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Short communication

The application of chiral, non-racemic *N*-alkylephedrine and *N*,*N*-dialkylnorephedrine as ligands for the enantioselective aryl transfer reaction to aldehydes

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Abstract

The catalytic enantioselective arylation of several aldehydes using arylboronic acids as the source of transferable aryl groups is described; the reaction is found to proceed in excellent yields and high enantioselectivities (up to 96% ee) in the presence of a chiral amino alcohol derived from ephedrines and congeners.

Keywords: Asymmetric catalysis; Organozinc reagents; Arylboronic acids; Diarylmethanols; Amino alcohols

1. Introduction

Nucleophilic addition of organometallic reagents to carbonyl compounds is a very important process in organic synthesis, and the asymmetric version of this reaction is particularly useful [1]. The face selective addition of organometallic reagents to prochiral aldehydes leading to optically active secondary alcohols have been extensively reported [2]. Among the organometallic compounds investigated, organozinc reagents proved to be one of the most versatile nucleophiles. Recently, the enantioselective arylation of aldehydes in the presence of chiral ligands has received special attention since it gives access to chiral diarylmethanols [3], which are useful intermediates in the synthesis of bioactive compounds and natural products [4].

In this context, the boron-to-zinc exchange reaction has emerged as a versatile tool for the generation of transferable aryl groups [5]. This method now allows the exploitation of a broader range of substituted aryl transfer reagents, since numerous arylboronic acids are easily accessible and available from commercial sources, respectively. Even more interesting is the feature that this methodology permits that both enantiomers of a given product can be prepared using the same chiral catalyst, just by appropriate choice of both reaction partners; the aryl boronic acid and the aldehyde (Scheme 1).

Since the catalytic asymmetric aryl transfer reaction to carbonyl compounds using boronic acids as the aryl source has been studied quite extensively, the search for efficient chiral ligands to generate high enantio-selectivities in such reactions still remains an important challenge in this area [6].

As part of a broader program to explore the preparation and application of chiral, non-racemic β-amino alcohol based ligands in asymmetric additions of organozinc reagents to aldehydes [7], we wish to describe herein the application of *N*-alkylephedrine and *N*,*N*-dialkylnorephedrine as efficient ligands for the face selective addition of an arylzinc reagent to aldehydes, generated from readily accessible aryl boronic acids.

2. Results and discussion

Our ligands were prepared using Soai's route [8] as outlined in Scheme 2. We selected ex-chiral pool starting materials (1*R*, 2*S*) ephedrine and (1*R*, 2*S*) norephedrine for the synthesis of our ligands, since they have been successfully used as the chiral framework in comparable systems [9]. Ligands

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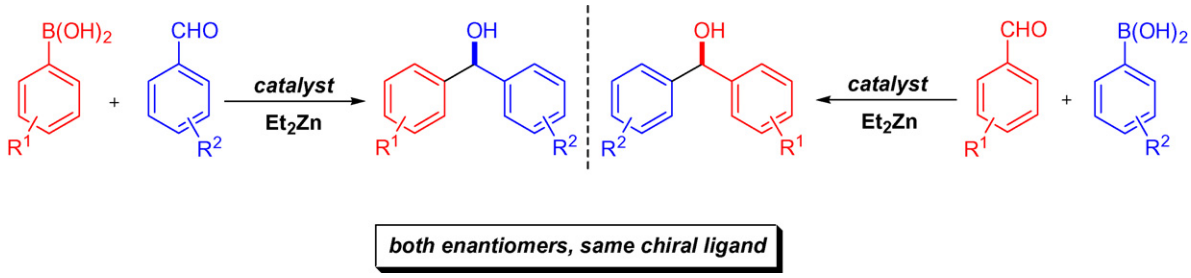
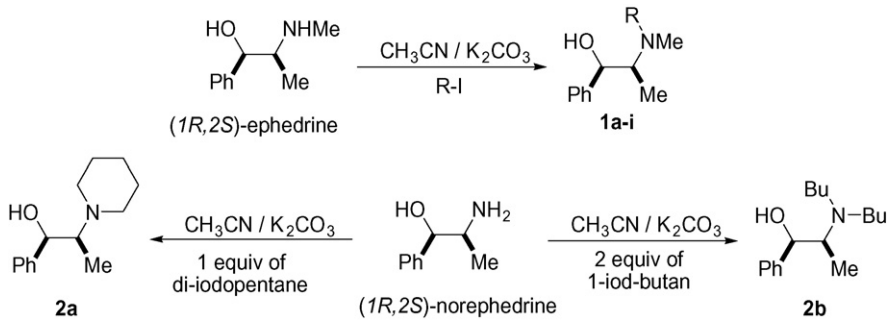


Scheme 1. Enantioconvergent synthesis of diarylmethanols using the same chiral ligand.



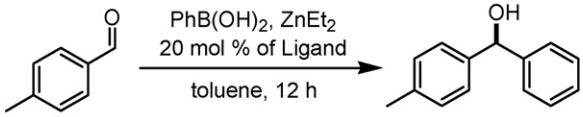
Scheme 2. Synthesis of ephedrine and norephedrine based chiral ligands **1a–i**, **2a** and **2b**.

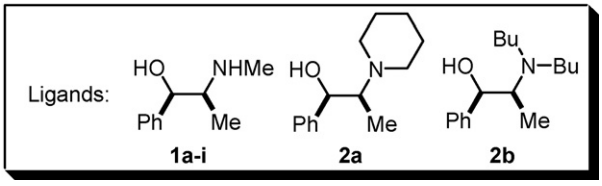
1a–i and **2a–b** were obtained in good yields from (1*R*, 2*S*) ephedrine or (1*R*, 2*S*) norephedrine by a one-step reaction of the appropriate amino alcohols with 1 and 2 equiv. of alkyl halide, respectively, in the presence of potassium carbonate in boiling acetonitrile. This substitution leads to a library of suitable ligands, amenable to influence the steric interactions between the ligand and the substrate, which are both coordinated to the metal. Therefore, the stereoselectivity is expected to improve as the stereogenic element of the ligand gets closer to the metal center.

With ligands **1a–i**, **2a** and **2b** in hand, arylzinc [10] addition to *p*-tolualdehyde was examined. A catalytic loading of 20 mol% of the ligand and toluene as solvent was used as the standard conditions [11]. Our initial goal was to evaluate the effect of the size of the alkyl group attached to the nitrogen atom on the level of enantioselectivity. The results from these experiments are shown in Table 1.

From these results it is evident that phenyl group addition proceeds in high yields utilizing ligands **1a–i** (entries 1–9). Furthermore, the size of the alkyl group on the nitrogen atom plays an important role in determining the levels of enantioselectivity. For example, reaction with ligand **1b** with a small methyl substituent is less selective (entry 2, 55% ee) compared to **1e** containing a *n*-butyl group (entry 5, 65% ee). This trend is confirmed for all the ligands except for **1d** (entry 4) with a *n*-propyl group. Catalysts with *N*-alkyl substituents of a chain length greater than four carbons gave alcohols of lower optical purity (entry 5 versus 6–8). Moreover, the chiral ligand **1i** with a flexible and more bulky benzyl group was found to be the most efficient ligand. Thus ligand **1i** catalyzed the addition of phenylboronic acid to *p*-tolualdehyde in toluene at room temperature to give (*S*)-phenyl(*p*-tolyl)methanol with 67% ee in 94% yield. These results suggest that the substituent attached at the nitrogen

Table 1
Evaluation of chiral relay ligands in catalytic arylations of *p*-tolualdehyde with phenylboronic acid[a]





Entry	Ligands	R^1	R^2	Yield (%)[b]	ee (%)[c,d]
1	**1a**	CH_3	H	89	36 (*S*)
2	**1b**	CH_3	CH_3	96	55 (*S*)
3	**1c**	CH_3	C_2H_5	94	63 (*S*)
4	**1d**	CH_3	C_3H_8	92	56 (*S*)
5	**1e**	CH_3	C_4H_9	97	65 (*S*)
6	**1f**	CH_3	C_5H_{11}	91	46 (*S*)
7	**1g**	CH_3	C_8H_{17}	98	56 (*S*)
8	**1h**	CH_3	$C_{12}H_{25}$	97	43 (*S*)
9	**1i**	CH_3	CH_2Ph	94	67 (*S*)
10[e]	**1i**	CH_3	CH_2Ph	92	83 (*S*)
11[e]	**2a**	-C_5H_{10}-		89	80 (*S*)
12[e]	**2b**	C_4H_9	C_4H_9	94	84 (*S*)
13[e,f]	**2b**	C_4H_9	C_4H_9	92	87 (*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 HPLC on a Chiralcel OD column.
[d] Configuration determined by comparison with the literature data [6].
[e] Reaction was carried out at 0 °C.
[f] 10 mol% of DiMPEG 1000 was added as an additive.

atom plays a critical role to influence the face selectivity of the addition reaction.

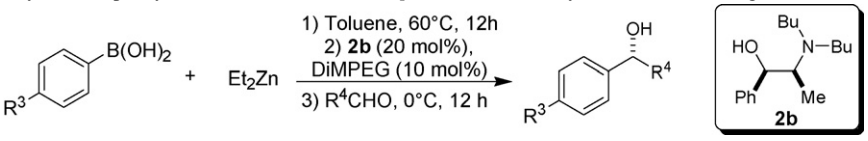
A significant enhancement in enantioselectivity arises, as depicted in entry 10, while carrying out the reaction at 0 °C. The desired biaryl carbinol was isolated in 83% ee while the reaction preceeded to 92% of yield. Increasing the size of the amine substituent (R^1) leads to higher stereoselectivities (entry 12), although catalyst **2a** (entry 11), bearing a piperidine, promotes the reactions less efficiently and with a lower enantioselectivity than **2b**. To increase the enantioselectivity even further, we evaluated the effect of DiMPEG (poly(ethylene glycol) dimethyl ether, M_W 1000) on the addition reaction of organozinc reagents to aldehydes using ligand **2b** [12]. To our delight, the desired biaryl alcohol was obtained in 87% ee and 92% yield (entry 13).

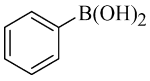
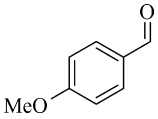
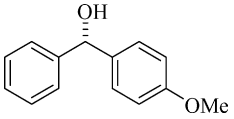
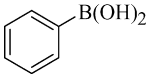
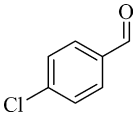
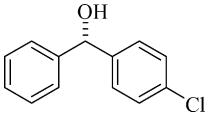
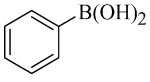
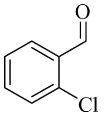
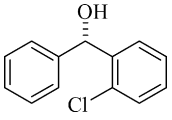
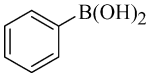
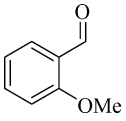
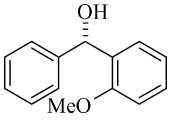
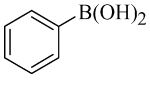
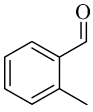
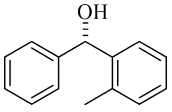
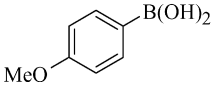
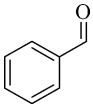
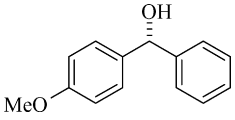
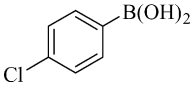
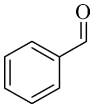
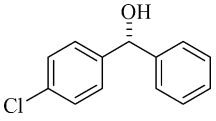
With ligand **2b** identified as the most effective, we examined the scope of our system in reactions with several aromatic aldehydes exhibiting diverse electronic and steric properties (Table 2).

A general trend with respect to yields was observed when electron donating and withdrawing substituents were compared. In the same way, the effect on the enantioselectivity was identified; electron donating substituents led to a decrease in enantiomeric excess while electron withdrawing substituents led to an increase. This resulted in an % ee value of 90% when a chloro substituent was present (entries 1 versus 2).

For the 2-chloro benzaldehyde, steric reasons or a potential chelating effect with the *ortho*-chloro substituent might be responsible for this relatively low ee (entry 3). The same argument could be relevant in the conversion of 2-methoxy benzaldehyde, which gave the desired product with 79% ee in 96% yield (entry 4). Interestingly, in contrast to the trends that have been observed previously, *ortho*-tolualdehydes gave higher ee

Table 2
Asymmetric phenyl transfer reaction to *o*- and *p*- substituted aldehydes initiatied with ligand 2b



Entry	Arylboronic acids	Aldehyde	Product	Yield[a] (%)	ee[b,c] (%)
1				87	86 (*S*)
2				98	90 (*S*)
3				98	80 (*S*)
4				96	79 (*S*)
5				92	96 (*S*)
6				97	60 (*R*)
7				85	72 (*R*)

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

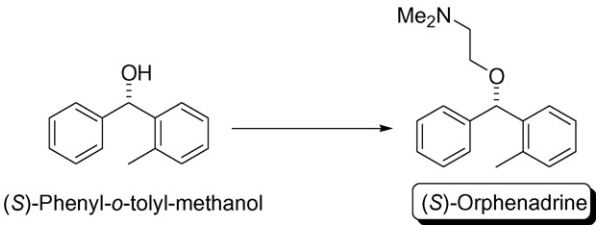


Fig. 1. Biologically active (*S*)-orphenadrine.

(96% ee) values than other substrates while employing ligand **2b** (entry 5).

In order to examine whether different aryl groups could be transferred also to aldehydes with high stereoselectivities while giving access to a range of substituted diaryl carbinols, the aryl transfer reactions of some substituted aryl boronic acids with benzaldehyde were studied. To our delight, excellent yields and good enantiomeric excesses were obtained (entries 6 and 7). For example, the aryl transfer reaction from 4-chlorophenyl boronic acid to benzaldehyde occurred in 72% ee (entry 7). This is one of the most interesting features of the methodology employed herein 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.

An application for the utilization towards important target molecules is shown in Fig. 1. The synthesis of a direct precursor for (*S*)-orphenadrine an anticholinergic and antihistaminic agent, can be achieved by the reaction of 2-tolualdehyde in quite high efficiency (ee = 96% and yield = 92%) [4].

3. Conclusions

In summary, we have described the asymmetric arylation of aldehydes in the presence of a catalytic amount of chiral amino alcohols readily available from norephedrine. The reactive arylzinc species is generated in situ via a boron–zinc exchange, using phenylboronic acids as a suitable source of transferable aryl groups, instead of employing the more expensive diphenylzinc and the air sensitive and flammable triphenylborane, respectively. Its reaction with aldehydes gives access to several chiral diaryl methanols in high yields and % ee's. The selectivities are comparable to the best ligands known for this transformation. The simple reaction protocol and the availability of substrates and ligands provide for an excellent opportunity for technical applications. Studies dealing with the mechanism of the reaction and application of this catalyst system in other asymmetric catalytic reactions are currently in progress in our laboratories.

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[11] General Procedure for the Asymmetric Arylation of Aldehydes: Diethylzinc (3.6 mmol, 1 M in toluene) was added dropwise 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 dimethoxy poly(ethylene glycol) (10 mol%, M_w = 1000 g/mol) dissolved in toluene (2 mL) is added. Then a toluene solution of chiral amino alcohol (20 mol%) was given to the solution. 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 hexane/ethyl acetate (90:10) afforded the pure diarylmethanols. HPLC-Analysis: All measurements were performed at a 20 °C column temperature using a UV detector at 254 nm. Phenyl(*p*-tolyl)methanol: Chiralcel OD, hexane/*i*-PrOH 90:10, 0.5 mL/min, (*S*): 19.1 min, (*R*): 21.1 min.

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