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Catalytic enantioselective aryl transfer: asymmetric addition of boronic acids to aldehydes using pyrrolidinylmethanols as ligands

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Abstract—Pyrrolidinylmethanols, easily accessible from readily available (*S*)-proline, were applied in zinc-catalyzed addition of arylboronic acids to aromatic aldehydes; the reaction was found to proceed in excellent yields and high enantioselectivities (up to 98% ee).

Due to the high biological activity of various derivatives, enantiopure diarylmethanols are important compounds for the pharmaceutical industry. For example, neobenodine, orphenadrine, and carbinoxamine show strong antihistaminic properties.[1] More recently, enantiomerically pure diarylmethanols have been used as key intermediates for the synthesis of diarylalkylmethanes, which are antimuscarinics, antidepressants, and endothelin antagonists.[2]

Besides the reduction of appropriate diarylketones, where the achievement of high enantioselectivities can become problematic when the two aryl groups are similar in volume or electronic nature,[3] the enantioselective arylation of aldehyde substrates appears to be the most promising alternative for the preparation of these molecular systems. Since the pioneering work of Fu,[4] several reports concerning the preparation of chiral diarylmethanols by arylzinc addition to aldehydes have been published.[5] In this context, the recently introduced procedure,[6] which takes advantage of the readily available aryl boronic acids appears to be very promising for effecting this transformation, since it allows the easy preparation of several substituted arylzinc reagents and therefore the synthesis of a wide range of substituted chiral diaryl methanols. Unfortunately, ligands which effectively catalyze the phenyl transfer reactions to aldehydes using boronic acids as the aryl source with high ee values are relatively rare.[6,7] Thus, the development of easily prepared and effective chiral ligands is an important challenge for the practical applications of phenyl transfer using boronic acids.

In connection with our current interests in the asymmetric addition of organozinc reagents to aldehydes,[8] we recently described the highly enantioselective addition of an arylzinc reagent to aldehydes, generated from readily accessible aryl boronic acids. The major advantage of this protocol is that almost any aryl group can be transferred to aromatic aldehydes with excellent enantioselectivities.[9]

In this letter, we wish to report our successful endeavor in this area by using readily accessible chiral proline-based amino alcohols **2a**–**c** as ligands.

A series of chiral and modular pyrrolidinylmethanols were obtained starting from readily available (*S*)-proline as shown in Scheme 1. Ligands **2a**–**c** were obtained in good yields from *N*-Boc proline methyl ester **1** by reaction with ArMgBr and subsequent reduction with lithium aluminum hydride in THF under reflux to afford the corresponding *N*-methyl derivatives in 82–87% overall yields.[10,11]

With the target ligands in hand, we focused our attention to investigating the enantioselective arylation of

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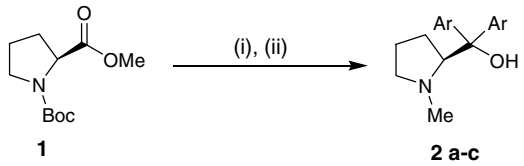


1 2 a-c

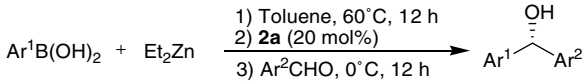
Scheme 1. General synthesis of chiral ligands **2a–c**. Reagents and conditions: (i) 2.5 equiv ArMgBr, THF, rt; (ii) $LiAlH_4$, THF, reflux.

p-tolualdehyde with phenylboronic acid. The results of this study are depicted in Table 1.

In order to optimize the reaction conditions, effects of catalyst loading, temperature, and amount of Et_2Zn were first investigated in some detail for ligand **2a** (Table 1, entries 1–8). The arylation of *p*-tolualdehyde in the presence of 20 mol % of ligand **2a** gave the corresponding product in a high yield (96%) and an enantiomeric excess of 87% (entry 1). Carrying out reaction at 0 °C, the ee was increased to 94% (entry 2). No changes in ee values were observed when the temperature of the reaction was decreased from 0 to −20 °C (entry 3). Decrease in the catalyst loading resulted in the formation of products with slightly or significantly lower enantiomeric excesses (entries 4, 5, and 6). We then examined the effect of the Et_2Zn–$PhB(OH)_2$ ratio on the reaction, and we found that decreasing the ratio of Et_2Zn 3:1 to 2:1 resulted in a decrease in the enantioselectivity. Further decrease in the amount of Et_2Zn–$PhB(OH)_2$ ratio to 1:1 and no product of arylation was observed (compare entries 7 and 8).

Under the best conditions,[12] we evaluated the electronic effect based on the different structures of ligand **2**. The study of the electronic effects of substituents on ligands **2b** and **2c** showed that neither electron-donating nor electron-withdrawing group on the *para*-position of the phenyl group could decrease the enantiomeric excess (entries 9 and 10).

Table 2. Catalytic arylation of aldehydes with aryl boronic acids using ligand **2a**



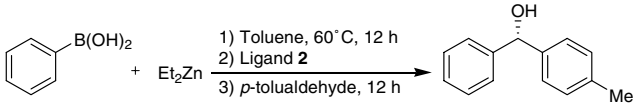
Entry	Ar^1	Ar^2	Yield[a] (%)	ee[b,c] (%)
1	Phenyl	4-Methylphenyl	95	94 (*S*)
2	Phenyl	2-Methylphenyl	98	98 (*S*)
3	Phenyl	4-Methoxyphenyl	97	93 (*S*)
4	Phenyl	2-Methoxyphenyl	92	84 (*S*)
5	Phenyl	4-Chlorophenyl	90	98 (*S*)
6	Phenyl	2-Chlorophenyl	88	90 (*S*)
7	Phenyl	2-Bromophenyl	91	80 (*S*)
8	4-Methylphenyl	Phenyl	90	93 (*R*)
9	4-Methoxyphenyl	Phenyl	98	86 (*R*)
10	4-Chlorophenyl	Phenyl	91	86 (*R*)

[a] Isolated yield of the corresponding product.
[b] Enantiomeric excesses were determined by chiral HPLC.
[c] Configuration determined by comparison with the literature data.[5e,6]

With ligand **2a** identified as the most effective, next we examined the scope of our system in reactions with several aromatic aldehydes with diverse electronic and steric properties. The presence of electron-donating groups in the aldehyde, such as methyl and methoxy, furnished the corresponding products in high levels of stereoselectivity (see Table 2, entries 1–4).

The presence of groups at the *ortho*-position at the aldehyde shows some differences in the enantioselection event. For example, *p*-chlorobenzaldehyde undergoes smooth aryl addition, delivering the corresponding diarylmethanol in 98% *ee*, while the *o*-chloro derivative resulted in much lower enantioselectivity (entries 5 and 6). This fact can be explained by the influence of steric effects, since when the chlorine atom is replaced by the more encumbered bromine, even lower *ee* was achieved (compare entries 6 and 7).

Table 1. Catalytic arylation of *p*-tolualdehyde with phenylboronic acid[a]



Entry[a]	Ligand (mol %)	Ar	*T* (°C)	$Et_2Zn/PhB(OH)_2$ ratio	Yield[b] (%)	ee[c,d] (%)
1	**2a** (20)	Phenyl	rt	3:1	96	87 (*S*)
2	**2a** (20)	Phenyl	0	3:1	95	94 (*S*)
3	**2a** (20)	Phenyl	−20	3:1	93	94 (*S*)
4	**2a** (15)	Phenyl	0	3:1	93	84 (*S*)
5	**2a** (10)	Phenyl	0	3:1	92	35 (*S*)
6	**2a** (5)	Phenyl	0	3:1	91	30 (*S*)
7	**2a** (20)	Phenyl	0	2:1	87	77 (*S*)
8	**2a** (20)	Phenyl	0	1:1	—	—
9	**2b** (20)	4-Methylphenyl	0	3:1	96	90 (*S*)
10	**2c** (20)	4-Chlorophenyl	0	3:1	98	91 (*S*)

[a] Reactions were performed on a 0.5 mmol scale with $PhB(OH)_2$ (2.4 equiv), Et_2Zn (7.2 equiv) in toluene (first at 60 °C for 12 h, then at room temperature for 12 h).
[b] Isolated yield of the corresponding product.
[c] Enantiomeric excesses were determined by chiral HPLC on a Chiralcel OD column.
[d] Configuration determined by comparison with the literature data.[5e,6]

In order to examine if different aryl groups could be transferred to aldehydes with the same stereoselectivity, the aryl transfer reaction of some substituted aryl boronic acids with benzaldehyde was studied, and to our delight, high yields and enantiomeric excesses were obtained (entries 8–10). For example, aryl transfer reaction from 4-methylphenyl boronic acid to benzaldehyde occurred with 93% ee (entry 8).

This is one of the most interesting features of this methodology, since both enantiomers of a given product can be easily prepared in excellent yields and high enantiomeric excesses with the same catalyst, just by appropriate choice of both reaction partners; aryl boronic acid and aldehyde.

In conclusion, we have described herein the catalytic asymmetric arylation of aldehydes in the presence of proline-based chiral ligands. The reactive arylzinc species are generated in situ from a boron–zinc exchange instead of employing the more expensive diphenylzinc.[5d,j] The reaction of these arylzinc species with aldehydes gives access to both enantiomers of the chiral diaryl methanols in high yields and enantiomeric excesses. These results are similar or even superior to those obtained by Bolm's or Chan's.[6,7b] Further work is in progress in our laboratory with the aim of expanding applications of these inexpensive chiral ligands to other enantioselective catalytic processes.

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11. *General procedure for the preparation of ligands* (**2a**–**c**): ArMgBr (40 mmol) in THF (40 mL, 1 M solution) was added to a THF (20 mL) solution of *N*-Boc methyl ester (10 mmol) at 0 °C, and the mixture was stirred for additional 4 h, before being quenched by pouring into 2 M NaOH. The heterogeneous mixture was filtered through a pad of Celite and washed with dichloromethane (3×50 mL). The combined organic phases were dried with $MgSO_4$, filtered, and the solvent removed under vacuum. The resulting product was used without further purification. The product was dissolved in THF (30 mL) and was cooled to 0 °C. Lithium aluminum hydride (0.759 g, 20 mmol) was added to the solution in several portions, and the mixture was refluxed for 2 h. After the mixture was cooled to 0 °C, water was added. The mixture was acidified to pH 3 with 1 M HCl, washed with dichloromethane, and made alkaline with concentrated aqueous NaOH. The precipitate was filtered off and washed with ethyl acetate. The organic layer was separated, and the filtrate was extracted with dichloromethane. The combined extract was dried under $MgSO_4$ and filtered. The solvent was removed under vacuum and the crude product was purified by flash chromatography in hexanes/ethyl acetate (90:10).
Selected spectral and analytical data for **2a**: Yield: 83%; mp 68.5–68.9; $[\alpha]_D^{20}$ +19 (*c* 1.2, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.63–7.61 (m, 2H); 7.53–7.51 (m, 2H); 7.25–7.21 (m, 4H); 7.10–7.09 (m, 2H); 4.54 (br s, 1H); 3.61–3.58 (m, 1H); 3.09–3.07 (m, 1H); 2.43–2.37 (m, 1H); 1.87–1.79 (m, 4H); 1.68–1.57 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.20; 146.68; 127.92; 126.05; 125.44; 125.38; 77.36; 71.94; 59.07; 42.90; 29.81; 23.94. HRMS-ESI: *m*/*z* calcd for $C_{18}H_{21}NO + H^+$: 268.1701; found: $C_{18}H_{21}NO + H^+$: 268.1696.

12. *General procedure for the asymmetric arylation of aldehydes*: Diethylzinc (3.6 mmol, toluene solution) was dropwise added to a solution of boronic acid (1.2 mmol) in toluene (2 mL) under an argon atmosphere. After stirring for 12 h at 60 °C, the mixture is cooled to 0 °C and a toluene solution of chiral amino alcohol (20 mol %) was introduced. The reaction is stirred for additional 15 min and the aldehyde (0.5 mmol) was subsequently added. After stirring for 12 h at 0 °C the reaction was quenched with water and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried with $MgSO_4$, filtered, and the solvents evaporated. Purification by flash chromatography eluting with a mixture of hexanes/ethyl acetate (90:10) afforded the pure diarylmethanols. *HPLC-analyses*: All measurements were performed at a 20 °C column temperature using a UV detector at 254 nm. Phenyl(*p*-tolyl)methanol (**4a**): Chiralcel OD, hexane/*i*-PrOH (90:10), 0.5 mL/min, (*S*): 19.1 min, (*R*): 21.1 min.