Catalytic enantioselective arylation of aldehydes: boronic acids as a suitable source of transferable aryl groups†

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The catalytic enantioselective arylation of several aldehydes using boronic acids as the source of transferable aryl groups is described; the reaction is found to proceed in excellent yields and high enantioselectivities (up to 97% ee) in the presence of a chiral amino alcohol.

Over the past decades, great progress has been made in the catalytic asymmetric addition of organozinc reagents to aldehydes using chiral amino alcohols as ligands, and products with excellent enantiomeric excesses have been achieved with all types of substrates.[1] More recently, the enantioselective arylation of aldehydes in the presence of a chiral ligand has received special attention since it gives access to chiral diarylmethanols, important precursors for pharmacologically and biologically important compounds.[2] Since the pioneering work of Fu,[3] several reports concerning the preparation of chiral diarylmethanols by arylzinc addition to aldehydes have been published.[4] One interesting approach to the synthesis of such compounds has been recently introduced by Bolm and co-workers.[5] It consists of using aryl boronic acids as the source of the transferable aryl group. This new methodology offers interesting advantages over the use of Ph_2Zn itself, or the most widely used Ph_2Zn–Et_2Zn mixture, because: (1) it allows the easy preparation of several substituted arylzinc reagents and therefore the synthesis of a wide range of substituted chiral diarylmethanols and (2) phenylboronic acids offer a cheaper alternative to the expensive diphenyl zinc.[6]

Since the catalytic asymmetric aryl transfer reaction to carbonyl compounds using boronic acids as the aryl source has not been extensively studied,[5,7] the search for efficient chiral ligands to generate high enantioselectivities in such reactions still remains an important challenge in this area.

In connection with our current interests in the asymmetric addition of organozinc reagents to aldehydes,[8] we describe herein our efforts toward the synthesis of optically active diarylmethanols, employing chiral β-amino alcohols as catalysts.[9] The modular structure of this type of ligands has attracted our attention since they are easily available in a few synthetic steps with a very flexible strategy.

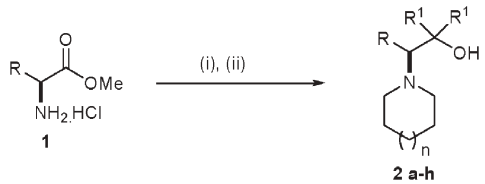
The chiral ligands were rapidly synthesized in a two step synthesis as described in Scheme 1. First, commercially available amino ester hydrochlorides were subjected to a double Grignard addition or hydride reduction to produce the corresponding amino alcohols, which were further converted to the aza-ring derivatives by treatment with diiodoalkane and potassium carbonate in boiling acetonitrile.

It is noteworthy that the structural features of amino alcohol **2** are easily changed at any step of the synthesis, since modifications can be introduced at several different positions of the molecule. For instance, these changes can be made in the R group, which corresponds to the amino acid residue, both R^1 groups, derived from the addition of the Grignard reagent, or the size of the nitrogen heterocycle.

With this sterically and electronically varied set of enantiopure amino alcohols in hand, we first examined the efficiency of these ligands as chiral catalysts in the enantioselective arylation of *p*-tolualdehyde with phenylboronic acid. The results of this study are depicted in Table 1.

All ligands were employed in the enantioselective arylation reaction and furnished the desired product in high yields with different levels of enantiocontrol. Initially we decided to examine the influence of the R^1 group while the R position was held constant as the aromatic ring of the side chain of phenylalanine (Table 1, Entries 1–5). Variations in the R^1 group have shown that it plays an import role in the enantioselectivity of the reaction and the best result was achieved with the catalyst with R^1 = Et (ee 92%, Entry 3). Steric factors appear to play the dominant role in determining enantioselectivity in this series of ligands. The size of the aza-ring is also important for the outcome of the reaction and a great decrease in the ee was observed when catalyst **2e**, with a smaller pyrrolidine ring was used instead of **2b** (compare Entries 3 and 8). Reaction temperature does not seem to have a significant impact on the enantioselectivity, which conveniently simplifies the experimental procedure. The influence of the solvent was also examined. The use of toluene is crucial for a high enantioselectivity, since lower ees were obtained by employing hexane and a mixture of toluene–hexane (Entries 3, 6 and 7). This fact is probably due to a poor solubility of the reactive zinc species resulting from the boron–zinc exchange reaction.

Extending our studies to other ligands with variations at the R position, we could gratifyingly observe that ligand **2f** (R = *i*-Pr,



Scheme 1 General synthesis of ligands **2**. *Reagents and conditions:* (i) 5 equiv. R^1MgBr, THF, rt; (ii) diiodoalkane, K_2CO_3, CH_3CN, reflux.

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b5/b501485a/

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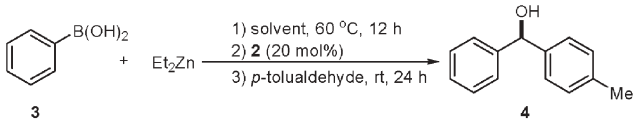
Table 1 Catalytic arylation of *p*-tolualdehyde with phenylboronic acid[a]



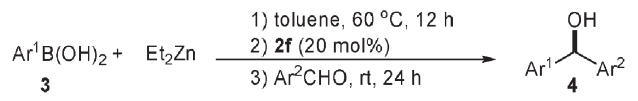
Entry	Ligand	R	R^1	*n*	Solvent	Yield[b] (%)	ee[c,d] (%)
1	**2a**	Bn	Ph	1	Toluene	93	70 (*R*)
2[e]	**2a**	Bn	Ph	1	Toluene	88	70 (*R*)
3	**2b**	Bn	Et	1	Toluene	97	92 (*R*)
4	**2c**	Bn	Me	1	Toluene	95	62 (*R*)
5	**2d**	Bn	H	1	Toluene	88	07 (*R*)
6[f]	**2b**	Bn	Et	1	Toluene–hexane	95	70 (*R*)
7	**2b**	Bn	Et	1	Hexane	64	50 (*R*)
8	**2e**	Bn	Et	0	Toluene	95	65 (*R*)
9	**2f**	*i*-Pr	Et	1	Toluene	97	97 (*R*)
10	**2g**	*s*-Bu	Et	1	Toluene	98	91 (*R*)
11	**2h**	*i*-Bu	Et	1	Toluene	88	91 (*R*)

[a] Reactions were performed on a 0.5 mmol scale with $PhB(OH)_2$ (2.4 equiv.) and Et_2Zn (7.2 equiv.) in toluene (first at 60 °C for 12 h, then at room temperature for 24 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 literature data.[4e,5] [e] Reaction was carried out at 0 °C. [f] A 1:1 mixture of toluene and hexane was used as solvent.

R^1 = Et, *n* = 1) had the best performance, delivering product **4** in a high yield and in an excellent ee of 97% (Table 1, Entry 9).

With ligand **2f** 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. Reactions with *o*- and *p*-tolualdehyde underwent smooth aryl addition in very high enantiomeric excesses and with nearly quantitative yields (Table 2, Entries 1 and 2). When *o*- and *p*-methoxybenzaldehyde were employed, decreased enantiomeric excesses of the corresponding products were achieved (Entries 3 and 4). On the other hand, when electron-withdrawing groups were present in the aldehyde, the enantioselectivity was also lower than when *p*-tolualdehyde was used. With regard to steric effects, we observed that steric hindrance does not play an important role in determining the degree of enantioselection. For instance, *ortho*-substituted benzaldehydes underwent aryl transfer with the same level of enantioselectivity as their *para* analogues (compare Entries 1 *vs.* 2 and Entries 3 *vs.* 4).

Table 2 Catalytic arylation of aldehydes with aryl boronic acids



Entry	Ar^1	Ar^2	Yield[a] (%)	ee[b,c] (%)
1	Phenyl	4-Methylphenyl (**4a**)	97	97 (*R*)
2	Phenyl	2-Methylphenyl (**4b**)	93	97 (*R*)
3	Phenyl	4-Methoxyphenyl (**4c**)	97	81 (*R*)
4	Phenyl	2-Methoxyphenyl (**4d**)	98	81 (*R*)
5	Phenyl	4-Chlorophenyl (**4e**)	87	89 (*R*)
6	Phenyl	2-Chlorophenyl (**4f**)	85	88 (*R*)
7	Phenyl	2-Bromophenyl (**4g**)	91	89 (*R*)
8	4-Methylphenyl	Phenyl (**4a**)	98	88 (*S*)
9	4-Methoxyphenyl	Phenyl (**4c**)	98	94 (*S*)
10	4-Chlorophenyl	Phenyl (**4d**)	97	94 (*S*)

[a] Isolated yield of the corresponding product. [b] Enantiomeric excesses were determined by chiral HPLC. [c] Configuration determined by comparison with literature data.[4e,5]

In order to examine if different aryl groups could be transferred to aldehydes with the same stereoselectivity, giving access to a range of substituted diaryl carbinols, the aryl transfer reactions of some substituted aryl boronic acids with benzaldehyde were studied and, to our delight, excellent yields and enantiomeric excesses were obtained (Entries 8–10). For example, the aryl transfer reaction from 4-methoxyphenyl boronic acid to benzaldehyde occurred in 94% ee (Entry 9).

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.

In summary, we have described the asymmetric arylation of aldehydes in the presence of a catalytic amount of chiral amino alcohol. The reactive arylzinc species is generated *in situ* from a boron–zinc exchange[10] instead of employing the more expensive diphenylzinc and its reaction with aldehydes gives access to several chiral diaryl methanols in high yields and ees. The selectivities are comparable to the best ligand known for this reaction. 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 laboratory.

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