Asymmetric Catalysis

DOI: 10.1002/ange.200703103

Practical Implications of Boron-to-Zinc Transmetalation for the Catalytic Asymmetric Arylation of Aldehydes**

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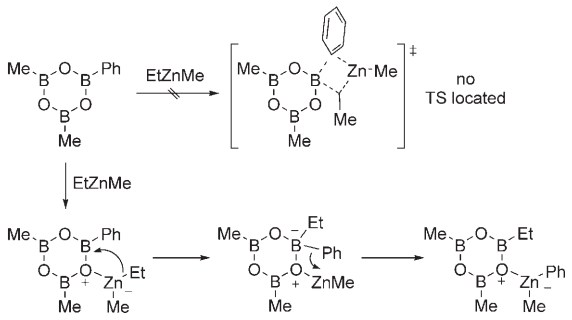
Enantiopure diaryl methanols are valuable compounds in the pharmaceutical field as active ingredients or as synthetic intermediates,[1] and the catalytic asymmetric arylation of aldehydes is now the method of choice for their preparation.[2] This straightforward process was initially hampered by complications arising from the undesired, fast, noncatalytic addition of diphenylzinc to aldehydes. However, the introduction of the highly selective arylating reagent Ph_2Zn/Et_2Zn by Bolm and co-workers,[3] and the subsequent proposal that PhZnEt is formed in a transmetalation reaction and is the real arylating agent,[4] boosted the practical application of the arylation of aldehydes.

While the enantioselectivity control of this process has been solved by varying the ligands,[3,4] substantial effort has been devoted in recent times to improving its economy by replacing the expensive reagent Ph_2Zn by more convenient aryl sources. A variety of aryl boron species have been used for this purpose,[5–7] as well as several other reagents.[8,9] In fact, a catalytic enantioselective aldehyde arylation involving a triaryl boroxine[10] as the ultimate source of the aryl group has recently found an industrial application.[11]

In spite of this practical importance, nothing is known about the mechanism of the boron-to-zinc transmetalation. Given the key role played by this fundamental process in the enantioselective arylation of aldehydes, and our current interest in transmetalation mechanisms,[12] we decided to undertake a theoretical and experimental study of the mechanism of this transmetalation with the ultimate goal of contributing to the development of truly practical approaches to the catalytic enantioselective arylation of aldehydes.

The theoretical study was performed with a slightly simplified system consisting of dimethyl(phenyl)boroxine and ethylmethylzinc. A thorough exploration of the possibility of a direct metathesis, in analogy with the Et_2Zn/Ph_2Zn exchange,[4] did not lead to the location of any transition state connecting reagents and products. Similarly, the participation of an external nucleophile leading to the formation of borates, from which phenyl groups could be more easily transferred, was also investigated. This route also turned out to be a dead end because no low-energy pathway compatible with a catalytic process (with respect to the external nucleophile) could be located.[13] Finally, a stepwise mechanism involving sequential zinc-to-boron and boron-to-zinc transmetalations (Scheme 1) proved to be a viable alternative, as indicated by the potential-energy profile calculated at the density functional theory level [B3LYP/6-31G(d)] for this reaction (Figure 1).



Scheme 1. Mechanisms considered for boron-to-zinc transmetalation.

The computed profile connecting the initial (**ADD1**) and final (**ADD2**) adducts is smooth, with the highest barrier (**TS1**) being only 16.2 kcal mol^{-1}. Our calculations predict the existence of an intermediate (**INT**) with a four-coordinate boron center and the zinc atom bound to oxygen. Intermediates with four-coordinate boron have been reported in calculations on the Suzuki–Miyaura reaction.[12] This intermediate is unlikely to be isolable because of the low barrier (9.4 kcal mol^{-1}) that separates it from the transmetalation product. The whole process is predicted to be easily reversible, with the equilibrium being shifted towards ethylphenylzinc. Overall, the key feature associated with this predicted pathway is the fact that the transmetalation process consists of two easy steps involving migration of a carbon chain from an anionic center to an adjacent site with Lewis acid characteristics.[14]

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[**] We thank the MEC (grant no.: CTQ2005-02193/BQU), DURSI (grant no.: 2005SGR225), the Consolider Ingenio 2010 (grant no.: CSD2006-0003), and the ICIQ Foundation for financial support. T.F. thanks the MEC for a predoctoral fellowship.

Supporting information for this article (cartesian coordinates of computed structures) is available on the WWW under http://www.angewandte.org or from the author.

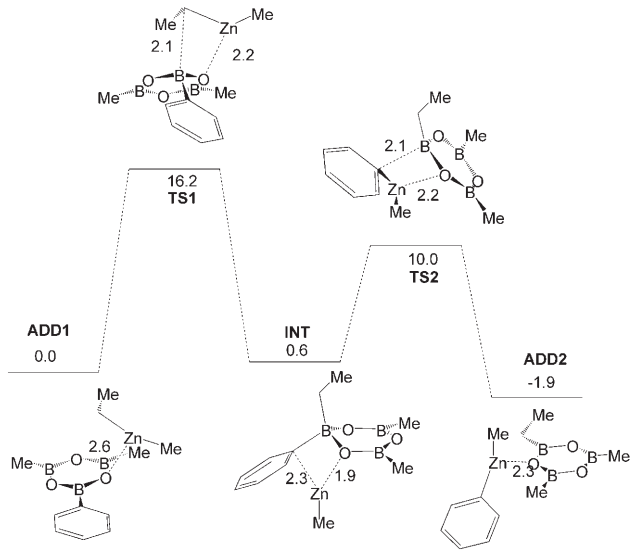


Figure 1. Computed B3LYP/6-31G(d) potential-energy profile [kcal mol^{-1}] for the boroxine system. Interatomic distances are given in [Å].

It should be noted that the theoretical study predicts that boron-to-zinc transmetalation should be a fast process at room temperature and even below. In apparent contradiction to this prediction, however, standard experimental procedures for transmetalation normally involve heating a mixture of boroxine or boronic acid and a large excess of diethylzinc for extended periods of time (typically 12 h at 60 °C).[5,6] These problems can be partially overcome by using triaryl boroxines, although several hours are still necessary for the transfer the aryl moieties from boron to zinc,[7] which is a drawback of this methodology for practical applications.

To test whether the transmetalation rate was in agreement with the results of the theoretical calculations or not, we next performed a series of reaction microcalorimetry experiments. Kinetic profiles were calculated from the heat flows[15] in reactions between a series of boroxines bearing aromatic groups with different electron-withdrawing or electron-donating substituents and diethylzinc (Figure 2). The corresponding reaction heats at 60 °C were also determined (Table 1).

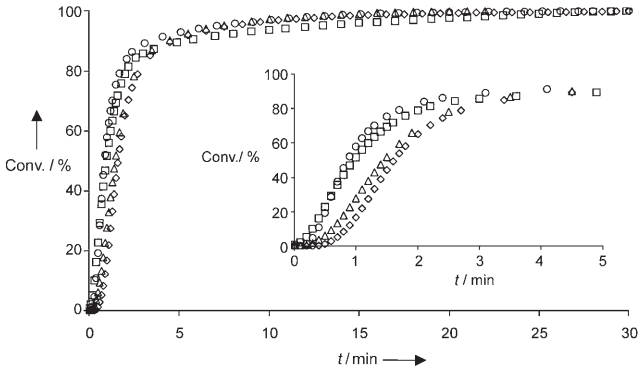


Figure 2. Kinetic profiles of the transmetalation of four different triaryl boroxines $(RBO)_3$ with Et_2Zn at 60 °C. Diamonds: R = 4-ClC_6H_4; squares: R = 3,5-$Me_2C_6H_3$; triangles: R = 4-$CF_3C_6H_4$; circles: R = Ph.

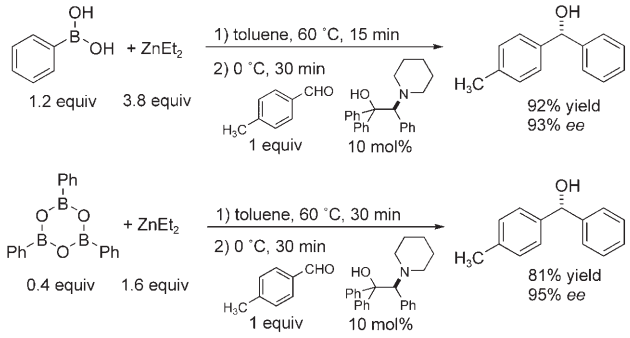
Table 1: Reaction heats for the transmetalation of four different boroxines.

Boroxine	Reaction heat[a]	Boroxine	Reaction heat[a]
Ph	15.2	4-ClC_6H_4	8.6
3,5-$Me_2C_6H_3$	12.7	4-$CF_3C_6H_4$	11.6

[a] At 60 °C, in kilocalories per mol of boroxine.

As can be seen from the kinetic profiles in Figure 2, the reactions are predicted to reach equilibrium in very short times (15–30 min) irrespective of the aryl substituent. Equally importantly, all the reactions are predicted to be exothermic (Table 1). The reaction heat per transmetalation step varies from 2.9 to 5.1 kcal mol^{-1} (exothermic), which is in excellent agreement with the predictions of the calculations (−1.9 kcal mol^{-1}). Although it cannot be ruled out that the small differences in reaction heat between the studied processes reflect slightly different positions in the transmetalation equilibrium, the theoretical and experimental results reported herein strongly suggest that the reaction of nearly stoichiometric amounts of triaryl boroxines and diethylzinc leads to the formation of aryl ethylzinc reagents through a fast reaction involving only reversible steps.

In an attempt to translate the results of the mechanistic study into a practical application, we investigated the enantioselective phenylation of *p*-tolualdehyde by generating PhZnEt from phenylboronic acid or triphenylboroxine under the conditions dictated by the above study, with amino alcohol **1** as the chiral ligand (Scheme 2).[4,16,17]

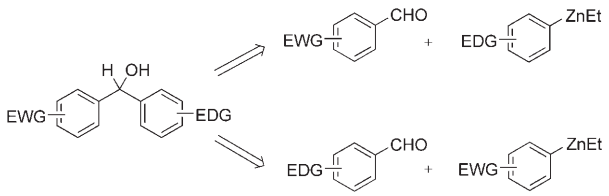


Scheme 2. Asymmetric phenylation of *p*-tolualdehyde with PhZnEt generated from phenylboron reagents.

In line with our expectations, the transmetalation reaction was found to go to completion in very short times at 60 °C (no residual $PhBO_2$ moieties could be detected by ^{11}B NMR spectroscopy after the transmetalation step and no ethylation product could be detected by NMR spectroscopy or HPLC of the crude reaction mixtures), and the target diaryl carbynol was obtained in high yield and enantiomeric purity following this optimized procedure. According to atom-economy principles applied to both phenyl transfer[10] and the amount of diethylzinc employed in the process,[18] triphenylboroxine should be used as the ultimate phenyl source in these reactions where possible. It is important to note that enantiopure diaryl carbynols should be available from

reactions that only require almost stoichiometric amounts of reagents with this combination. To confirm this, the enantioselective synthesis of a diverse family of diaryl methanols was planned following the optimized procedure (Scheme 2). The results of these reactions are shown in Table 2, with both the yield and enantioselectivity being very high (>90%) for the phenylation of substituted benzaldehydes (entries 1–4 in Table 2).

Generally speaking, a chiral diaryl carbynol can always be prepared from two alternative sets of reagents (Scheme 3), although it is known from the work of Bolm with aryl boronic acids that the efficiency of these complementary approaches can differ substantially.[5a] A similar behavior is observed in the present case. For example, it is better to use triphenylboroxine and 2-tolualdehyde than tri(2-tolyl)boroxine and benzaldehyde (entries 4 and 5, Table 2). Similar differences are observed in the preparation of **2e** (entries 6 and 7, Table 2) and, more dramatically, in the preparation of **2f** (entries 8 and 9, Table 2). On the other hand, aryl-disubstituted boroxines can be used as the aryl source (entry 10, Table 2). Finally, a pharmacologically relevant product (**2h**) was also prepared successfully by this method.[19]

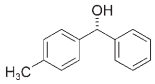
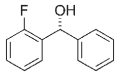
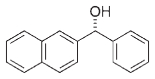
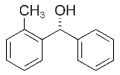
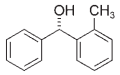
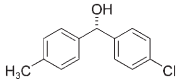
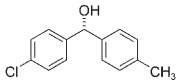
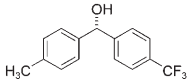
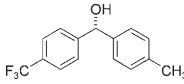
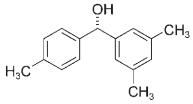
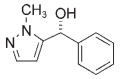


Scheme 3. Alternative ways to arylate aryl aldehydes.

Since the transmetalation process appears to be rather independent of the electronic nature of the aryl groups on the starting boroxine (see above), the differences in performance between reagent pairs that lead to the same alcohol are likely to be related to the arylation step. It is known that the noncatalytic reaction between arylethylzinc reagents and aldehydes, which is highly detrimental to the enantiomeric purity of the resulting diaryl carbynols, takes place at an appreciable rate at 0°C.[4] We therefore thought that this effect could be minimized if the catalytic arylation step was selected to take place in the fastest possible way. To clarify this point, we studied the reference reaction between PhZnEt and PhCHO mediated by *N*,*N*-dimethylaminoethanol at the density functional level of theory (B3LYP/LANL2DZ)[4,20] and analyzed the effect of 4-methoxy and 4-nitro substituents on either the organozinc or the aldehyde partners on the activation energy of the reaction. The results of this analysis are summarized in Table 3, where it can be seen that faster reactions can be achieved by placing electron-donating groups on the aryl group being transferred and electron-withdrawing groups on the aldehyde substrate. This is in perfect agreement with the results of the different preparations of **2e** and **2f**.

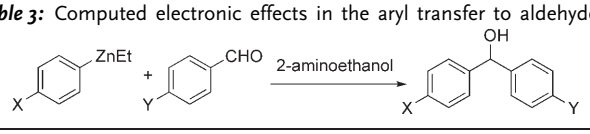
In summary, the mechanism of the boron-to-zinc transmetalation has been clarified by theoretical calculations and reaction microcalorimetry studies, and the results of these studies have guided the development of an optimized procedure for the enantioselective

Table 2: Catalytic asymmetric addition of triaryl boroxines to aldehydes in the presence of 10 mol% (*S*)-**1**.

Entry	Boroxine	Aldehyde	Product		Yield [%][a]	*ee* [%][b]
1	phenyl[c]	4-tolyl		(*R*)-**2a**	94	95
2	phenyl[c]	2-fluorophenyl[d]		(*R*)-**2b**	98	91[e]
3	phenyl[c]	2-naphthyl[d]		(*R*)-**2c**	90	91
4	phenyl[c]	2-tolyl[f]		(*R*)-**2d**	98	94
5	2-tolyl[c]	phenyl		(*S*)-**2d**	84	65
6	4-chlorophenyl[c]	4-tolyl		(*S*)-**2e**	96	73
7	4-tolyl[g]	4-chlorophenyl		(*R*)-**2e**	93	94
8	4-(trifluoromethyl)phenyl[c]	4-tolyl		(*S*)-**2f**	18	2
9	4-tolyl[g]	4-(trifluoromethyl)phenyl		(*R*)-**2f**	72	88
10	3,5-dimethylphenyl[c]	4-tolyl		(*S*)-**2g**	96	86
11	phenyl[c]	*N*-methylpyrazol-5-yl		(*R*)-**2h**	81[h]	87[h]

[a] Yield of product isolated after purification by flash chromatography. [b] Determined by HPLC on a chiral stationary phase. [c] 0.6 equiv of boroxine used. [d] Aldehyde addition performed at 10°C. [e] About 5% of ethyl addition was estimated from the ^{1}H NMR spectrum of the crude product. [f] 3 h at 0°C after the aldehyde addition. [g] 0.4 equiv of boroxine used. [h] Addition step performed at −10°C for 1 h using 20 mol% of ligand.

Table 3: Computed electronic effects in the aryl transfer to aldehydes.



Entry	X	Y	$E_{rel}^{\neq}$ [kcal mol^{-1}]
1	H	H	0
2	MeO	H	−0.54
3	H	MeO	+1.64
4	NO_2	H	+2.69
5	H	NO_2	−3.33

synthesis of diaryl carbynols from triaryl boroxines and aldehydes. Finally, calculations have been used as a guide to select the optimal reagent combination for this synthesis in conflicting cases.

Experimental Section

Typical procedure: Triphenylboroxine (171 mg, 0.55 mmol) was dissolved in anhydrous toluene (1 mL) in a flame-dried flask under argon. A solution of 1.1M Et_2Zn in toluene (2 mL, 2.2 mmol) was added dropwise and the resulting mixture was heated at 60 °C in a pre-heated bath for 30 min to give a clear solution. Once this solution had cooled to room temperature, a solution of ligand **1** (33 mg, 0.092 mmol) in toluene (1 mL) was added and, after cooling to 0 °C, *p*-tolualdehyde (108 μL, 0.92 mmol) was added with a syringe. After 30 min the reaction was quenched with aqueous saturated NH_4Cl, extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, and the solvents evaporated. Purification by flash chromatography on silica (2.5% Et_3N), eluting with hexane/EtOAc mixtures, gave 170 mg of (*S*)-phenyl-*p*-tolylmethanol (94% yield, 95% *ee*). The *ee* value was determined by HPLC with a Chiralcel OD-H column (0.5 mL min^{-1}, hexane/2-propanol (95:5), 254 nm).

Received: July 11, 2007
Revised: September 5, 2007
Published online: December 28, 2007

Keywords: asymmetric catalysis · boron · density functional calculations · reaction mechanisms · zinc

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