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Catalyzed Asymmetric Aryl Transfer Reactions to Aldehydes with Boronic Acids as Aryl Source

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Chiral diaryl methanols **1** are important intermediates for the synthesis of biologically active compounds.[1] Two general approaches exist for their catalytic enantioselective synthesis. They can either be obtained by reduction of the corresponding unsymmetrical diaryl ketones[2] or are accessible by enantioselective aryl transfer reactions to aldehydes.[3−5] However, both methods have severe limitations and work well only for a limited range of substrates. For example, the reduction methodology requires the presence of an *ortho* substituent on one of the aryls or electronically very different aryl groups. In the catalyzed additions to aldehydes, only phenyl transfer reactions have been developed to a satisfying level affording arylphenylmethanols with high enantioselectivities. Other protocols employing arylboronic acids,[6] arylstannanes,[7] or arylsilanes[8] are either nonasymmetric or lead to products with low enantiomeric excess.[9] Here, we report on a new approach toward optically active diaryl methanols, which employs readily accessible, commercially available arylboronic acids as aryl source. The catalysis with ferrocene **2** is easy to perform and yields a broad range of products with excellent enantioselectivities.

Currently, the most successful asymmetric aryl tranfer reactions rely on the use of pure diphenylzinc.[4,5] In principle, diarylzincs can be prepared from lithium or Grignard reagents by transmetalations, but in this case their preparation is tideous since salt-free reagents are required for achieving high enantioselectivities.[10] Furthermore, many functionalized diarylzincs remain inaccessible due to the high reactivity of the intermediate lithium or magnesium reagents. We therefore initiated a study on the applicability of other organometallic reagents in asymmetric aryl transfer reactions, and our first attempts were focused on the use of **3**, since arylboronic acid esters can easily be prepared under mild conditions from the corresponding aryl halides by palladium catalysis[11] or through condensation reaction of the arylboronic acid with the appropriate diol.[12] To our delight we found that after optimizing the reaction conditions, **1a** could indeed be obtained in high yield and with excellent ee using phenyl boronic ester **3** and *p*-chlorobenzaldehyde (**4a**) as starting materials (Scheme 1). Unfortunately, the purification of **1a** was difficult due to the presence of boron-containing byproducts, which were difficult to separate from the target compound. Assuming that the process involved an arylzinc species, which was formed in situ by boron-to-zinc exchange,[13] we decided to attempt to further simplify the catalysis by using arylboronic acids as aryl source. In this case, the transmetalation required harsher reaction conditions than before, and the procedure involved stirring of a toluene solution of the arylboronic acid in the presence of a 3-fold excess of $ZnEt_2$ at 60 °C for 12 h prior to the catalysis (with 10 mol % of **2** at 10 °C).[14] Starting from phenylboronic acid (**5a**) and various aldehydes **3**, this new protocol afforded arylphenylmethanols **1a**−**e** with ee values of up to 95% (Table 1).

Scheme 1

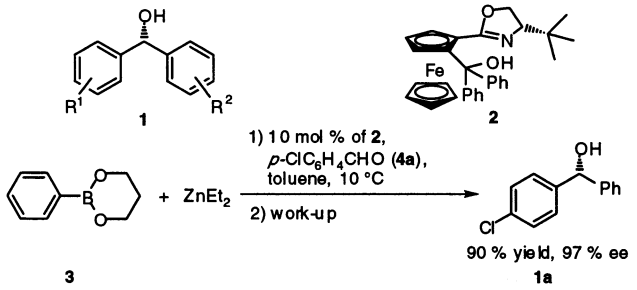
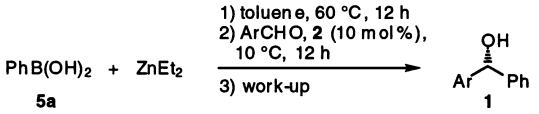


Table 1. Catalyzed Phenyl Transfer from **5a** to Various Aldehydes[a]



entry	aldehyde (ArCHO)	product	% yield[b]	% ee[c,d]
1	4-chlorobenzaldehyde (**4a**)	**1a**	95	92 (*R*)
2	4-biphenylcarbaldehyde (**4b**)	**1b**	93	95
3	4-methylbenzaldehyde (**4c**)	**1c**	88	90
4	ferrocenecarbaldehyde (**4d**)	**1d**	33	94
5	2-methoxybenzaldehyde (**4e**)	**1e**	79	90

[a] In toluene, 10 mol % of **2**, 7.2 equiv of $ZnEt_2$, and 2.4 equiv of $PhB(OH)_2$ with respect to ArCHO. [b] After column chromatography. [c] Determined by HPLC using a chiral stationary phase. [d] Comparison of the HPLC peak elution order of **1a** with known data revealed that the *R* enantiomer was formed in excess. Assuming an analogous mechanism for the aryl transfer and based on the HPLC elution order, we assume that the other products have *R* configuration as well.

Compared to the results obtained by the original protocol involving aryl transfer reagents derived from pure diphenylzinc,[5] those ee values are very good. Furthermore, even substrate **4e** bearing an *ortho* substituent, which previously proved to be difficult, afforded the corresponding product in good yield and with high ee (Table 1, entry 5).

Next, we investigated the possibility to vary the structure of the aryl source and studied the asymmetric aryl transfer from various (commercially available) substituted phenylboronic acids (**5a**−**i**) to benzaldehyde (**4f**) (Table 2).

To our delight we found that even some substituted aryls were transferred very well, affording the corresponding products in good yields and with high ee. Unfortunately, arylboronic acids with *ortho* substituents and those with other sterically more demanding groups were problematic and both product yield and enantioselectivity were lower (Table 2, entries 4, 7, and 8). Presumably due to hindered transmetalation, *ortho*-disubstituted **5f** did not react at all (Table 2, entry 5).

Since previous studies on the aryl transfer from diphenylzinc-derived arylation reagents had shown that the presence of polyethers

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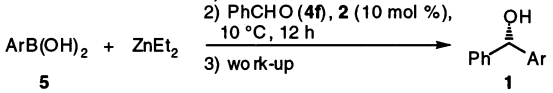
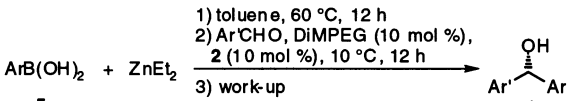
Table 2. Catalyzed Aryl Transfer from **5** to Benzaldehyde (**4f**)[a]



entry	$ArB(OH)_2$ with Ar =	product	% yield[b]	% ee[c,d]
1	4-chlorophenyl (**5b**)	**1a**	89	95 (*S*)
2	4-biphenyl (**5c**)	**1b**	75	65
3	4-methylphenyl (**5d**)	**1c**	87	89
4	2-methoxyphenyl (**5e**)	**1e**	77	45
5	2,6-dimethylphenyl (**5f**)	**1f**	<5	n.d.
6	4-methoxyphenyl (**5g**)	**1g**	84	80
7	1-naphthyl (**5h**)	**1h**	56	31
8	2-bromophenyl (**5i**)	**1i**	54	73
9	4-bromophenyl (**5j**)	**1j**	94	80

[a–c] See Table 1. [d] Comparison of the HPLC peak elution order of **1a** with known data revealed that the *S* enantiomer was formed in excess. Assuming an analogous mechanism for the aryl transfer and based on the HPLC elution order, we assume that the other products have *S* configuration as well.

Table 3. Catalyzed Aryl Transfer from **5** to Aldehydes (**4**) in the Presence of DiMPEG[a]



entry	$ArB(OH)_2$ with Ar =	Ar′CHO	product	% yield[b]	% ee[c]
1	phenyl (**5a**)	**4a**	**1a**	93	97 (*R*)
2	4-chlorophenyl (**5b**)	**4f**	**1a**	61	97 (*S*)
3	4-biphenyl (**5c**)	**4f**	**1b**	75	97
4	4-methylphenyl (**5d**)	**4f**	**1c**	91	96
5	4-methoxyphenyl (**5g**)	**4f**	**1g**	86	90
6	1-naphthyl (**5h**)	**4f**	**1h**	91	85
7	2-bromophenyl (**5i**)	**4f**	**1i**	58	88
8	4-bromophenyl (**5j**)	**4f**	**1j**	48	96
9	phenyl (**5a**)	**4d**	**1d**	85	98

[a] In toluene, 10 mol % of **2**, 10 mol % of DiMPEG, 7.2 equiv of $ZnEt_2$, and 2.4 equiv of $ArB(OH)_2$ with respect to Ar′CHO. [b,c] See Table 1.

could lead to a significant increase in enantioselectivity at low catalyst loading,[15] we decided to investigate the influence of such modifiers in this new protocol as well. Gratisfyingly, this improved the process even further. Thus, by the addition of 10 mol % of DiMPEG (M = 2000 g·mol^{-1}) to the reaction mixture, higher ee values were achieved for a wide range of substrates (Table 3).

In particular, arylboronic acids, which previously gave unsatisfying results, showed a strong effect. For example, the aryl transfer starting from 1-naphthylboronic acid (**5h**) and benzaldehyde (**1f**) now afforded **1h** in 91% yield having 85% ee (Table 3, entry 6). In the absence of the polyether, this reaction gave **1h** in only 56% yield and 31% ee (Table 2, entry 7).

In summary, we developed a flexible method for the catalyzed synthesis of optically active diarylmethanols with very high enantiomeric excesses from readily available starting materials. Noteworthy is the fact that with a single catalyst both enantiomers of the product are accessible simply by choosing the appropriate combination of arylboronic acid or aldehyde as aryl donor and acceptor, respectively.

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Supporting Information Available: Separation conditions of the diarylmethanols on chiral HPLC system. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Meguro, K.; Aizawa, M.; Sohda, T.; Kawamatsu, Y.; Nagaoka, A. *Chem. Pharm. Bull.* **1985**, *33*, 3787. (b) Toda, F.; Tanaka, K.; Koshiro, K. *Tetrahedron: Asymmetry* **1991**, *2*, 873. (c) Stanev, S.; Rakovska, R.; Berova, N.; Snatzke, G. *Tetrahedron: Asymmetry* **1995**, *6*, 183. (d) Botta, M.; Summa, V.; Corelli, F.; Pietro, G. Di; Lombardi, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1263.

(2) (a) Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659. (b) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153. (c) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 4837.

(3) (a) Soai, K.; Kawase, Y.; Oshio, A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1613. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (c) For a diastereoselective version, see: Hübscher, J.; Barner, R. *Helv. Chim. Acta* **1990**, *73*, 1068.

(4) (a) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444. (b) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7940. (c) Huang, W.-S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 145. (d) Blacker, J. In *Third International Conference on the Scale Up of Chemical Processes*, Conference Proceedings, Laird, T., Ed.; Scientific Update: UK, 1998; p 74.

(5) (a) Bolm, C.; Muñiz, K. *Chem. Commun.* **1999**, 1295. (b) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem., Int Ed.* **2000**, *39*, 3465. (c) Bolm, C.; Kesselgruber, M.; Hermanns, N.; Hildebrand, J. P. *Angew. Chem., Int. Ed.* **2001**, *39*, 1488. (d) Bolm, C.; Kesselgruber, M.; Grenz, A.; Hermanns, N.; Hildebrand, J. P. *New J. Chem.* **2001**, *25*, 13. (e) Bolm, C.; Hermanns, N.; Kesselgruber, M.; Hildebrand, J. P. *J. Organomet. Chem.* **2001**, *624*, 157. (f) For a recent review on catalyzed asymmetric arylation reactions, see: Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284.

(6) (a) Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 4450. (b) Fürstner, A.; Krause, H. *Adv. Synth. Catal.* **2001**, *343*, 343.

(7) Oi, S.; Moro, M.; Inoue, V. *Chem. Commun.* **1997**, 1621.

(8) (a) Oi, S.; Moro, M.; Inoue, Y. *Organometallics* **2001**, *20*, 1036. (b) Murata, M. Shimazaki, R.; Ishikura, M.; Watanabe, S.; Masuda, Y. *Synthesis* **2002**, 717.

(9) For an enantioselective Rh-catalyzed aryl transfer reaction using phenylboronic acid as aryl source (41% ee), see: Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 3279.

(10) Presumably, the Lewis-acidic achiral metal salts, which are formed during the transmetalation, catalyze the aryl transfer as well and afford racemic products. By this parallel reaction the overall enantioselectivity of the process is reduced.

(11) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447. (c) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458. (d) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164. (e) Baidoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268.

(12) For recent developments in this area, see: Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394 and references therein.

(13) For B-to-Zn exchange reactions involving alkenylboranes, see: (a) Srebnik, M. *Tetrahedron Lett.* **1991**, *32*, 2449. (b) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170. (c) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593. (d) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229. (e) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414. (f) Dahmen, S.; Bräse, S. *Org. Lett.* **2001**, *3*, 4119.

(14) A toluene solution (3 mL) of the boronic acid (2.4 equiv) is mixed with neat diethylzinc (7.2 equiv) in a sealed vessel under argon atmosphere. After 12 h of stirring at 60 °C, the vessel is cooled to 10 °C and a toluene solution of ferrocene **2** (10 mol %) is added. The mixture is stirred for additional 15 min and the aldehyde (1 equiv) is subsequently added. After stirring overnight followed by standard workup as described earlier,[5] the diarylmethanols are obtained in analytically pure form after column chromatography (silica gel, pentane:diethyl ether = 85:15).

(15) Bolm, C.; Hermanns, N.; Rudolph, J., manuscript in preparation.

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