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Catalytic β-Boration/Oxidation of 1-Azadienes

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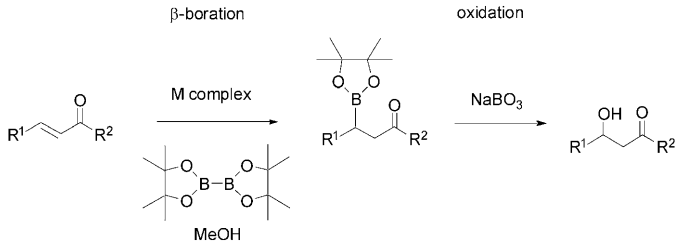
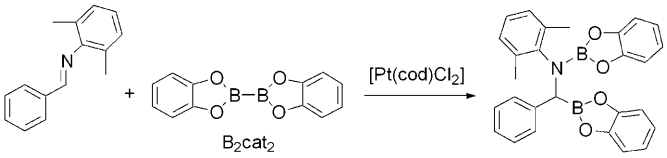
Dedicated to Dr. J. M. Brown on his 35 years at Oxford University

Metal-mediated B addition to the C_β atom of α,β-unsaturated carbonyl compounds, which is traditionally called the β-boration reaction, has been developed as an attractive route for the synthesis of valuable functionalized products,[1] and it is even available in a convenient asymmetric version.[2] The great stability of the anionic carbonyl moiety guarantees the success of the catalytic Michael addition reaction with MeOH as the electrophilic reagent (Scheme 1). We anticipated that the analogous β-boration/oxidation of α,β-unsaturated imines would provide an alternative synthesis of β-boryl imino derivatives as interesting intermediates toward β-aminoalcohols.



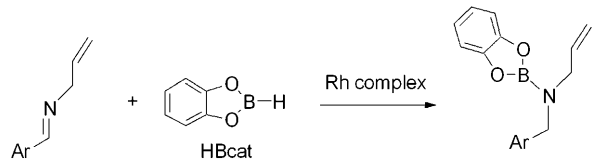
Scheme 1. Catalytic β-boration of α,β-unsaturated carbonyl compounds.

The catalytic B addition to imines and allylimines has been successfully carried out through metal-catalyzed diboration and hydroboration, respectively. Therefore bis(catecolato)diboron (B_2cat_2) was efficiently added to aldimines in the presence of [Pt(cod)Cl_2], providing the first direct route to α-aminoboronate esters[3] (Scheme 2). Alternatively, rhodium complexes mediated the hydroboration of allylimines



Scheme 2. Catalytic diboration of imines.

and it was particularly interesting that catecholborane (HBcat) reacted initially at the more reactive imine functionality to give unsaturated borylamines[4] (Scheme 3). However, to the best of our knowledge, no previous studies have been made about the catalytic B addition on electron-deficient olefins with a conjugated imine functional group.



Scheme 3. Catalytic hydroboration of allylimine.

We were interested in determining how the electronic nature of the imino group could stabilize the anionic intermediates in the ionic borylation process. We therefore focused on preparing a series of α,β-unsaturated imines and oximes with different electronic and steric properties. To this end, the related ketones reacted with substituted amines and hydroxylamine in the presence of montmorillonite K-10 (MK10)[5] (Scheme 4). The condensation of these reactants with MK10 is comparable to the use of molecular sieves in terms of catalytic and dehydrating properties.[6] Yields of pure isolated α,β-unsaturated imines were high and comparable to other synthetic methods described in the literature.[7,8]

The uncatalyzed addition of one equivalent of bis(pinacolato)diboron (B_2pin_2) or bis(cetecholato)diboron (B_2cat_2) to

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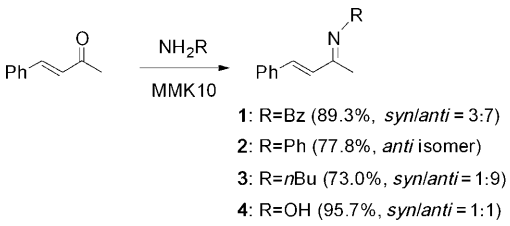
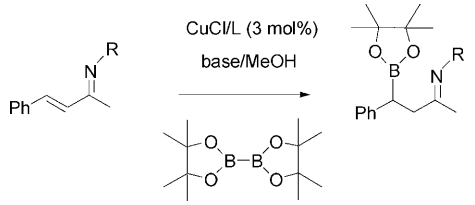


Scheme 4. Synthesis of α,β-unsaturated imines and oximes (% yields of isolated product and *syn*/*anti* ratio).

the imine (*E*)-1-phenyl-*N*-(4-phenylbutan-2-ylidene)methanamine (**1**) did not lead to any borylated product at room temperature. Therefore, the catalytic version was suggested instead. Since the use of inexpensive metals for the catalytic β-boration of α,β-unsaturated carbonyl compounds is considered to be the main goal of this reaction,[1g] we selected catalytic systems based on Cu^I salts modified with phosphine ligands. In early reports by Miyaura et al.,[1a,b] copper efficiently promoted the selective β-boron addition from diboron to α,β-unsaturated ketones, esters, and nitriles, and transmetalation from diboron to Cu^I salts was the key step in the mechanistic cycle, favoring the formation of B–Cu species. When imine **1** and B_2pin_2 reacted in the presence of 3 mol% of CuCl, no β-borated product was observed. B_2cat_2 was not so reactive in this reaction, despite previous related studies on Cu-catalyzed alkene diboration reaction.[9] However, when PCy_3 was added as the modifying ligand, conversions into the β-boryl imino derivative of about 32% were observed (Table 1, entry 1). Results were similar when MeOH was added as an additive, despite the enhanced reaction outcome observed by Yun et al.[2a] (Table 1, entry 2). However, the addition of one equivalent of NaO*t*Bu as base favored the quantitative transformation into the desired product (Table 1, entry 3). Alternative bases such as NaOAc, NaOMe, and NaOH were also highly efficient at promoting total conversion (Table 1, entries 4–6).

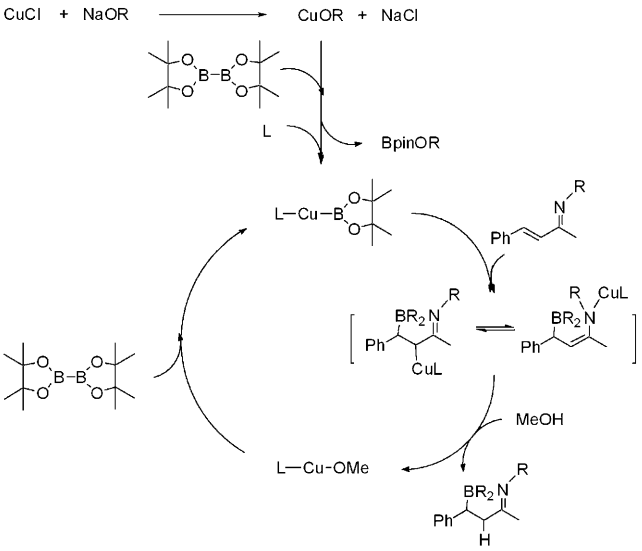
Table 1. Cu-mediated catalytic β-boration of α,β-unsaturated imines with B_2pin_2.[a]



Entry	Imine	Catalytic system	Additive	Base	Conv. [%][b]
1	**1**	$CuCl/PCy_3$	–	–	32
2	**1**	$CuCl/PCy_3$	MeOH	–	29
3	**1**	$CuCl/PCy_3$	MeOH	NaO*t*Bu	99
4	**1**	$CuCl/PCy_3$	MeOH	NaOAc	99
5	**1**	$CuCl/PCy_3$	MeOH	NaOMe	99
6	**1**	$CuCl/PCy_3$	MeOH	NaOH	99
7	**2**	$CuCl/PCy_3$	MeOH	NaO*t*Bu	99
8	**3**	$CuCl/PCy_3$	MeOH	NaO*t*Bu	99
9	**4**	$CuCl/PCy_3$	MeOH	NaO*t*Bu	34
10	**1**	$CuCl/PPh_3$	MeOH	NaO*t*Bu	99
11	**1**	CuCl/josiphos	MeOH	NaO*t*Bu	99

[a] Standard conditions: substrate/Cu = 1:0.03. B_2pin_2 = 1.1 equiv, NaO*t*Bu = 9 mol%, MeOH = 20 μL Solvent: THF (2.5 mL). T = 25 °C, t = 6 h. [b] Determined by ^1H NMR spectroscopy.

The base has a perceptible beneficial influence on the reaction outcome. It probably acts on the Cl^- displacement from the catalyst precursor and favors the transmetalation step between the Cu-OR catalytic species and the diboron reagent.[10] Recently we have demonstrated that (NHC)CuOMe (NHC = N-heterocyclic carbene ligands) can promote the β-boration of crotonaldehyde even in the absence of the base.[11] Shibasaki et al.[7a] also attributed LiO*i*Pr the role of an effective generator of active nucleophile allylcopper from CuF/phosphine and allylboronate. In this context, we have postulated a reaction mechanism based on a catalytic cycle in which the base favors the cleavage of the diboron reagent to promote the formation of the boryl copper intermediate. The formation of the metallo-enamine intermediate might be slower than the related anionic carbonyl moiety from the ketone. However, the fact that MeOH does not seem to be necessary to accelerate the reaction might indicate that the reactivity of the metallo-enamine towards the electrophile is quicker, as was expected (Scheme 5).



Scheme 5. Plausible mechanism for β-boration of α,β-unsaturated imines with B_2pin_2.

In order to gain further insight into the accelerated metallo-enamine pathway with the electrophile, a competitive reaction experiment was carried out in which α,β-unsaturated imine and ketone reacted with B_2pin_2 under the same reaction conditions but in the absence of MeOH. As Figure 1 shows, while imine **1** is consistently transformed into the β-borated product, the related ketone stays almost unreacted.

Under optimized reaction conditions, imines **2** and **3** were also conveniently β-borated (Table 1, entries 7 and 8). The electronic and steric nature of R in the imino group does

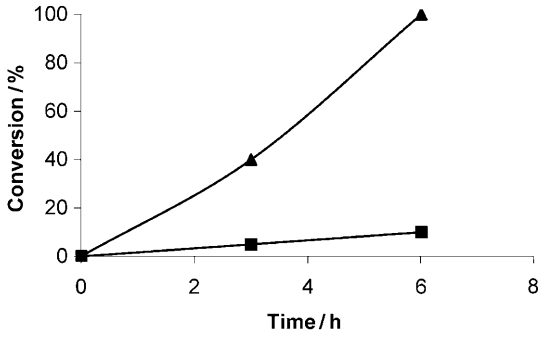
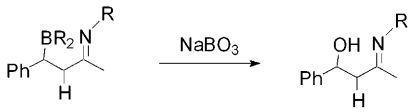


Figure 1. Competitive β-boration of imine (*E*)-1-phenyl-*N*-(4-phenylbutan-2-ylidene)methanamine (▲) and *trans*-4-phenyl-3-buten-2-one (■) with B_2pin_2.

not seem to influence the B addition reaction. However, when the oxime **4** was β-borated, only 34% of the substrate was transformed under mild reaction conditions (Table 1, entry 9). Higher reaction temperatures did not allow the reaction to go to completion. Alternative ligands were used with identical success, in the presence of NaO*t*Bu as base, but no asymmetry was induced in the new C–B bond even though chiral ligands were used (Table 1, entries 10 and 11).

To the best of our knowledge, β-imino boronate esters have only been previously prepared by Whiting et al.,[12] through an elegant condensation of β-keto boronate esters and primary amines, in the presence of molecular sieves. The corresponding β-keto boronate compound was prepared by alkylation of an enolate with an α-haloboronate ester[13] and alternatively via the hydrogenolysis of the oxime ether derivative.[11] Our methodology allows the synthesis of β-imino boronate esters even with substituents at the β-position of the C=N bond.

Eventually, the β-imino boronate intermediates were efficiently oxidized into their β-iminoalcohols in the presence of $NaBO_3$ as oxidizing reagent (Scheme 6). Remarkably, this



5: R=Bz (95.2%)
6: R=Ph (93.4%)
7: R=*n*Bu (91%)

Scheme 6. Oxidation of β-imino boronate esters.

was the first time that these products had been prepared, although the β-oxime boronate ester failed to be oxidized under these reaction conditions.

We can conclude at this point that β-iminoalcohols can be easily prepared in high yields through a copper-mediated β-boration/oxidation reaction in the presence of a diboron reagent. A base seems to be beneficial for quantitative C–B bond formation in the intermediate compounds. Further work will be devoted to the "in situ" reduction of the C=N bond but also to the asymmetric version of the reaction.

Experimental Section

General methodology for the synthesis of the imines and oxime: To a solution of the corresponding amine or hydroxylamine (5 mmol) in $CHCl_2$ (25 mL) was added the ketone (5 mmol) and montmorillonite K10 (1 g). The resulting solution was stirred for 16 h at room temperature, and then filtered through celite. Neat α,β-unsaturated imine or oxime was obtained after distillation.

Typical catalytic β-boration of α,β-unsaturated imines and oxime: Bis(catecholato)diboron (1.1 equiv) was added to a solution of the catalyst (2 mol%) and base (3 mol%) in tetrahydrofuran (2 mL) under nitrogen. The solution was stirred for 5 min and the substrate (0.05 mmol) was then added with 2 mL of MeOH. The mixture was stirred for 6 h at room temperature. The products obtained were analyzed by ^{1}H NMR spectroscopy to determine the degree of conversion and the nature of the reaction products. Products were purified by flash column. (*E*)-*N*-(4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)butan-1-amine: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.71–7.19$ (m, 5H), 3.54 (t, $J = 8$ Hz, 2H), 3.03 (dd, $J = 20$, 8 Hz, 1H), 2.81 (dd, $J = 20$, 8 Hz, 1H), 2.65 (m, 1H), 2.18 (s, 3H), 1.43 (m, 2H), 1.24 (m, 14H), 0.88 ppm (t, $J = 8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 160.99$, 134.62, 129.00, 128.35, 127.07, 87.76, 61.72, 52.15, 32.70, 29.73, 27.79, 21.21, 13.98 ppm; ^{11}B NMR ($CDCl_3$, 128.3 MHz): $\delta = 21.72$ ppm. (*E*)-*N*-(4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)aniline: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.46–7.19$ (m, 10H), 3.09 (m, 1H), 2.91 (m, 1H), 2.64 (m, 1H), 2.19 (s, 3H), 1.32 ppm (m, 12H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 169.99$, 148.93, 145.35, 132.77, 132.42, 131.39, 131.08, 130.11, 129.46, 87.27, 52.63, 29.53, 25.62, 19.67 ppm; ^{11}B NMR ($CDCl_3$, 128.3 MHz): $\delta = 21.38$ ppm. (*E*)-1-phenyl-*N*-(4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)methanamine: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35–7.07$ (m, 10H), 4.80 (dd, $J = 12$ Hz, 1H), 4.65 (dd, $J = 12$ Hz, 1H), 3.03 (dt, $J = 20$, 8 Hz, 1H), 2.77 (dd, $J = 20$, 8 Hz, 1H), 2.25 (m, 1H), 2.10 (s, 3H), 1.19 ppm (m, 12H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 167.90$, 139.54, 136.63, 136.24, 132.94, 128.37, 126.65, 126.34, 125.7, 88.16, 51.19, 36.72, 29.40, 22.17, 13.25 ppm; ^{11}B NMR ($CDCl_3$, 128.3 MHz): $\delta = 21.18$ ppm.

The oxidation protocol: A solution of sodium perborate (2.5 mmol) in THF/water (1:1, 4 mL) was added to the reaction mixture of the β-boration before product purification. The mixture was stirred vigorously for 4 h. After this time, it was quenched with a saturated solution of NaCl and then extracted into AcOEt (3×20 mL). The organic phase was dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent. The β-iminoalcohols were purified by flash chromatography with hexane/ethyl acetate (5:1) as an eluent. (*E*)-3-(benzylimino)-1-phenylbutan-1-ol: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.80–7.20$ (m, 10H), 5.11 (dd, $J = 20$, 12, MHz, 1H), 4.77 (s, 2H), 2.87–2.79 (m, 2H), 2.13 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): $\delta = 162.97$, 136.14, 132.76, 128.20, 127.05, 69.74, 55.13, 51.27, 18.9 ppm. (*E*)-3-(butylimino)-1-phenylbutan-1-ol: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.74–7.25$ (m, 5H), 5.03 (dd, $J = 20$, 12.3 Hz, 1H), 3.56 (t, $J = 20$, 6.8 Hz, 2H), 2.88–2.72 (m, 2H), 2.13 (s 3H), 1.65–1.59 (m, 2H), 1.38–1.31 (m, 2H), 1.07 ppm (t, $J = 7.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): $\delta = 162.69$, 128.72, 128.59, 128.32, 127.68, 69.82, 51.98, 34.66, 30.79, 24,84, 18.94, 13.82 ppm. (*E*)-1-phenyl-3-(phenylimino)butan-1-ol: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.80–7.20$ (m, 10H), 5.11 (dd, $J = 17.6$, 11 Hz 1H), 2.87–2.79 (m, 2H), 2.13 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): $\delta = 169.71$, 129.12, 128.54, 127.32, 127.68, 126.239, 125.614, 69.82, 51.98, 19.54 ppm.

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