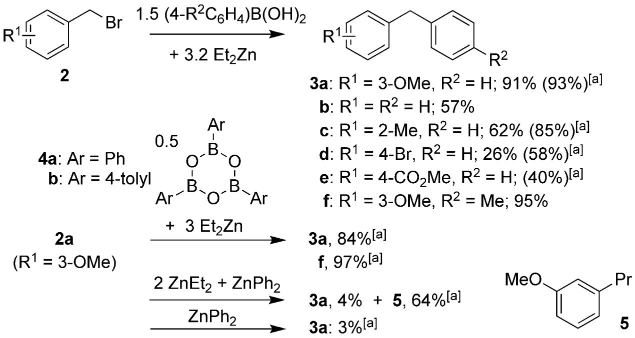
DOI: 10.1002/anie.201202219

Exploiting Boron–Zinc Transmetallation for the Arylation of Benzyl Halides: What are the Reactive Species?**

Robin B. Bedford, Nicholas J. Gower, Mairi F. Haddow, Jeremy N. Harvey, Joshua Nunn, Rukeme A. Okopie, and Rosalind F. Sankey*

Following pioneering work by Bolm and co-workers,[1] B–Zn transmetallation reactions between arylboronic acids and diethylzinc have been exploited in a range of asymmetric nucleophilic addition reactions to carbonyl and related compounds in the presence of catalytic amounts of chiral ligands and, in some cases, transition-metal catalysts.[2–7] These reactions usually require a pre-activation step, in which $ArB(OH)_2$ and Et_2Zn are heated in the absence of the electrophile, and it is presumed that the active species thus obtained are the mixed alkyl-aryl zinc reagents, EtZnAr, **1**.

We have recently examined the catalytic formation of diarylmethanes from benzyl halides[8,9] and wondered whether species **1** would be sufficiently reactive to give the arylation of these substrates in the absence of catalyst. Gratifyingly, this proved to be the case and Scheme 1 highlights representative examples.[10]



Scheme 1. Selected examples of the arylation of benzyl halides[10] in dioxane at 60 °C for 18 h. [a] ¹H NMR spectroscopic yields.

Reactions in dioxane gave the best results, but 1,2-dimethoxyethane (glyme) could also be used, although the reaction was slower, whereas the use of toluene gave competing Friedel–Crafts benzylation of the solvent. Aryl boroxines **4** could also be exploited as the boron reagent.[3c,11]

The reagent **1a** (Ar = Ph) can also be generated in situ by the reaction of Ph_2Zn with Et_2Zn.[12] Therefore we were highly surprised to find that under these conditions, very little of the desired product **3a** was produced, instead substantial ethylation occurred, giving **5** (Scheme 1).[13] Diarylzinc reagents are more reactive than the mixed species **1**, yet Ph_2Zn also performed very poorly. If neither **1** nor Ar_2Zn can account for the reactivity alone, what other species are present in the B–Zn mixture that might?

Figure 1 a–d shows the ^{11}B NMR spectra obtained upon mixing Et_2Zn with $PhB(OH)_2$ in a range of solvents. Clearly, several boron-containing products are formed in a solvent-dependent manner. The spectrum of the reaction mixture formed in toluene (Figure 1 a) shows peaks at $\delta = 85.7$, 77.4, and 71.9 ppm, assigned as BEt_3,[14] BEt_2Ph,[15] and $BEtPh_2$, respectively. Triphenylboron has been shown to act as a useful aryl source in B–Zn transmetallation processes,[7a,16] thus the observed arylboranes may well act as "reservoirs" for the aryl nucleophile. A very similar spectrum was obtained when triphenylboroxine, **4a**, was used as the boron source,[10] demonstrating that the species obtained in the equilibria are independent of the "$ArB(OY)_2$" precursor.

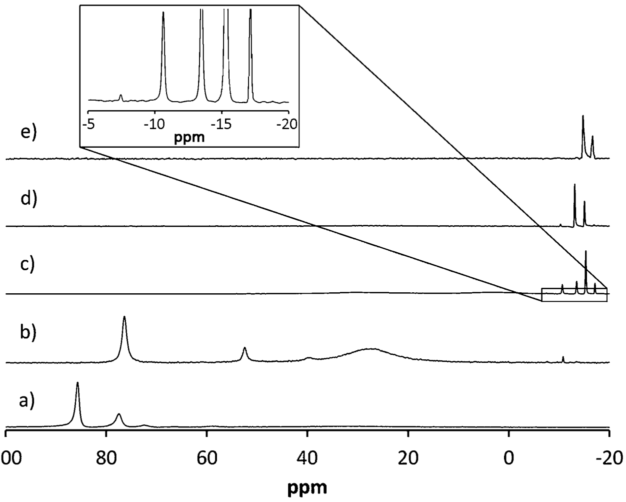


Figure 1. ^{11}B NMR spectra (rt) of the reactions between $PhB(OH)_2$ and 3–3.2 equivalents of Et_2Zn at 60 °C after 30 min under various conditions: a) in toluene, b) in THF, c) in glyme, d) in DMF, and e) in toluene with PMDETA (1 equivalent per $PhB(OH)_2$).

The reaction in tetrahydrofuran (THF), another solvent used in B–Zn transmetallations, gave the spectrum shown in Figure 1 b which shows a broad peak at 28 ppm, consistent with an $RB(OY)_2$ (R = Et or Ph) species and a smaller peak at $\delta = 52.3$ ppm assigned as an "$Et_2B(OY)$" intermediate, prob-

---

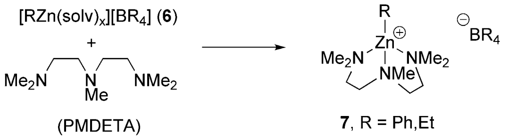
[*] Prof. Dr. R. B. Bedford, N. J. Gower, Dr. M. F. Haddow,
Prof. Dr. J. N. Harvey, J. Nunn, R. A. Okopie, Dr. R. F. Sankey
School of Chemistry, University of Bristol
Cantock's Close, Bristol, BS8 1TS (USA)
E-mail: r.bedford@bristol.ac.uk

[**] We thank the EPSRC and Syngenta for funding.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201202219.

ably $Et_2B(OZnR)$.[17,18] A particularly intriguing peak was observed at $\delta = -10.8$ ppm, consistent with a tetraorganoborate anion. When the reaction was repeated in glyme, another solvent exploited in B–Zn transmetallation reactions,[6] a substantial quantity of ZnO precipitated and the ^{11}B NMR spectrum of the supernatant (Figure 1 c) showed five peaks in this region, between $\delta = -7.5$ and -17.1 ppm, corresponding to all five possible organoborates: $[BPh_4]^-$ (trace); $[BEtPh_3]^-$; $[BEt_2Ph_2]^-$; $[BEt_3Ph]^-$ (major species) and $[BEt_4]^-$, respectively. This necessitates the concomitant formation of a counterion, most likely $[RZn(solv)_x]^+$ (R = Et, Ph).[19] Presumably the glyme acts as a good ligand for the organozinc cation, shifting the equilibrium entirely in favor of the ion pairs $[RZn(solv)_x][BR_4]$, **6**. Similarly the use of dimethylformamide (DMF), a solvent known to stabilize alkyl zinc cations,[20] gave substantial borate peaks (Figure 1 d).

While no borates were detected in toluene solution (Figure 1 a), the ion pairs **6** may still be present at concentrations too low to be observed by ^{11}B NMR spectroscopy. If this is the case then, according to the Curtin–Hammett principle,[21] they may still be expected to play a significant role in subsequent reactions. Pentamethyldiethylenetriamine (PMDETA) should react with the organozinc cation in **6** and thus shift the equilibrium in favor of triamine coordinated analogues **7** (Scheme 2).[22] The results in Figure 1 e show that this is indeed the case: on addition of PMDETA the only boron-containing species in the reaction mixture were borate anions.



Scheme 2. Trapping ion-pairs, **6**, with PMDETA.

While ^{11}B NMR spectroscopy can only reveal the presence of the borate anions of **6**, evidence for the existence of the $[RZn(solv)_x]^+$ counterion in solution was provided by high-resolution electrospray ionization mass spectrometry of the reaction mixture in DMF, which showed a peak at 239.0733, precisely that expected for $[EtZn(DMF)_2]^+$.[23] Furthermore cooling a THF solution of a 1:2 mixture of $PhB(OH)_2$ and Et_2Zn gave crystals of $[EtZn(THF)_3][BPh_4]$, **6a**, suitable for X-ray crystallography (Figure 2).[10] The structure obtained is broadly similar to that of the closely related complex $[EtZn(OEt_2)_3][B(C_6F_5)_4]$,[24] except that the smaller anion in **6a** allows considerably closer contact between the ions (Zn···B separation of 6.55 vs. 7.63 Å).

Maseras, Pericàs, and co-workers recently probed the mechanism of the B–Zn transmetallation of phenylboroxine (or $PhB(OZnR)_2$, **8**) with Et_2Zn using a combined experimental and computational approach. The results from their study are summarized in Scheme 3.[3c] While this mechanism elegantly describes the initial transmetallation step between $PhB(OY)_2$ and Et_2Zn, it needs to be extended to account for the presence of $R_2B(OY)$, R_3B, and $[RZn(solv)_x][BR_4]$. We suggest that this occurs through the equilibria shown in Scheme 4. Our NMR results suggest that these steps can occur with both boroxine **4a** and $PhB(OH)_2$ as the precursors.

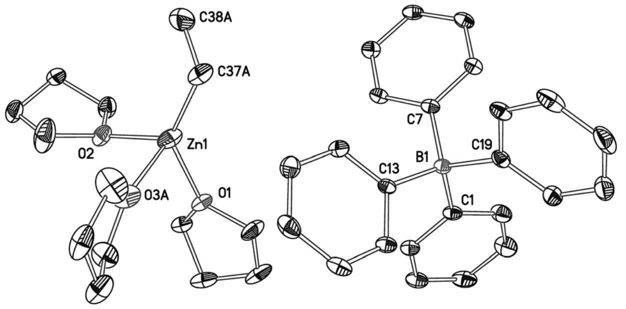
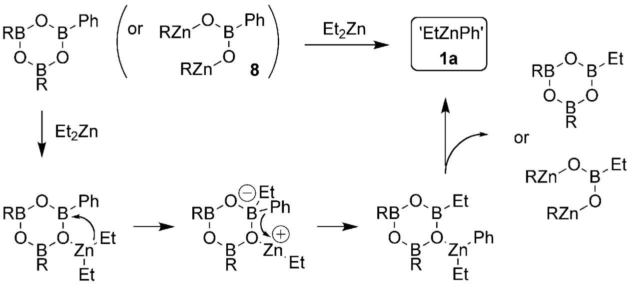
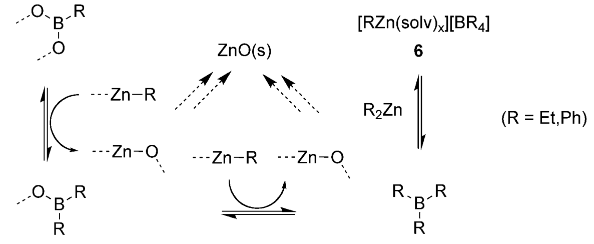


Figure 2. Crystal structure of $[ZnEt(THF)_3][BPh_4]$, **6a**. Thermal ellipsoids set at 30% probability. Disorder of the ethyl and one of the THF ligands omitted for clarity.



Scheme 3. Proposed mechanism for the formation of **1**.[3c]



Scheme 4. Extending the equilibria beyond the formation of **1**.

B3LYP-D3 DFT calculations[25] predict that the Δ_rG^0 for formation of $PhBEt_2$ from $ZnEt_2(THF)_2$ and either **4a** or $PhB(OH)_2$ is negative. Formation of one plausible intermediate, $PhB(Et)(OZn(Et)(THF)_2)$, is mildly uphill in free energy terms.

Figure 3 shows the calculated free-energy profile for the ensuing transmetallation between $Me_2Zn(OMe_2)_2$ and $PhBMe_2$ (in these calculations, Me was used instead of Et for convenience).[25] The transmetallation is modeled as occurring through an ion pair species **9**. The calculated barriers for formation and reaction of **9** are low, consistent with the rapid exchange processes that are observed experimentally. Formation of **6b** is predicted to be unfavorable in free energy terms. This appears to be due to the use of

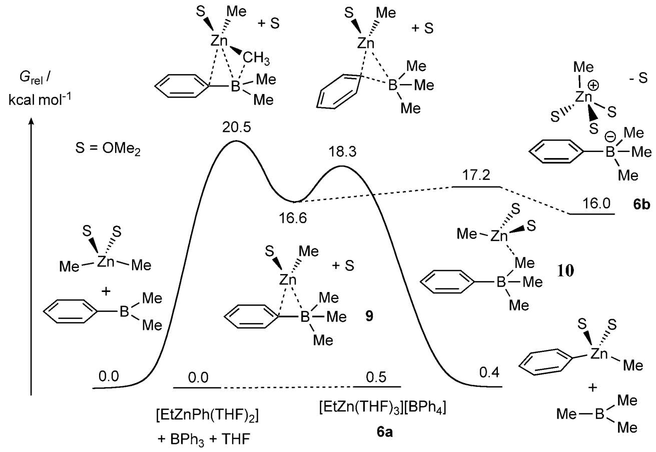
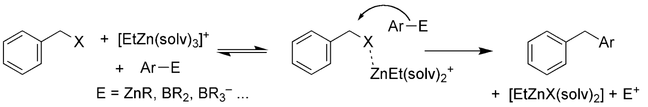


Figure 3. DFT relative free energies at 298 K for transmetallation in a simplified model system.[25] Also shown the relative free energy for forming the representative ion pair **6a**.

a truncated model: at the same level of theory,[25] the calculated Δ_rG^0 for formation of **6a** from BPh_3 and EtZnPh-$(THF)_2$ is just $+0.5\,kcal\,mol^{-1}$. The B–Zn distance in the optimized full system **6a** was found to be 6.36 Å, and the sum of the Mulliken charges for the Zn fragment was calculated as $+0.85$.[26]

Having observed both BR_2Ph and $[BR_3Ph]^-$ as potential alternative nucleophiles in the B–Zn transmetallation processes we next investigated whether isolated representative examples of these nucleophiles would react directly with benzyl halides and found that the reaction of **2a** with BPh_3, $Na[BPh]_4$, $Li[BPhEt_3]$, or $Li[BPh_3Et]$ again gave little or no **3a**. The lack of arylation with either Zn- or B-based nucleophiles implies that a halophilic species that can activate the benzyl halide is also necessary and it seems highly likely that the Lewis acid $[RZn(solv)_x]^+$ plays this role (Scheme 5).



Scheme 5. Suggested mechanism for the activation of benzyl halides.

Finally we were interested to see whether the results obtained had significance beyond the arylation of benzyl halides. The asymmetric arylation of aldehydes, the archetypal B–Zn transmetallation reaction, usually exploits catalytic amounts of chiral aminoalcohols, such as 1,1,2-triphenyl-2-(piperidin-1-yl)ethanol **11**,[12c] as ligands. When the reaction described in Figure 1a was repeated in the presence of 8 mol% of (*S*)-**11**, the ^{11}B NMR spectrum obtained was essentially identical.[10] Adding PMDETA to this reaction mixture gave a very similar spectrum to that shown in Figure 1e.[10] This shows that both the ion pairs **6** and BR_2Ph species form even in the presence of aminoalcohols and therefore that they *must* be present in most if not all of the B–Zn transmetallation reactions reported. However, given the propensity of aldehydes to react with arylzinc and $ArBR_2$ species, both of which are present in the complex reaction mixture, it is not feasible at this stage to delineate the precise role of the ion pairs **6** in aldehyde arylation.

In conclusion, we have exploited B–Zn transmetallation as a method for arylating benzyl halides in the absence of added catalyst. Probing the B–Zn mixtures showed that the transmetallation reactions between $ArB(OH)_2$ or $Ar_3B_3O_3$ and Et_2Zn give complex solvent- and condition-dependent equilibria. These mixtures not only contain the boroxines (or $RB(OY)_2$) suggested previously but also $R_2B(OY)$ and BR_3 species and the ion pairs $[RZn(solv)_x][BR_4]$. Given the complex mixtures observed, it should not be assumed that the simple organozinc species **1** are the sole nucleophiles responsible for the reported activity in B–Zn arylation reactions.

Received: March 20, 2012

Keywords: arylation · benzyl halides · boron · transmetallation · zinc

---

[1] a) C. Bolm, J. Rudolph, *J. Am. Chem. Soc.* **2002**, *124*, 14850; b) C. Bolm, L. Zani, J. Rudolph, I. Schiffers, *Synthesis* **2004**, 2173; c) J. Rudolph, F. Schmidt, C. Bolm, *Synthesis* **2005**, 840; d) S. Öçubukçu, F. Schmidt, C. Bolm, *Org. Lett.* **2005**, *7*, 1407; e) F. Schmidt, J. Rudolph, C. Bolm, *Adv. Synth. Catal.* **2007**, *349*, 703.

[2] Reviews: a) F. Schmidt, R. T. Stemmler, J. Rudolph, C. Bolm, *Chem. Soc. Rev.* **2006**, *35*, 454; b) M. W. Paixão, A. L. Braga, D. S. Lüdtke, *J. Braz. Chem. Soc.* **2008**, *19*, 813.

[3] Examples of additions to aldehydes and ketones: a) J. Ruan, G. Lu, L. Xu, Y.-M. Li, A. S. C. Chan, *Adv. Synth. Catal.* **2008**, *350*, 76; b) M.-C. Wang, Q.-J. Zhang, W.-X. Zhao, X.-D. Wang, X. Ding, T.-T. Jing, M.-P. Song, *J. Org. Chem.* **2008**, *73*, 168; c) C. Jimeno, S. Sayalero, T. Fjermestad, G. Colet, F. Maseras, M. A. Pericàs, *Angew. Chem.* **2008**, *120*, 1114; *Angew. Chem. Int. Ed.* **2008**, *47*, 1098; d) M.-J. Jin, S. M. Sarkar, D.-H. Lee, H. Qiu, *Org. Lett.* **2008**, *10*, 1235; e) A. L. Braga, M. W. Paixão, B. Westermann, P. H. Schneider, L. A. Wessjohann, *J. Org. Chem.* **2008**, *73*, 2879; f) A. D. Wouters, G. H. G. Trossini, H. A. Stefani, D. S. Lüdtke, *Eur. J. Org. Chem.* **2010**, 2351; g) R. Infante, J. Nieto, C. Andrés, *Org. Biomol. Chem.* **2011**, *9*, 6691; h) M. Hatano, R. Gouzu, T. Mizuno, H. Abe, T. Yamada, K. Ishihara, *Catal. Sci. Technol.* **2011**, *1*, 1149.

[4] Ti-catalyzed addition to ketones: a) O. Prieto, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2003**, *14*, 1955; b) V. J. Forrat, O. Prieto, D. J. Ramón, M. Yus, *Chem. Eur. J.* **2006**, *12*, 4431.

[5] Other additions: a) S. Wang, M. B. Onaran, C. T. Seto, *Org. Lett.* **2010**, *12*, 2690; b) K. Kobayashi, Y. Kondo, *Org. Lett.* **2009**, *11*, 2035.

[6] Ni-catalyzed cross-coupling with propargyl halides: S. W. Smith, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 12645.

[7] Conjugate addition to enones: a) D. Peña, F. López, S. R. Harutyunyan, A. J. Minnaard, B. L. Feringa, *Chem. Commun.* **2004**, 1836; b) L. Dong, Y.-J. Xu, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, *Synthesis* **2004**, 1057.

[8] Fe-catalyzed coupling with aryl zinc reagents: R. B. Bedford, M. Huwe, M. C. Wilkinson, *Chem. Commun.* **2009**, 600.

[9] Fe-catalyzed arylation using tetraorganoborates and co-catalytic Zn: R. B. Bedford, M. A. Hall, G. R. Hodges, M. Huwe, M. C. Wilkinson, *Chem. Commun.* **2009**, 6430.

[10] See supporting information for full details.

[11] N. A. Magnus, P. B. Anzeveno, D. S. Coffey, D. A. Hay, M. E. Laurila, J. M. Schkeryantz, B. W. Shaw, M. A. Staszak, *Org. Process Res. Dev.* **2007**, *11*, 560.

[12] a) C. Bolm, N. Herrmans, J. P. Hildebrand, K. Muñiz, *Angew. Chem.* **2000**, *112*, 3607; *Angew. Chem. Int. Ed.* **2000**, *39*, 3465; b) J. Rudolph, T. Rasmussen, C. Bolm, P.-O. Norrby, *Angew. Chem.* **2003**, *115*, 3110; *Angew. Chem. Int. Ed.* **2003**, *42*, 3002; c) M. Fontes, X. Verdaguer, L. Solà, Miquel A. Pericàs, A. Riera, *J. Org. Chem.* **2004**, *69*, 2532.

[13] The Et may be from Et_2Zn rather than a mixed species **1a**. Et_2Zn alone gave $>98\,\%$ of **5**. See also: K. A. Agrios, M. Srebnik, *J. Org. Chem.* **1993**, *58*, 6908.

[14] δ^{11}B for $BEt_3 = 84$ ppm, see: L. H. Toporcer, R. E. Dessy, S. I. E. Green, *Inorg. Chem.* **1965**, *4*, 1649.

[15] J. J. Eisch, B. W. Kotowicz, *Eur. J. Inorg. Chem.* **1998**, 761.

[16] For example: a) J. Rudolph, F. Schmidt, C. Bolm, *Adv. Synth. Catal.* **2004**, *346*, 867; b) J. Rudolph, N. Hermanns, C. Bolm, *J. Org. Chem.* **2004**, *69*, 3997.

[17] Compare with δ^{11}B (THF) $Et_2B(OEt) = 52.4$ ppm.

[18] Large peak at $\delta = 76.3$ ppm assigned as $BEt_{3,}$ (δ^{11}B pure BEt_3 in THF = 75.7).

[19] This contrasts with Mg– and Li–Zn transmetallation which can yield Zn-based anions because of the lower electronegativities of Li and Mg compared with Zn. For instance: a) E. Hevia, J. Z. Chua, P. García-Álvarez, A. R. Kennedy, M. D. McCall Hevia, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 5294; b) M. Westerhausen, *Dalton Trans.* **2006**, 4755.

[20] L. Caggiano, R. F. W. Jackson, A. J. H. M. Meijer, B. T. Pickup, K. A. Wilkinson, *Chem. Eur. J.* **2008**, *14*, 8798.

[21] J. I. Seeman, *Chem. Rev.* **1983**, *83*, 83.

[22] H. Tang, H. G. Richey Jr., *Organometallics* **1996**, *15*, 4891.

[23] Calculated m/z for $C_{12}H_{19}N_2O_2Zn = 239.0733$. See Figure S3 (in the Supporting Information) for the isotope pattern.

[24] D. A. Walker, T. J. Woodman, D. L. Hughes, M. Bochmann, *Organometallics* **2001**, *20*, 3772.

[25] The calculations at the B3LYP-D3 level include continuum solvation. See the Supporting Information for full details.

[26] **9**: Zn-B = 2.37 Å; Zn-C_{Ph} = 2.16 Å; B−C_{Ph} = 1.73 Å (c.f. 1.57 Å in the free borane). **10**: Zn−B = 3.98 Å; Zn−C_{Ph} = 4.47 Å; B−C_{Ph} = 1.64 Å. **6b**: Zn−B = 6.00 Å; Zn−C_{Ph} = 5.73 Å; B−C_{Ph} bond length remained similar at 1.65 Å. The sum of the Mulliken charges calculated for the Zn fragments = +0.17, +0.41, and +0.87 for **9**, **10**, and **6b**, respectively.