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Triarylborane Ammonia Complexes as Ideal Precursors for Arylzinc Reagents in Asymmetric Catalysis

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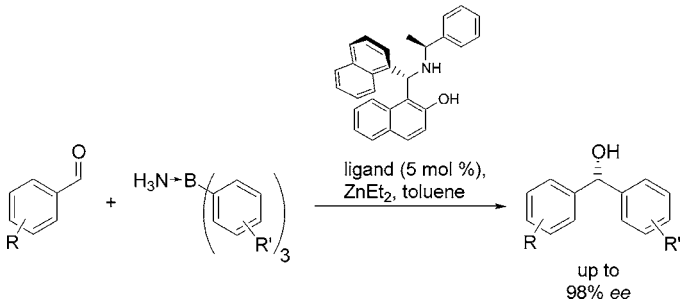
ABSTRACT



The value of arylboranes as precursors for arylzinc reagents in asymmetric catalysis is demonstrated. Kinetic studies on the transmetalation reaction with zinc reagents rationalize the observed differences of three classes of arylboranes in catalytic applications. By using the stable and easily accessible triarylborane ammonia complexes, an array of chiral diarylmethanols in high yield and enantioselectivity was synthesized.

Besides the transfer of alkyl, alkenyl, and alkynyl groups to aldehydes, the addition of aromatic zinc reagents and in particular diphenylzinc has attracted a lot of attention recently.[1] The products of this reaction are diarylmethanols, some of which are important precursors for pharmacologically active compounds.[2]

The advantage of arylzinc additions to aldehydes over other methods of making such diarylmethanol products (like hydrogenation[3] or CBS-reduction[4]) resides in the possibility of making products with electronically and sterically similar aryl rings.

The first protocols for the phenyl transfer to aldehydes relied on diphenylzinc as a phenyl source[5] and required at least 1 equiv of this expensive starting material for optimum enantioselectivity. Pu et al. initially even used methanol as an additive thus quenching a part of the reagent to obtain better results.[6] An improvement in terms of efficiency was made by adding diethylzinc to the reaction mixture.[7] It was

(1) For a review on arylation reactions, see: (a) Bolm, C.; Hildebrand, J. P.; Muniz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284. For recent additions to this field, see: (b) Ko, D.-H.; Kim, K. H.; Ha, D.-C. *Org. Lett.* **2002**, *4*, 3759. (c) Fontes, M.; Verdagner, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532. (d) Ji, J.-X.; Wu, J.; Au−Yeung, T. T.-L.; Yip, C.-W.; Haynes, R. K.; Chan, A. S. C. *J. Org. Chem.* **2005**, *70*, 1093. (e) Braga, A. L.; Lüdtke, D. S.; Vargas, F.; Paixão, M. W. *Chem. Commun.* **2005**, 2512.

(2) For selected active pharmaceutical ingredients (APIs), see: Cizolirtine (a) Torrens, A.; Castrillo, J. A.; Claparols, A.; Redondo, J. *Synlett* **1999**, *6*, 765. (b) Farré, A. J.; Frigola, J. *Drug. Future* **2002**, *27*, 721. Carbinoxamine: (c) Roszowski, A. P.; Govier, W. M. *Pharmacologist* **1959**, *1*, 60. (d) Hunt, J. H. *J. Chem. Soc.* **1961**, 2228. (e) Barouh, V.; Dall, H.; Patel, D.; Hite, G. *J. Med. Chem.* **1971**, *14*, 834. (f) James, M. N. G.; Williams, G. J. B. *Can. J. Chem.* **1974**, *52*, 1872.

(3) (a) Okhuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659. (b) Noyori, R.; Okhuma, T. *Pure Appl. Chem.* **1999**, *71*, 1493.

(4) (a) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153. (b) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 4837. (c) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 5675. (d) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

(5) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444.

(6) (a) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 5222. (b) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7940.

(7) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465.

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thus possible to reduce the necessary amount of diphenylzinc to 0.65 equiv and still transfer both aryl groups to the aldehyde. Mechanistic studies suggested that the active zinc species is a mixed phenylzincethyl, which is less active than diphenylzinc and thus more selective.[8,1b] However, the interchange of phenyl and ethyl groups in this reaction is consistently difficult to monitor under relevant reaction conditions. Three further improvements were recently made in this field. The use of boronic acids as an aryl source enabled the transfer of functionalized aryl rings to aldehydes.[1c,9] Triphenylborane was demonstrated to be a viable phenyl source[10] and finally, additives enabled the use of simple, commercially available ligands for the triphenylborane protocol.[11]

A serious drawback of all these protocols is in our eyes still to be seen in the price and availability of the aryl sources. While the expensive and sensitive diphenylzinc is only available and reasonably employable for research purposes, the arylboronic acid protocol calls for a huge excess of diethylzinc (6 to 7 equiv) and drastic conditions for the transmetalation step. Triphenylborane (**1**) on the other hand is a reasonably priced but still a rather air sensitive and flammable compound.

We therefore searched for other aryl sources for the transmetalation step yielding active arylzinc reagents. Our attention was first drawn to complexes of triphenylborane. Triphenylborane sodium hydroxide complex is a commercially available compound that is sold by DuPont as a flame retardant. Various other complexes of triphenylborane are known, many of which can easily be prepared by addition of, e.g., a nitrogen nucleophile to the triphenylborane solution. We chose to prepare the well-known ammonia complex **2** via a simple protocol.[12] Initial experiments showed that this ammonia complex is an outstandingly stable, versatile, and economic precursor for arylzinc reagents in asymmetric catalysis. We here describe a detailed study on its transmetalation behavior, as well as its application in asymmetric catalysis.

To gain some understanding of the two occurring processes, namely transmetalation and (enantioselective) 1,2-addition of the intermediary formed active zinc reagent to the aldehyde, we undertook kinetic studies of the ammonia complex (**2**). Additionally, we studied the transmetalation of diphenyl borinate (**3**) and triphenylborane (**1**) to compare reactivity patterns and enantioselectivity of the intermediary formed arylzinc reagents in addition reactions to aldehydes.

The transmetalation reactions of compounds **1** to **3** were studied at room temperature (20 °C) in toluene, the solvent of choice for most reported enantioselective addition reactions. After the given reaction time, a sample of the reaction mixture was quenched by addition of iodine in absolute dichloromethane and analyzed by GC, using decane as internal standard (see the Supporting Information).

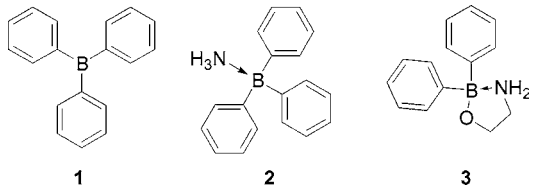


Figure 1. Boron compounds as phenylzinc precursors.

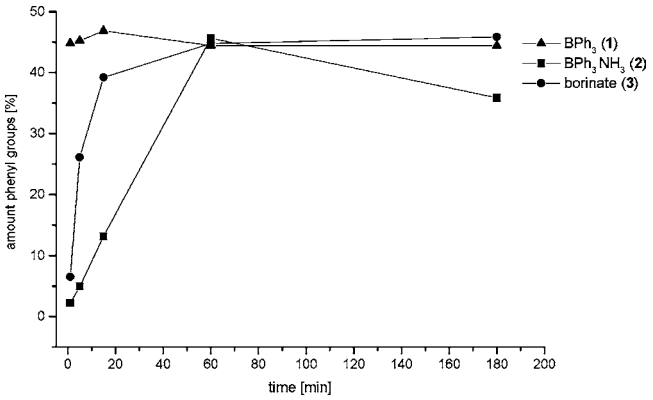


Figure 2. Transmetalation of boron compounds in toluene.

As it can be seen from Figure 2, the rate of the transmetalation reaction of the three compounds is different. While triphenylborane exchanges about 50% of its three phenyl groups practically immediately (first sample was taken after 1 min of reaction time), the two complexes take longer. Borinate **3** shows a rather fast transmetalation reaction, exchanging one of its two phenyl groups within 60 min. The rate of transmetalation for the ammonia complex **2** is decisively slower. However, after 60 min all three borane compounds have exchanged about half of their available phenyl groups. For triphenylborane and the borinate, the amount of exchanged phenyl groups remains constant over several hours.[13] A slight decrease of active phenylzinc reagent generated from ammonia complex **2** was observed in several kinetic experiments and an experimental artifact can therefore be ruled out.[14]

The dissimilar transmetalation patterns should result in a changed behavior in catalysis. To examine the catalytic reaction, we performed the addition of phenylzinc generated from the corresponding borane (**1**−**3**) to benzaldehyde in

(8) Hermanns, N. Ph.D. Thesis, RWTH Aachen, Germany, 2002.
(9) (a) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850. (b) Rudolph, J.; Schmidt, F.; Bolm, C. *Synthesis* **2005**, 840.
(10) (a) Rudolph, J.; Hermanns, N.; Bolm, C. *J. Org. Chem.* **2004**, *69*, 3997. (b) Rudolph, J.; Schmidt, F.; Bolm, C. *Adv. Synth. Catal.* **2004**, *346*, 867.
(11) Rudolph, J.; Lormann, M.; Bolm, C.; Dahmen, S. *Adv. Synth. Catal.* **2005**, *347*, 1361.
(12) Layton, W. J.; Niedenzu, K.; Niedenzu, P. M.; Trofimenko, S. *Inorg. Chem.* **1985**, *24*, 1454.
(13) Even after 16 h the amount of "active" phenyl groups remains unchanged.
(14) The formation of an equilibrium could be discussed giving rise to an ammonia stabilized Ph_2BEt + PhZnEt. It is unclear, however, which process could lead to an intermediary higher level of detectable phenylzinc.

the presence of a chiral ligand. Previous experience had shown that amino alcohol **5** is one of the most powerful catalyst precursors for the envisaged reaction.[15] A closely related ligand structure was recently used by the group of Chan for the addition of phenylzinc generated by the boronic acid protocol.[1d] Although no chiral product is obtained in these reactions, the reactivity pattern closely resembles that of any other benzaldehyde substrate in the asymmetric variant of this catalytic reaction. The kinetic profile with use of triphenylborane is depicted in Figure 3.

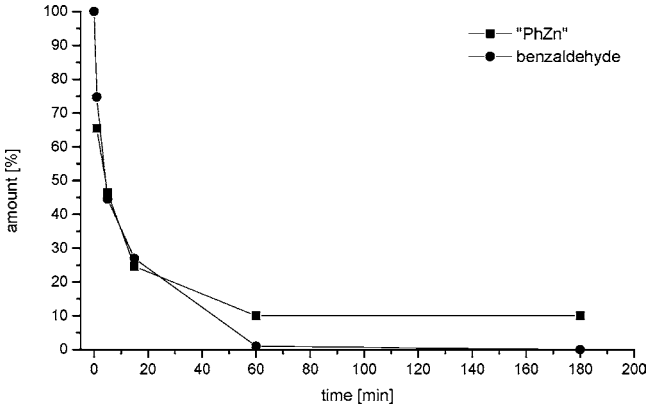


Figure 3. Kinetic profile of catalysis with BPh_3 (**1**).[16]

As already reported in the literature,[8,1b] the addition reaction of phenylzinc is fast, giving complete conversion to the desired product in 60 min. The stoichiometry chosen for the reaction calls for the transfer of two out of three phenyl groups (67%) of the triphenylborane. This is more than the initially observed 45% of transmetalated groups which are found in the absence of aldehyde and ligand. It is also clear from the "PhZn" graph in Figure 2 that the required phenylzinc reagent is generated rapidly from the excess borane as no depletion of phenylzinc reagent is observed during the catalysis. During the whole process, the amounts of phenylzinc reagent and benzaldehyde are comparable. It is also apparent that after consumption of aldehyde the level of active phenylzinc does not rise above 11% although one of three phenyl groups remains (representing a theoretical amount of 33%).

This picture is quite different for triphenylborane ammonia complex **2** (Figure 4). While the overall reaction rate is similar (85% conversion of aldehyde after 60 min), the available amount of phenylzinc reagent during the catalysis is much lower (usually below 5% during the reaction). This can be explained by the much slower transmetalation rate as described above. Additionally and in contrast to the free triphenylborane, the triphenylborane ammonia complex does

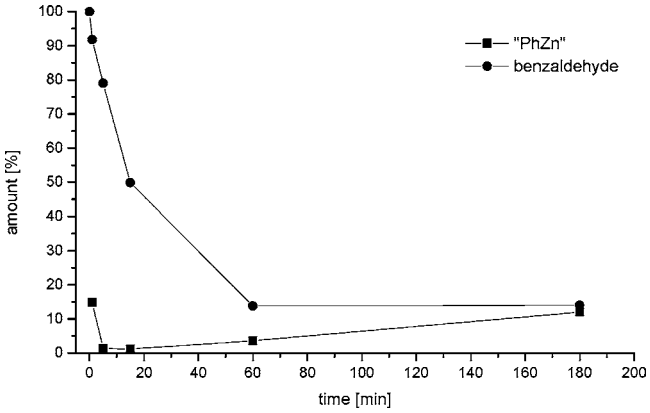


Figure 4. Kinetic profile of catalysis with $BPh_3 \cdot NH_3$ (**2**).[16]

not readily exchange more than 55% of its three phenyl groups. This results in lower overall conversion of aldehyde, which freezes at 85%. Nevertheless, after 3 h, 14% phenylzinc is detected. As this phenylzinc does not react with the aldehyde, we assume it to be trapped in a coordination complex of either the catalyst or the product.

However, the finding that only small amounts of the active phenylzinc reagent are present during catalysis can be essential for the enantioselectivity of the asymmetric variant. This is because phenylzinc reagents are powerful nucleophiles which can result in a considerable (undirected) background reaction diminishing the enantioselectivity. A complete conversion of aldehyde is easily achieved by adjustment of the stoichiometry (see below).

The kinetic profile of the reaction with borinate **3** is also very interesting (Figure 5). As could be expected from the

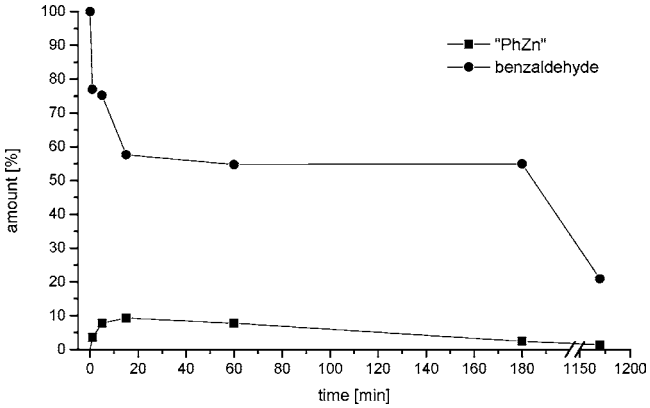


Figure 5. Kinetic profile of catalysis with borinate (**3**).[16]

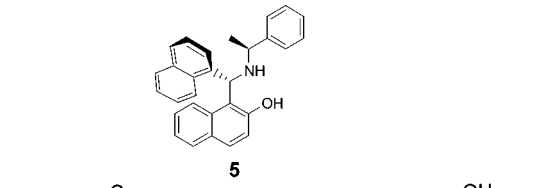
transmetalation reaction described above, generation of phenylzinc and therefore overall reaction rate is high. Compared to the two prior examples, the initial reaction rate is even higher and over 40% conversion is reached after only 15 min at room temperature. After transfer of the first phenyl

(15) As a member of cynora's screening library, the ligand has been employed in various asymmetric reactions. In an internal ligand screening it proved to be among the best *N,O*-ligands for this reaction. The synthesis of this compound was first described in: Cimarelli, C.; Mazzanti, A.; Palmieri, G.; Volpini, E. *J. Org. Chem.* **2001**, *66*, 4759.

group of the borinate, however, the reaction drastically slows down but does not stop because after a reaction time of 19.5 h a conversion of 80% is achieved. This clearly shows that although exchange of the second phenyl group of the borinate is possible, it is much slower under the chosen reaction conditions.

To compare the different phenylzinc sources in terms of enantioselectivity, asymmetric catalyses were carried out with ligand **5** and 4-chlorobenzaldehyde as substrate (Table 1).

Table 1. Comparison of Phenylzinc Sources and Optimization of Ligand Loading



4a 6a

entry	borane	amount of **5** (mol %)	yield (%)	ee (%)
1	1	5	95	36 (*R*)
2	2	5	97	97 (*R*)
3	3	5	94	87 (*R*)
4	2	1	89	78 (*R*)
5	2	2.5	91	92 (*R*)
6	2	10	96	97 (*R*)

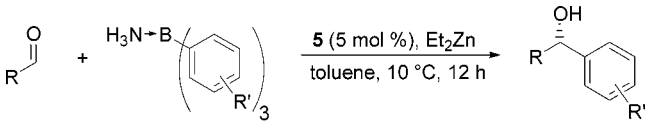
The obtained results reflect the expectations from the above-described kinetic studies. The quickly transmetalating triphenylborane (**1**) gives 36% ee in the presence of 5 mol % of ligand presumably due to the relatively large influence of undirected background reaction.[17] With the somewhat more slowly transmetalating borinate **3**, 87% ee is achieved while the ammonia complex **2** gives rise to the product in 97% ee.

As can also been deduced from Table 1, a ligand loading of 5 mol % is sufficient to obtain optimal enantioselectivity.

(16) Conditions: ligand **5** (2.5 mol %), borane or borinate (0.5 mmol), benzaldehyde (1.0 mmol), decane (96 μL), toluene (2.0 mL), diethylzinc (1.75 mL, 1 M in hexane), 20 °C.

(17) Especially the BPh_3 system is highly sensitive to the quality of the employed diethylzinc. Trace impurities which are contained in commercial charges of diethylzinc can have significant influence on the enantioselectivity of the catalysis.

Table 2. Aryl Transfer to Aldehydes[a]



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entry	aldehyde (R =)	arylborane complex (R′ =)	yield (%)	ee (%)
1	2-Br-C_6H_5	H	96	98 (*R*)
2	2-Me-C_6H_5	H	94	98 (*R*)
3	2-MeO-C_6H_5	H	89	92 (*R*)
4	3-Cl-C_6H_5	H	93	95 (*R*)
5	4-Cl-C_6H_5	H	94	97 (*R*)
6	4-Me-C_6H_5	H	97	98 (*R*)
7	4-MeO-C_6H_5	H	91	95 (*R*)
8	Ph	4-Me	92	94 (*S*)
9	Ph	4-Cl	91	95 (*S*)
10	Ph	4-MeO	86	96 (*S*)
11	C_6H_{11}	H	88	70 (*S*)
12	*n*-heptyl	H	85	71 (*S*)

[a] Conditions: ligand **5** (5 mol %), $BPh_3{\cdot}NH_3$ (**2**) (0.19 mmol), toluene (1.0 mL), aldehyde (0.25 mmol), diethylzinc (0.6 mmol, 0.6 mL, 1.0 M in hexane), 10 °C, 12 h.

The catalytic system can also be employed for various other aldehydes (Table 2). With benzaldehydes, very good enantioselectivity could be achieved for all substitution patterns (entry 1−7). The transfer of substituted aryl rings to benzaldehyde can also be achieved with high enantioselectivity (entries 8−10). Only aliphatic aldehydes resulted in lower ee values with the chosen ligand.

In conclusion, we have demonstrated the value of arylborane conplexes as precursors for arylzinc reagents in asymmetric catalysis. In a kinetic approach we were able to monitor the transmetalation reaction and rationalize the observed differences of the three classes of arylboranes in catalytic applications. Using the stable and easily accessible triarylborane ammonia complexes, we synthesized an array of chiral diarylmethanols in high yield and enantioselectivity. The simple reaction protocol and the ready availability of substrates and ligand provide for the first time an excellent opportunity for technical applications.

Supporting Information Available: Experimental procedures, HPLC analyses, and NMR characterization for compounds **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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