 (*S*) min.

(4-Chlorophenyl)-4-methylphenylmethanol: (*R*)-product, 105 mg (91%); (*S*)-product, 107 mg (92%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.3 (s, 3 H, CH_3), 5.7 (s, 1 H, CH), 7.1–7.3 (m, 8 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21, 75.3, 126.4, 127.7, 128.4, 129.2, 133, 137.5, 140.5, 142.3 ppm. HPLC (Chiralcel OD-H, 10% *i*PrOH/hexane, 0.2 mL min^{-1}): t_R = 40.1 (*R*), 42.1 (*S*) min.

(4-Biphenyl)-(4-tolyl)methanol: Yield: 126 mg (92%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.3 (s, 3 H, CH_3), 2.4 (s, 1 H, OH), 5.7 (s, 1 H, CH), 7.1–7.5 (m, 13 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21, 75.8, 126.4, 126.8, 127, 127.12, 127.18, 128.6, 129.1, 137.2, 140.2, 140.7, 140.8, 142.9 ppm. HPLC (Chiralcel OD-H, 10% *i*PrOH/hexane, 0.2 mL min^{-1}): t_R = 40.1 (*R*), 42.1 (*S*) min.

Cyclohexyl(phenyl)methanol: Yield: 80 mg (84%). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.9–1.2 (m, 5 H), 1.35–1.40 (m, 1 H), 1.51–1.65 (m, 3 H), 1.75–1.83 (m, 2 H, CH_2), 1.99–2.01 (m, 1 H, CH), 4.33 (d, J = 7.0 Hz, 1 H, CH), 7.2–7.35 (m, 5 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.0, 26.2, 26.7, 29.0, 29.6, 45.1, 79.9, 126.7, 127.6, 128.4, 143.7 ppm. HPLC (Chiralcel OD-H, 5% *i*PrOH/hexane, 0.5 mL min^{-1}): t_R = 14.6 (*S*), 18.1 (*R*) min.

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[1] For a review on B–Zn exchange and its application in asymmetric arylations, see: M. W. Paixão, A. L. Braga, D. S. Lüdtke, *J. Braz. Chem. Soc.* **2008**, *19*, 813–830.
[2] C. Bolm, J. Rudolph, *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851.
[3] a) P. I. Dosa, J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1997**, *62*, 444–445; b) W. S. Huang, Q. S. Hu, L. Pu, *J. Org. Chem.* **1999**, *62*, 7940–7956; c) C. Bolm, K. Muñiz, *Chem. Commun.* **1999**, 1295–1296; d) D. H. Ko, K. H. Kim, D. C. Ha, *Org. Lett.* **2002**, *4*, 3759–3762.
[4] a) C. Bolm, N. Hermanns, J. P. Hildebrand, K. Muñiz, *Angew. Chem. Int. Ed.* **2000**, *39*, 3465–3467; b) C. Bolm, M. Kesselbruger, N. Hermanns, J. P. Hildebrand, *Angew. Chem. Int. Ed.* **2001**, *40*, 1488–1490; c) M. Fontes, X. Verdaguer, L. Solà, M. A. Pericàs, A. Riera, *J. Org. Chem.* **2004**, *69*, 2532–2543; d) S. Rodriguez-Escrich, K. R. Reddy, C. Jimeno, G. Colet, C. Rodriguez-Escrich, L. Solà, A. Vidal-Ferran, M. A. Pericàs, *J. Org. Chem.* **2008**, *73*, 5340–5353.
[5] a) F. Schmidt, R. T. Stemmler, J. Rudolph, C. Bolm, *Chem. Soc. Rev.* **2006**, *35*, 454–470; b) V. Dimitrov, K. Kostova, *Lett. Org. Chem.* **2006**, *3*, 176–182.
[6] a) K. Meguro, M. Aizawa, T. Sohda, Y. Kawamatsu, A. Nagaoka, *Chem. Pharm. Bull.* **1985**, *33*, 3787–3797; b) R. F. Rekker, H. Timmerman, A. F. Harms, W. T. Nauta, *Arzneim.-Forsch.* **1971**, *21*, 688–691.
[7] a) C. M. Spencer, D. Foulds, D. H. Peters, *Drugs* **1993**, *46*, 1055–1080; b) J. L. Devalia, C. De Vos, F. Hanotte, E. Baltes, *Allergy* **2001**, *56*, 50–57.
[8] a) Y. Bolshan, C.-Y. Chen, J. R. Chilenski, F. Gosselin, D. J. Mathre, P. D. O'Shea, A. Roy, R. D. Tillyer, *Org. Lett.* **2004**, *6*, 111–114; b) P. D. O'Shea, C.-Y. Chen, W. R. Chen, P. Dagneou, L. F. Frey, E. J. J. Grabowski, K. M. Marcantonio, R. A. Reamer, L. Tan, R. D. Tillyer, A. Roy, X. Wang, D. L. Zhao, *J. Org. Chem.* **2005**, *70*, 3021–3030.
[9] L. Nilvebrandt, K.-E. Andersson, P.-G. Gillberg, M. Stahl, B. Sparf, *Eur. J. Phamacol.* **1997**, *327*, 195–207.
[10] W. M. Welch, A. R. Kraska, R. Sarges, B. K. Koe, *J. Med. Chem.* **1984**, *27*, 1508–1515.
[11] P. C. Astles, T. J. Brown, F. Halley, C. M. Handscombe, N. V. Harris, T. N. Majid, C. McCarthy, I. M. McLay, A. Morley, B. Porter, A. G. Roach, C. Sargent, C. Smith, R. J. Walsh, *J. Med. Chem.* **2000**, *43*, 900–910.
[12] a) J.-X. Ji, J. Wu, T. T.-L. Au-Yeung, C. W. Yip, K. R. Haynes, A. S. C. Chan, *J. Org. Chem.* **2005**, *70*, 1093–1095; b) A. L. Braga, D. S. Lüdtke, F. Vargas, M. W. Paixao, *Chem. Commun.* **2005**, 2512–2514; c) G. Lu, F. Y. Kwong, J. W. Ruan, Y. M. Li, A. S. C. Chan, *Chem. Eur. J.* **2006**, *12*, 4115–4120; d) F. Schmidt, J. Rudolph, C. Bolm, *Adv. Synth. Catal.* **2007**, *349*, 703–708; e) J. W. Ruan, G. Lu, L. Xu, Y. Li, A. S. C. Chan, *Adv. Synth. Catal.* **2008**, *350*, 76–84; f) A. M. DeBerardins, M. Turlington, L. Pu, *Org. Lett.* **2008**, *10*, 2709–2712; g) A. L. Braga, M. W. Paixao, B. Westermann, P. H. Schneider, L. A. Wessjohann, *J. Org. Chem.* **2008**, *73*, 2879–2882; h) M. C. Wang, Q. J. Zhang, W. X. Zhao, X. D. Wang, X. Ding, T. T. Jing, M. P. Song, *J. Org. Chem.* **2008**, *73*, 168–176; i) C. Jimeno, S. Sayalero, T. Fjermestad, G. Colet, F. Maseras, M. A. Pericàs, *Angew. Chem. Int. Ed.* **2008**, *47*, 1098–1101; j) M. C. Wang, S. D. Wang, X. D. Ding, Z. K. Liu, *Tetrahedron* **2008**, *64*, 2559–2564; k) L. Salvi, J. G. Kim, P. J. Walsh, *J. Am. Chem. Soc.* **2009**, *131*, 12483–12493.
[13] a) P.-Y. Wu, H.-L. Wu, B.-J. Uang, *J. Org. Chem.* **2006**, *71*, 833–835; b) A. L. Braga, P. Milani, F. Vargas, M. W. Paixão, J. A. Sehnem, *Tetrahedron: Asymmetry* **2006**, *17*, 2793–2797; c) M.-J. Jin, S. M. Sarkar, D.-H. Lee, H. Qiu, *Org. Lett.* **2008**, *10*, 1235–1237; d) Z. Chai, X.-Y. Liu, X.-Y. Wu, G. Zhao, *Tetrahedron: Asymmetry* **2006**, *17*, 2442–2447.
[14] a) O. Prieto, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2003**, *14*, 1955–1957; b) V. J. Forrat, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2005**, *16*, 3341–3344.
[15] a) K. Ito, Y. Tomita, T. Katsuki, *Tetrahedron Lett.* **2005**, *46*, 6083–6086; b) X. B. Huang, L. L. Wu, J. Q. Xu, L. L. Zong, H. W. Hu, Y. X. Cheng, *Tetrahedron Lett.* **2008**, *49*, 6823–6826.
[16] a) O. Pàmies, M. Dièguez, *Chem. Eur. J.* **2008**, *14*, 944–960; b) M. Dièguez, C. Claver, O. Pàmies, *Eur. J. Org. Chem.* **2007**, 4621–4634; c) M. K. K. Boysen, *Chem. Eur. J.* **2007**, *13*, 8648–8659; d) M. Dièguez, O. Pàmies, C. Claver, *Chem. Rev.* **2004**, *104*, 3189–3215; e) M. Dièguez, O. Pàmies, A. Ruiz, Y. Díaz, S. Castillón, C. Claver, *Coord. Chem. Rev.* **2004**, *248*, 2165–2192.
[17] a) A. L. Braga, W. A. Severo Filho, R. S. Schwab, O. E. D. Rodrigues, L. Dornelles, H. C. Braga, D. S. Lüdtke, *Tetrahedron Lett.* **2009**, *50*, 3005–3007; b) H. R. Appelt, J. B. Limberger, M. Weber, O. E. D. Rodrigues, J. S. Oliveira, D. S. Lüdtke, A. L. Braga, *Tetrahedron Lett.* **2008**, *49*, 4956–4957; c) A. S. Vieira, P. F. Fiorante, T. L. S. Hough, F. P. Ferreira, D. S. Lüdtke, H. A. Stefani, *Org. Lett.* **2008**, *10*, 5215–5218.
[18] B. T. Cho, N. Kim, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2901–2907.
[19] D. P. G. Emmerson, R. Villard, C. Mugnaini, A. Batsanov, J. A. K. Howard, W. P. Hems, R. P. Tooze, B. G. Davis, *Org. Biomol. Chem.* **2003**, *1*, 3826–3838.
[20] Theoretical studies on the arylation of aldehydes: a) J. Rudolph, C. Bolm, P.-O. Norrby, *J. Am. Chem. Soc.* **2005**, *127*, 1548–1552; J. Rudolph, T. Rasmussen, C. Bolm, P.-O. Norrby, *Angew. Chem. Int. Ed.* **2003**, *42*, 3002–3005.
[21] a) M. Yamakawa, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 6327–6335; b) M. Kitamura, S. Suga, H. Oka, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 9800–9809.
[22] a) M. C. Kozlowski, S. L. Dixon, M. Panda, G. Lauri, *J. Am. Chem. Soc.* **2003**, *125*, 6614–6615; b) M. Panda, P. W. Phuan, M. C. Kozlowski, *J. Org. Chem.* **2003**, *68*, 564–571; c) B. Goldfuss, M. Steigelmann, S. I. Kahn, K. N. Houk, *J. Org. Chem.* **2000**, *65*, 77–82; d) J. Vazquez, M. A. Pericàs, F. Maseras, A. Lledos, *J. Org. Chem.* **2000**, *65*, 7303–7309.
[23] M. Yamakawa, R. Noyori, *Organometallics* **1999**, *18*, 128–133.
[24] W. L. F. Armarego, C. L. L. Chai in *Purification of Laboratory Chemicals*, 5th ed., Butterworth-Heinemann, Bodmin, Cornwall, **2003**.
[25] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

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