Metal-catalysed multiple boration of ketimines†

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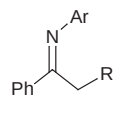
Metal-catalysed addition of $B_2cat'_2$ (cat′ = 4-Bu^t-1,2-$O_2C_6H_3$) to ketimines affords *N*-borylenamines and HBcat′. Analogous catalysed reactions of ketimines with HBcat′ in tetrahydrofuran afford multiply borated products, providing the first examples of metal-catalysed hydroboration of enamines.

Transition metal catalysed diboration of alkenes and alkynes is receiving considerable attention as a convenient and efficient method of generating alkyl- and alkenyl-boronic esters with well defined selectivities.[1] These compounds are valuable substrates for Suzuki coupling,[2] and new developments in this field include the direct synthesis of arylboronic esters from the corresponding aryl halides using diboron compounds[3] or dialkoxyboranes.[4] To date, catalysed diborations have been restricted to functionalizing unsaturated hydrocarbons, with the exception of a recent report by Marder and coworkers describing the 1,4-diboration of α,β-unsaturated ketones.[5] Our interest in aminoboron chemistry prompted us to investigate the diboration of imines. Transition metals can be used to catalyse the hydroboration of imines[6] and we recently found that the corresponding diboration of aldimines provides a direct route to the potent enzyme inhibitors, α-aminoboronic acids.[7,8] In this report we describe the versatility of metal-catalysed boron additions to ketimines which give a variety of novel aminoboronate esters and provide the first examples of metal-catalysed enamine hydroboration.

Reaction of acetophenone-derived imine, PhN=C(CH_3)Ph **1a**, with $B_2cat'_2$ (cat′ = 4-Bu^t-1,2-$O_2C_6H_3$) did not proceed without a catalyst, even at elevated temperatures (90 °C for 1 week).[9] Using 2 mol% $RhCl(PPh_3)_3$ at 25 °C, the reaction produced equal amounts of *N*-borylenamine **2a** and *N*-borylamine **3a**, as ascertained by NMR spectroscopy.[10] These products arise presumably from initial oxidative addition of the diboron compound to the metal center, followed by coordination of the ketimine with subsequent regioselective insertion into the M–B bond. Finally, β-H elimination generates *N*-borylenamine **2a** and 1 equiv. of HBcat′ which can subsequently add to unreacted **1a** to give **3a** (Scheme 1). Similar boration reactions have been observed previously in analogous diboration[1c] and hydroboration[11] reactions of alkenes. Ketimine diborations carried out using a catalytic amount of $Pt(dba)_2$ (dba = dibenzylidene acetone) gave primarily **2a** and HBcat′, as the resulting Pt complex is less effective in catalysing the competitive hydroboration of **1a**. Variation of the steric and electronic properties of the ketimine had a nominal effect on the product distribution as analogous reactions with a variety of ketimines **1b**–**e** gave similar results, as determined by NMR spectroscopy.‡

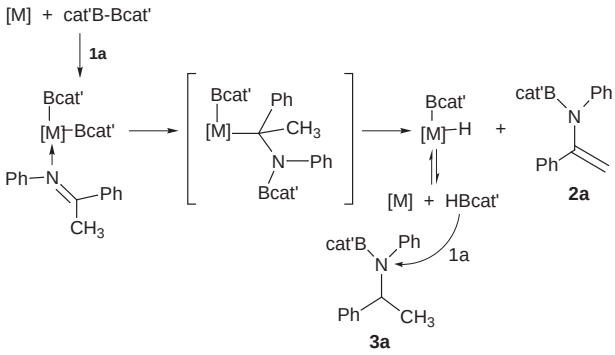


	R	Ar
1a	H	Ph
1b	H	$C_6H_4CF_3$-*p*
1c	H	C_6H_4OMe-*o*
1d	Ph	C_6H_4OMe-*p*
1e	Me	$C_6H_4CF_3$-*p*

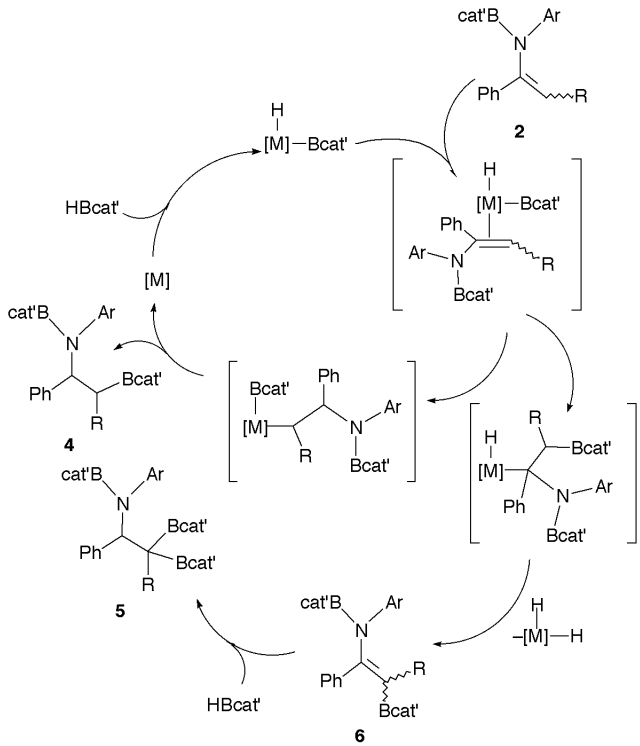
In order to obtain evidence for the mechanistic pathway discussed above, we examined the stoichiometric reaction of the unsaturated bis(boryl) complex $RhCl(Bcat')_2(PPh_3)_2$ (generated *in situ* from $RhCl(PPh_3)_3$ and $B_2cat'_2$) with ketimine **1a** and observed quantitative formation of dihydride $RhH_2Cl(PPh_3)_3$[11a,12] along with 2 equiv. of *N*-borylenamine **2a**. This surprising result suggests that intermediate RhHCl(Bcat′)$(PPh_3)_2$,[13] arising from the boration step, reacts with **1a** to give **2a** at a comparable rate to that of the bis(boryl) complex. Previous theoretical studies of metal-catalysed hydroboration indicated that alkene insertion into both M–H and M–B bonds is energetically feasible.[14] Our observation of quantitative formation of *N*-borylenamine indicates that only insertion of ketimine into the M–B bond results in product formation.

These intriguing results prompted us to investigate the metal-catalysed hydroboration of ketimines. Uncatalysed addition of HBcat′ to **1a** in toluene, THF, or chloroform proceeds slowly (days) at 25 °C to give **3a**.[15] Using 2 mol% $RhCl(PPh_3)_3$ in toluene, however, gave a mixture of **2a** and **3a** along with a small amount of the 1,3-diboration product, cat′BN(Ph)CH(Ph)CH_2Bcat′ **4a**, derived from an unprecedented catalysed hydroboration of enamine **2a**. Remarkably, reactions carried out in $CDCl_3$ gave predominantly hydroborated ketimine **3a**, while those in THF afforded predominantly **4a** and the 1,1,3-triboration product, cat′BN(Ph)CH(Ph)CH(Bcat′)$_2$ **5a** in a 3 : 1 ratio.‡ The **4a** : **5a** ratio determined by ^{1}H NMR was confirmed by hydrolysis, which gives elimination products styrene and *E*-vinylboronate ester,[1a] respectively.[16]

Several reactivity trends were observed in the catalysed hydroborations of substituted ketimines.‡ Reaction of the electron poor ketimine, (*p*-$CF_3C_6H_4$)N=C(CH_3)Ph **1b**, with HBcat′ in THF gave more rapid conversion (*cf.* **1a**) of the intermediate enamine and afforded analogous multiply borated amines **4b** and **5b** in a 5 : 1 ratio. The sterically hindered, electron-rich ketimine, (*o*-$MeOC_6H_4$)N=C(CH_3)Ph **1c**, on the other hand, gave primarily enamine **2c** and amine **3c**. Deoxybenzoin-derived imine, (*p*-$MeOC_6H_4$)N=C(CH_2Ph)Ph **1d**, gave both *E*- and *Z*-enamines and only one isomer was hydroborated to a single diastereomer of the 1,3 diboration product **4d**. Steric hindrance also precludes formation of the triborated product and gives rise to Rh-mediated HBcat′ degradation leading to minor



Scheme 1



Scheme 2

amounts of aminoborane side-products derived from 'BH_3' addition.[11a] Propiophenone-derived imine, (p-$CF_3C_6H_4$)-N=C(CH_2CH_3)Ph **1e**, is readily converted to isomeric *N*-borylenamines, but subsequent catalysed hydroboration is accompanied by significant HBcat′ degradation.

We propose that formation of the multiply borated products is due to competitive insertion of enamine **2** into M–H and M–B bonds to give **4** and *N*,*C*-diborylenamine **6**; the latter is subsequently hydroborated to **5** (Scheme 2). The enamine hydroboration/boration ratio depends on the substrate, solvent, and catalyst, and further catalyst development is ongoing.

In summary, we have shown that metal-catalysed diboration of ketimines affords *N*-borylenamines and that catalysed hydroboration of these products gives multiply borated amines proposed to result from competing enamine insertion into M–H *vs*. M–B bonds. The first examples of metal-catalysed enamine hydroboration reported herein afford boronate esters which may subsequently be used as substrates to prepare novel functionalized amines. This work is currently in progress.

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Notes and references

† Dedicated to Professor Warren R. Roper on the occasion of his 60th birthday.

‡ *Reaction of* **1** *with* $B_2cat'_2$: to a solution of ketimine **1a** (97 mg, 0.5 mmol) dissolved in 0.5 ml of C_6D_6 was added $B_2cat'_2$ (119 mg, 0.5 mmol) and catalyst (2 mol%). The reaction was monitored by ^1H and ^{11}B NMR until **1a** was consumed (*ca.* 48 h). Similar reactions were conducted for **1b**–**e** and faster rates were observed for more electron-rich imines. The ratio of **2**:**3** was 4, 3.3, 2, 1.5, and 6 for **1a**–**e**, respectively. For **1c**, one equiv. of HBcat′ was added to the reaction mixture upon completion in order to cleanly generate **4c** from **2c**.

Reaction of **1** *with* HBcat′: to a solution of ketimine **1a** (40 mg, 0.2 mmol) dissolved in 0.5 ml of [$^2H_8$]THF was added HBcat′ (106 mg, 0.6 mmol) and catalyst (2 mol%). The reaction was monitored by ^1H and ^{11}B NMR until the intermediate *N*-borylenamine **2** was entirely consumed. The ratio of **3**:**4**:**5** was determined by ^1H NMR before and after hydrolysis (see electronic supplementary material for NMR data: http://www.rsc.org./suppdata/cc/1998/2395). Product Ratios for **1a**–**e** + HBcat′ in THF after 4 days at 25 °C: **3a**:**4a**:**5a** = 3:6:2; **2b**:**3b**:**4b**:**5b** = 1:8:12:2; **2c**:**3c**:**4c**:**5c** = 6:8:2:1; **2d**:**3d**:**4d** = 2:5:1; **2e**:**3e**:**4e** = 4:4:1.

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9 Uncatalysed addition of diboron compounds to aldimines gives stereoselective coupling to C_2-symmetric *N*-boryldiamines: R. T. Baker, T. M. Cameron and S. A. Westcott, unpublished results.

10 NMR data in [$^2H_8$]THF: **2a**: ^1H, δ 7.6–6.8 (ov m, Ph + cat′, 13H), 5.73, 5.42 (s, =CH_2), 1.30 (9H, Bu^t); ^{13}C, δ 148.3 (*C*=CH_2), 149.4, 147.2, 146.4, 144.8, 138.4 (*ipso* of CPh, NPh, and cat′), 129.4, 129.0, 127.5, 123.4 (*o*-, *m*-C of NPh and CPh), 128.9, 124.1 (*p*-C of NPh and CPh), 119.3, 111.4, 110.2 (cat′), 112.5 (=CH_2), 35.4 (Bu^t C), 32.1 (Bu^tCH_3). ^{11}B (90 °C), δ 23.5. **3a**: ^1H, δ 7.6–6.9 (ov m, Ph + cat′, 13H), 5.19 (q, *J* 7, Hz, C*H*Ph), 1.64 (d, *J* 7 Hz, 3H, CH_3), 1.29 (9H, Bu^t); ^{13}C, δ 149.6, 147.5, 146.1, 144.6, 143.6 (*ipso*-C of CPh, NPh and cat′), 129.2, 129.0, 128.9, 127.9 (*o*-, *m*-C of NPh and CPh), 127.7, 126.2 (*p*-C of NPh and CPh), 118.9, 111.1, 109.8 (cat′), 58.4 (CN), 35.3 (Bu^t C), 32.1 (Bu^t CH_3), 20.0 (CH_3); ^{11}B (90 °C), δ 26.3. **4a**: ^1H, δ 7.5–6.8 (ov m, Ph + cat′, 16H), 5.59 ('tr', *J* 8 Hz, C*H*Ph), 2.25 (dd, *J* 16, 8.5 Hz, CH_2B), 2.12 (dd, *J* 16, 8 Hz, CH_2B), 1.30 (9H, Bu^t of NBcat′), 1.27 (9H, Bu^t of CBcat′); ^{13}C, δ 149.6, 149.2, 147.5, 147.0, 146.9, 146.0, 144.6, 143.5 (*ipso*-C of CPh, NPh, NBcat′ and CBcat′), 129.5, 129.2, 129.0, 128.1, (*o*-, *m*-C of NPh and CPh), 127.9, 126.5 (*p*-C of NPh and CPh), 119.9, 118.9, 111.8, 111.1, 110.3, 109.8 (cat′), 60.1 (CN), 35.4, 35.3 (Bu^t C), 32.1 (ov, 6C, Bu^t CH_3), 17.8 (br, CB); ^{11}B (90 °C), δ 35.7 (BC), 20.3 (BN). **5a**: ^1H, δ 7.6–6.9 (ov m, Ph + cat′, 19H), 6.06 (d, *J* 13 Hz, C*H*Ph), 3.17 (d, *J* 13 Hz, CHB_2), 1.32 (9H, Bu^t of NBcat′), 1.26, 1.25 (9H, Bu^t of CBcat′); ^{13}C, δ 62.2 (CN), 18.1 (br, CB).

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