Asymmetric Catalysis

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From Aryl Bromides to Enantioenriched Benzylic Alcohols in a Single Flask: Catalytic Asymmetric Arylation of Aldehydes**

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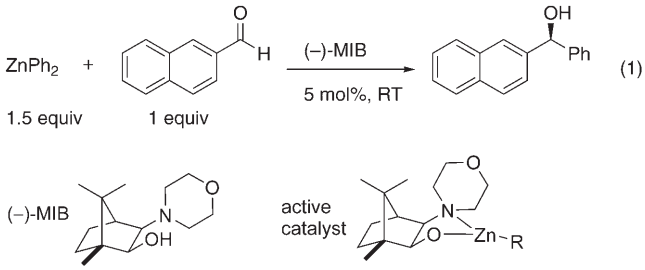
Dedicated to Professor Madeleine Joullié

The catalytic asymmetric addition of aryl groups to aldehydes has generated an enormous amount of attention.[1] The resulting diarylmethanols are important constituents of biologically active compounds, such as clemastine,[2] orphenadrine,[3,4] neobenodine,[3,4] chloropheniramine,[5,6] cizolirtine,[7] and carbinoxamine.[8] Although the majority of enantioselective aldehyde arylation reactions rely on the use of costly diphenylzinc ($55–75 g^{-1}), important advances in the use of other aryl transfer reagents, such as arylboronic acids[9,10] and $Ph_2Si(OMe)_2$,[11] have been reported. Although a limited number of aryl boronic acids are commercially available, they are quite expensive as well (e.g., $PhB(OH)_2$ $225.00 mol^{-1} from Aldrich). A more practical and versatile method would begin with aryl bromides, many of which are commercially available and inexpensive (compare PhBr $2.50 mol^{-1} from Aldrich). There are no reports, however, of successful catalytic asymmetric aryl additions to aldehydes that begin with aryl bromides.[12,13] Herein, we disclose a one-pot method that begins with aryl bromides for the in situ generation of aryl zinc intermediates and their catalytic asymmetric addition to aldehydes to afford highly enantioenriched diarylmethanols and benzylic alcohols.

We chose to examine the amino alcohol ligand MIB developed by Nugent[14,15] in the asymmetric addition of commercial $ZnPh_2$ to 2-naphthylaldehyde [Eq. (1)]. We were



pleased to find that phenylation proceeded in toluene with 94% enantioselectivity (Table 1, entry 1). Unfortunately, transmetalation of phenyllithium with $ZnCl_2$ in toluene was unsuccessful because of the insolubility of $ZnCl_2$ in this medium. In contrast, ethereal solvents are known to promote transmetalation reactions. The asymmetric addition in diethyl ether, however, gave a low enantioselectivity (60%; Table 1, entry 2). In an attempt to balance both the solvating properties of diethyl ether, needed for the transmetalation, and the low polarity of toluene, we examined *tert*-butyl methyl ether (*t*BuOMe). A reaction mixture of commercial $ZnPh_2$, (−)-MIB, and 2-naphthylaldehyde in *t*BuOMe furnished the product in 88% *ee* (Table 1, entry 3). A solvent system of *t*BuOMe and hexanes (1:3) exhibited about the same

Table 1: Commercially available $ZnPh_2$ versus $ZnPh_2$ formed in situ.

Entry	$ZnPh_2$	Solvent	*ee* [%]
1	commercial	toluene	94
2	commercial	Et_2O	60
3	commercial	*t*BuOMe	88
4	commercial	*t*BuOMe/Hex (1:3)	89
5	in situ	*t*BuOMe/Hex (1:3)	2

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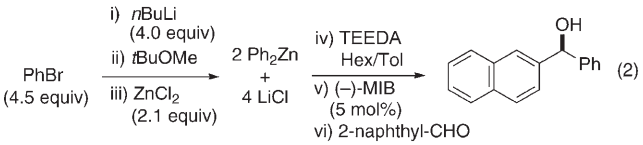
enantioselectivity as *t*BuOMe alone (89%; Table 1, entry 4). Having identified a suitable solvent for the asymmetric addition, we focused on the in situ generation of diphenylzinc.

The preparation of $ZnPh_2$ was performed by metalation of 4.5 equivalents bromobenzene in *t*BuOMe with 4 equivalents of a freshly titrated solution of *n*BuLi (2.5 M in hexanes), transmetalation of the resultant PhLi with 2.1 equivalents of $ZnCl_2$, and the addition of hexanes to precipitate LiCl. The use of solutions prepared as described in the asymmetric addition to 2-naphthylaldehyde in the presence of 5 mol% of (−)-MIB resulted in the formation of the product with 2% enantioselectivity (Table 1, entry 5). We hypothesized that the LiCl, generated en route to $ZnPh_2$, likely promoted the addition faster than the amino alcohol based catalyst promotes the asymmetric addition. Similar proposals were advanced by Seebach[12] and Bolm[16] in reactions that began with Grignard reagents or PhLi. Based on their observations, we set out to design an inhibitor to reduce the undesired LiCl promoted addition.

To develop a selective inhibitor for lithium chloride we took advantage of the differences in coordination chemistry between the lithium salts and the zinc-based catalyst. It is proposed that three coordinate amino alcohol based catalysts possess a single open coordination site [Eq. (1)].[17] In contrast, the lithium salts likely have at least two available coordination sites. Structures of $[tmeda{\cdot}LiCl]_n$ (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylene diamine) contain four-coordinate lithium centers with bridging chlorides.[18,19] Furthermore, we expected that the zinc catalyst is more sterically saturated than the lithium salts. Based on these points, we chose to examine bulky multidentate diamines as inhibitors that would chelate to lithium, but bind to the zinc catalyst in a monodentate fashion.

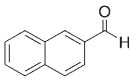
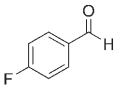
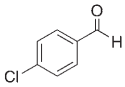
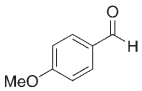
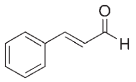
A series of chelating diamines was evaluated as LiCl inhibitors in the asymmetric addition with $ZnPh_2$ prepared in situ under the conditions employed in Table 1, entry 5. In this study, it was found that addition of toluene (or hexanes) after transmetalation aided the precipitation of the lithium salts. Subsequent injection of tetraethylethylene diamine (TEEDA, 0.8 equiv) resulted in addition with 89% enantioselectivity, the same value obtained under salt-free conditions with commercially available diphenylzinc [Eq. (2) and Table 1, entry 4]. Achieving of the same enantioselectivity in the absence or presence of LiCl indicates that the diamine effectively inhibits the LiCl-promoted addition pathway.



(2)

Under the conditions outlined above, unfunctionalized aryl bromides (bromobenzene, 2-bromotoluene, and 2-bromonaphthalene) were employed to prepare diarylzinc reagents [Eq. (2)]. TEEDA was then added followed by MIB and the aldehyde. In this fashion, aryl aldehydes gave addition products with high enantioselectivities (80–92%) and yields (78–99%). *trans*-Cinnamaldehyde and cyclohexanecarboxaldehyde underwent addition with 84 and 85% enantioselectivities (Table 2, entries 12 and 13, respectively).

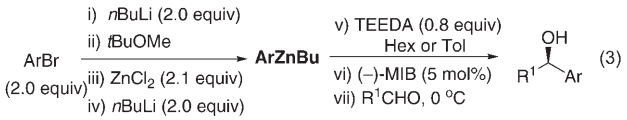
Table 2: Catalytic asymmetric aryl additions to aldehydes from Ar_2Zn.

Entry	ArBr	Aldehyde	*ee* [%]	Yield [%]
1	phenyl		92	99
2	2-tolyl		92	90
3	2-naphthyl		89	96
4	phenyl		84	89
5	2-tolyl		80	92
6	phenyl		90	85 (*S*)[a]
7	2-tolyl		80	86
8	2-naphthyl		87	96
9	phenyl		90	90 (*S*)[a]
10	2-tolyl		87	78
11	2-naphthyl		91	99
12	phenyl		84	91
13	phenyl		85	92
14	2-naphthyl		82	92

[a] Absolute configuration.

During early investigations of phenyl additions with $ZnPh_2$, it was realized that the uncatalyzed addition was fast and competitive with the catalyzed reaction pathway, thus resulting in low enantioselectivity.[20–22] To circumvent this problem, Bolm and co-workers introduced the mixed zinc reagent Et/Zn/Ph formed from combination of $ZnEt_2$ and $ZnPh_2$.[22–28] Enantioselectivities with Et/Zn/Ph and planar chiral catalyst were up to 38% higher than those that employed the same catalyst with $ZnPh_2$ alone.

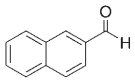
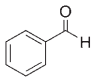
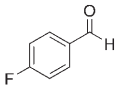
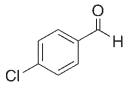
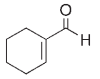
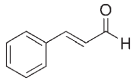
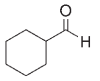
Based on the successful application by Bolm of mixed alkyl aryl zinc reagents,[9] we wished to develop an in situ route to these species to increase the levels of enantioselectivity in the aryl addition reactions. In our strategy to prepare the mixed alkyl aryl zinc intermediates in situ, we chose to avoid the use of dialkyl zinc reagents and focused on the more readily available alkyl lithium reagents instead. Thus, 2.0 equivalents of aryl bromide and 2.1 equivalents of $ZnCl_2$ were employed. Metalation of PhBr with *n*BuLi and addition to $ZnCl_2$ resulted in the generation of Ph/Zn/Cl. A second equivalent of *n*BuLi was then added to produce Ph/Zn/Bu, which was used in situ in the asymmetric addition reaction after the addition of 0.8 equivalents of TEEDA [Eq. (3)]. We were pleased to find that the enantioselectivity observed with



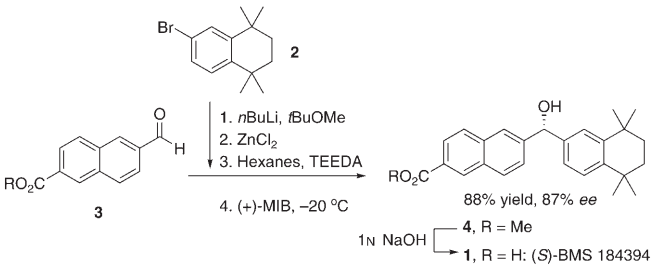
the Ph/Zn/Bu generated in situ was higher than that with Ph_2Zn and equal to that of Ph/Zn/Et (generated from commercial Ph_2Zn and Et_2Zn), despite the 4 equivalents of LiCl formed in the preparation of Ph/Zn/Bu.

A variety of substituted and functionalized aryl bromides underwent enantioselective addition to benzaldehyde derivatives under the conditions in Equation (3) with enantioselectivities around 95% (Table 3, entries 2–9). These include 2-bromotoluene, 2-bromonaphthylene, 4-bromoanisole, 4-bromofluorobenzene, and 4-bromochlorobenzene. α,β-Unsaturated aldehydes underwent addition with enantioselectivities between 81 and 88%, whereas cyclohexanecarboxaldehyde again gave slightly lower enantioselectivities (78 and 82%). The results in Table 3 indicate that various aryl bromides can now be employed as starting materials in the catalytic asymmetric arylation of aldehydes.

Table 3: Catalytic asymmetric aryl additions to aldehydes with ArZnBu.

Entry	ArBr	Aldehyde	*ee* [%]	Yield [%]
1	Ph_2Zn + Et_2Zn		97	98
2	phenyl		97	90
3	4-methoxyphenyl		93	96
4	4-fluorophenyl		97	75
5	4-chlorophenyl		95	78
6	phenyl		96	80
7	4-methoxyphenyl		93	84
8	2-tolyl		95	73
9	2-naphthyl		96	79
10	4-methoxyphenyl		83	82
11	4-fluorophenyl		88	64
12	4-chlorophenyl		87	55
13	phenyl		88	95
14	4-fluorophenyl		84	74
15	4-chlorophenyl		81	68
16	2-naphthyl		82	76
17	4-methoxyphenyl		78	84

To demonstrate the utility of our method, we chose to prepare the precursor to BMS184394 (**1**, Scheme 1), an retinoic acid receptor (RAR) γ-selective retinoid with activity against various skin diseases and cancers, in particular breast cancer and acute promyelocytic leukemia.[29–31] Although



Scheme 1. Formal synthesis of (*S*)-BMS184394.

both (*R*)- and (*S*)-BMS184394 are RAR γ-selective, the *S* enantiomer is significantly more potent than the *R* enantiomer.[30] Enantioselective synthesis of this compound proved difficult. Currently, the only enantioselective route to this drug candidate employed two sequential enzymatic kinetic resolutions that required 2 and 3.5 days (43% yield and 95% *ee*).[30] As with any kinetic resolution, the maximum yield is 50% and the desired compound must be separated from the undesired derivatized product. In principle, secondary diarylmethanols could be prepared enantioselectively by asymmetric reduction of diaryl ketones. This approach has proven quite challenging, however, because it is difficult for catalysts to differentiate between the lone pairs on the carbonyl oxygen atom when the aryl groups are similar in size, thus resulting in low enantioselectivities.[32–36]

Using our method, 3.0 equivalents aryl bromide (**2**, Scheme 1) were combined with *n*BuLi followed by $ZnCl_2$ to generate the mixed aryl butyl zinc reagent. TEEDA (1.5 equiv) in hexanes was added followed by (+)-MIB (5 mol%) and the aldehyde **3**. The addition product **4** was produced with 87% enantioselectivity in 88% yield (Scheme 1). Conversion into (*S*)-BMS184394 can be accomplished by saponification of the ester.[30] The one-pot enantioselective arylation of **3** demonstrates the potential utility of our method for the synthesis of enantioenriched biologically active benzylic alcohols.

In summary, we have developed a versatile method to generate secondary benzylic alcohols with high levels of enantioselectivity and yields. The importance of this method is that one can now begin the asymmetric arylation of aldehydes with aryl bromides, many of which are readily available. In contrast, previous methods employed preformed aryl boron reagents to generate salt-free aryl zinc intermediates or began with diphenylzinc. The introduction of a diamine, such as TEEDA, was the key to the success of this method. In the absence of TEEDA, the addition reaction is promoted by LiCl, thus generating racemic products. TEEDA prohibits the LiCl by-product from promoting the addition reaction, thus allowing the addition to proceed through the chiral zinc catalyst. Importantly, it is not necessary to filter,[16] centrifuge,[13] or isolate the pyrophoric aryl zinc reagents, as required with previous methods, in the presence of the diamine, thus increasing the attractiveness of our method for large-scale applications. This method enables the synthesis of a variety of benzylic alcohols that were previously difficult to access in enantioenriched form.

Experimental Section

Preparation of (4-fluorophenyl-4-methoxyphenyl)methanol (Table 3, entry 7): A nitrogen-purged Schlenk flask was charged with 4-bromoanisole (100.1 μL, 0.8 mmol) and *t*BuOMe (1 mL) and cooled to −78 °C. Freshly titrated *n*BuLi (0.32 mL, 2.5 M in hexanes, 0.8 mmol) was added dropwise, and the solution was stirred for 1 h. The dry-ice bath was replaced with an ice bath, $ZnCl_2$ (114.5 mg, 0.84 mmol) was added, and the reaction mixture was stirred for 30 min. Additional *n*BuLi (0.32 mL, 2.5 M in hexanes, 0.8 mmol) was added to the reaction mixture, which was then stirred for 4.5 h at room temperature. Toluene (5 mL) and TEEDA (68 μL, 0.32 mmol) were added, and the solution was stirred for 1 h. After the addition of (−)-MIB (4.8 mg, 0.02 mmol, 5 mol %), the reaction cooled to 0 °C for 30 min, and *p*-fluorobenzaldehyde (43 μL, 0.4 mmol) was added. The reaction was stirred at 0 °C and monitored by TLC. After completion (18 h), the reaction mixture was quenched with H_2O (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc, 95:5) to give the product (77.7 mg, 84 % yield, 93 % *ee*) as a white solid. M.p. 52 °C; $[\alpha]_D^{20} = (+)13.846$ ($c = 0.195$, THF); ^{1}H NMR (C_6D_6, 300 MHz): $\delta = 2.17$ (s, 1H), 3.38 (s, 3H), 5.50 (s, 1H), 6.81–6.95 (m, 4H), 7.17–7.29 (m, 4H) ppm; $^{13}C\{^1H\}$ NMR (C_6D_6, 75 MHz): 55.0, 75.3, 114.3, 115.4 (d, $J = 21.2$ Hz), 128.4, 128.7 (d, $J = 8.0$ Hz), 136.9, 141.0 (d, $J = 3.0$ Hz), 159.7, 162.6 ppm (d, $J = 243$ Hz); IR (neat): $\tilde{\nu} = 3421$, 2957, 2837, 1609, 1504, 1248, 1033, 831 cm^{-1}; HRMS calcd for $C_{13}H_{13}FO_2$ $[M]^+$: 232.0900, found: 232.0900; determination conditions for the *ee*: Chiralpak AS-H, hexanes/isopropylamine (95:5), flow rate = 0.5 mL min^{-1}, $t =$ 20.0 min, 22.1 min.

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[1] C. Bolm, J. P. Hildebrand, K. Muñiz, N. Hermanns, *Angew. Chem.* **2001**, *113*, 3382; *Angew. Chem. Int. Ed.* **2001**, *40*, 3284.
[2] A. Ebnother, H.-P. Weber, *Helv. Chim. Acta* **1976**, *59*, 2462.
[3] A. F. Casy, A. F. Drake, C. R. Ganellin, A. D. Mercer, C. Upton, *Chirality* **1992**, *4*, 356.
[4] P. Müller, P. Nury, G. Bernardinelli, *Eur. J. Org. Chem.* **2001**, 4137.
[5] M. N. G. James, G. J. B. Williams, *Can. J. Chem.* **1974**, *52*, 1872.
[6] A. Shafi'ee, G. Hite, *J. Med. Chem.* **1969**, *12*, 266.
[7] A. Torrens, J. A. Castrillo, A. Claparols, J. Redondo, *Synlett* **1999**, 765.
[8] V. Barouh, H. Dall, D. Patel, G. Hite, *J. Med. Chem.* **1971**, *14*, 834.
[9] C. Bolm, J. Rudolph, *J. Am. Chem. Soc.* **2002**, *124*, 14850.
[10] J. Rudolph, F. Schmidt, C. Bolm, *Synthesis* **2005**, 840.
[11] D. Tomita, R. Wada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 4138.
[12] Two additions of aryl groups to aldehydes beginning from aryl bromides are reported; each gave less than 10 % enantioselectivity; see: B. Weber, D. Seebach, *Tetrahedron* **1994**, *50*, 7473.
[13] Seebach reported that transmetalation of PhLi with [TiCl(O*i*Pr)$_3$] and addition to benzaldehydes gave high enantioselectivities only if the reactions were subject to centrifugation to remove LiCl and the addition of 30 mol % of [12]crown-4 to inhibit the remaining LiCl; see reference [12].
[14] W. A. Nugent, *Chem. Commun.* **1999**, 1369.
[15] Y. K. Chen, S. J. Jeon, P. J. Walsh, W. A. Nugent, *Org. Synth.* **2005**, *82*, 87.
[16] Generation of $ZnPh_2$ from PhLi and $ZnBr_2$ followed by filtration through Celite and addition of dimethoxy poly(ethylene glycol) (to inhibit traces of remaining LiBr) and addition to 4-chlorobenzaldehyde afforded the diaryl methanol in up to 93 % enantioselectivity in 8–31 % yield; see: J. Rudolph, N. Hermanns, C. Bolm, *J. Org. Chem.* **2004**, *69*, 3997.
[17] M. Kitamura, S. Okada, S. Suga, R. Noyori, *J. Am. Chem. Soc.* **1989**, *111*, 4028.
[18] D. Hoffmann, A. Dorigo, P. von R. Schleyer, H. Reif, D. Stalke, G. M. Sheldrick, E. Weiss, M. Geissler, *Inorg. Chem.* **1995**, *34*, 262.
[19] S. Chitsaz, J. Pauls, B. Neumüller, *Z. Naturforsch. B* **2001**, *56*, 245.
[20] P. I. Dosa, J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1997**, *62*, 444.
[21] W.-S. Huang, L. Pu, *J. Org. Chem.* **1999**, *64*, 4222.
[22] J. Rudolph, C. Bolm, P.-O. Norrby, *J. Am. Chem. Soc.* **2005**, *127*, 1548.
[23] C. Bolm, N. Hermanns, J. P. Hildebrand, K. Muñiz, *Angew. Chem.* **2000**, *112*, 3607; *Angew. Chem. Int. Ed.* **2000**, *39*, 3465.
[24] C. Bolm, M. Kesselgruber, N. Hermanns, J. P. Hildebrand, G. Raabe, *Angew. Chem.* **2001**, *113*, 1536; *Angew. Chem. Int. Ed.* **2001**, *40*, 1488.
[25] C. Bolm, N. Hermanns, M. Kesselgruber, J. P. Hildebrand, *J. Organomet. Chem.* **2001**, *624*, 157.
[26] S. Ozcubukcu, F. Schmidt, C. Bolm, *Org. Lett.* **2005**, *7*, 1407.
[27] J. Rudolph, T. Rasmussen, C. Bolm, P.-O. Norrby, *Angew. Chem.* **2003**, *115*, 3110; *Angew. Chem. Int. Ed.* **2003**, *42*, 3002.
[28] M. Fontes, X. Verdaguer, L. Solà, M. A. Pericàs, A. Riera, *J. Org. Chem.* **2004**, *69*, 2532
[29] B. P. Klaholz, A. Mitschler, D. Moras, *J. Mol. Biol.* **2000**, *302*, 155.
[30] K. L. Yu, P. Spinazze, J. Ostrowski, S. J. Currier, E. J. Pack, L. Hammer, T. Roalsvig, J. A. Honeyman, D. R. Tortolani, P. R. Reczek, M. M. Mansuri, J. E. Starrett, *J. Med. Chem.* **1996**, *39*, 2411.
[31] S. M. Thacher, J. Vasudevan, R. A. S. Chandraratna, *Curr. Pharm. Des.* **2000**, *6*, 25.
[32] R. Noyori, M. Yamakawa, S. Hashiguchi, *J. Org. Chem.* **2001**, *66*, 7931
[33] E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1996**, *37*, 4837.
[34] T. Ohkuma, M. Koizumi, H. Ikehira, T. Yokozawa, R. Noyori, *Org. Lett.* **2000**, *2*, 659.
[35] E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1995**, *36*, 9153.
[36] H. Ushio, K. Mikami, *Tetrahedron Lett.* **2005**, *46*, 2903.

