The selective catalytic formation of β-boryl aldehydes through a base-free approach†

Amadeu Bonet,[a] Vanesa Lillo,[a] Jesús Ramírez,[a] M. Mar Díaz-Requejo[b] and Elena Fernández*[a]

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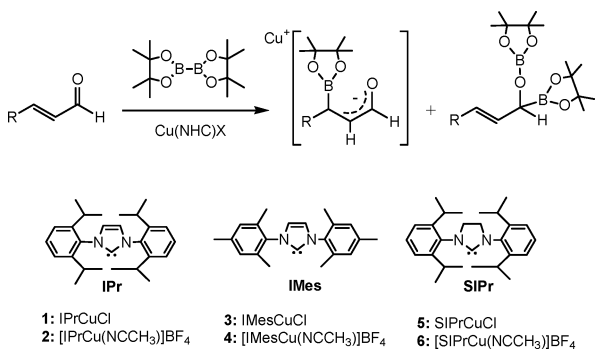
(NHC)Cu(I) complexes are key in a new strategy to selectively add a boron unit at the β-position of α,β-unsaturated aldehydes in the absence of a base.

In the catalytic diboration of alkenes,[1] the metal-mediated 1,4-addition of diboron reagents to electron-deficient olefins is the most convenient approach for preparing β-boryl carbonyl compounds.[2] Of particular interest is the recent work on the asymmetric version of this reaction.[3] Conceptually, only one boryl unit from the diboron reagent is catalytically added to the β-position of the substrate, affording the 1,4-hydroborated product after a hydrolytic workup. The range of α,β-unsaturated carbonyl substrates that undergo 1,4-addition with bis(pinacolato)diboron (B_2pin_2) is indeed broad.[2,3] It includes acetylenic esters,[4] vinylic esters, vinylic ketones, vinylic nitriles and vinylic phosphonates, and extends to allylic carbonates.[5] However, the metal-catalysed β-boration of the most challenging α,β-unsaturated aldehydes has only previously been reported with Rh[2d] and Pt[2e] catalysts because the reaction suffers from a competitive 1,2-diboron addition reaction.[6] Taking advantage of the benefits of copper-mediated B-addition reactions,[2a] we decided to establish a general methodology for copper-catalysed β-boration of α,β-unsaturated aldehydes (Scheme 1). To this end, and because of their success in the selective diboration of alkenes and alkynes,[7] and more recently in the carboxylation of organoboronic esters,[8] we have investigated the potential of several complexes containing the (NHC)Cu core as the catalyst for this reaction.



Scheme 1 Catalytic β-boration of α,β-unsaturated aldehydes.

[a]*Univeridad Rovira i Virgili, C/Marcel.lí Domingo s/n, 43005, Tarragona, Spain. E-mail: mariaelena.fernandez@urv.cat; Fax: +34 977 559563; Tel: +34 977 558046*
[b]*Univeridad de Huleva Campus de El Carmen, 21007, Huelva, Spain*

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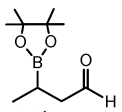
Table 1 (NHC)CuCl- and $[(NHC)Cu(NCCH_3)]BF_4$-catalysed β-boration of crotonaldehyde with B_2pin_2[a]

Entry	Catalyst	Base	Conv. (%)[b]	 (%)[b,c]
1	**1**	NaO^{t}Bu	99	52
2	**2**	NaO^{t}Bu	99	43
3	**3**	NaO^{t}Bu	99	60
4	**4**	NaO^{t}Bu	99	39
5	**5**	NaO^{t}Bu	99	48
6	**6**	NaO^{t}Bu	99	39
7	**3**	NaOMe	99	59
8	**3**	NaOAc	99	41
9	**3**	—	99	33
10[d]	**3**	NaO^{t}Bu	80	75

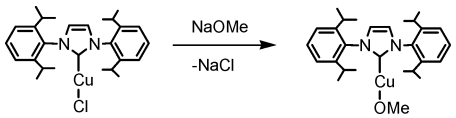
[a] Standard conditions: Substrate/Cu complex = 0.5/0.01, 3 mol% base, 1.1 eq. of bis(pinacolato)diborane (B_2pin_2), 2 eq. MeOH, THF, 25 °C, 6 h. [b] Determined by ^{1}H NMR. [c] The 1,2-diborated product was a byproduct. [d] Temperature = 90 °C.

The catalytic effect of copper modified with NHC ligands on the β-boration was first established when 2 mol% of complexes **1–6** were used as catalyst precursors to react crotonaldehyde (R = Me) with B_2pin_2 in THF. A base and MeOH were added to enhance the reactivity, in agreement with the optimised protocol suggested by Yun *et al.*[3] While the crotonaldehyde substrate was quantitatively consumed in all cases (Table 1, entries 1–6), chemoselectivity on the expected β-boryl carbonyl compound was only moderate. The neutral IMesCuCl catalytic system was the most chemoselective (Table 1, entry 3), within 6 h, at room temperature.

We next explored the role of the base, as it has been postulated that it acts on the Cl^- displacement from the precursor of catalyst LCuCl and favours the transmetallation step between the Cu catalytic species and the diboron, in the mechanism proposed by Yun *et al.*[3] The presence of a base might also stabilise the fragments from the heterolytic cleavage of B_2pin_2, as we postulated in a previous study.[9] The nature of the base and even the need for it were therefore taken into consideration. The β-boration of crotonaldehyde in the presence of cationic catalyst precursor **3** provided 41%, 59% and 60% of the β-borated product when AcO^-, MeO^- and $^tBuO^-$ were used, respectively (Table 1, entries 3, 7–8). More remarkably, the β-boration of crotonaldehyde proceeded in the absence of a base, but the chemoselectivity was lower (Table 1, entry 9). Only a slight increase in chemoselectivity was observed when the reaction temperature was higher (90 °C, Table 1, entry 10).

We envisaged the possibility of using (NHC)CuOR′ as a catalyst precursor to prevent the activation of the catalyst, and therefore

prevent the use of the base. To this end we prepared, for the first time, the complex IPrCuOMe from the corresponding chloride, by reacting with sodium methoxide (Scheme 2). The characterization of the complex IPrCuOMe comes directly from spectroscopic data. The ^{1}H NMR spectrum shows a set of resonances that indicate the existence of two equivalent aromatic substituents, as well as two equivalent C–H groups in the imidazolydene ring, in a similar manner to that previously observed for related complexes of formulae (NHC)CuCl.[10] This equivalence is also observed in the corresponding resonances in the ^{13}C{^{1}H} NMR spectrum. The most significant resonance is that of the OMe group, which gives rise to a broad singlet centred at 3.78 ppm in the ^{1}H NMR spectrum. Heteronuclear experiments have shown that the resonance of the carbon nucleus appears at 51.3 ppm as a very broad hump.

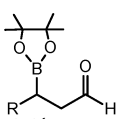


Scheme 2 Synthesis of (NHC)CuOMe complex.

When catalyst precursor IPrCuOMe was involved in the β-boration of crotonaldehyde in the absence of base, the substrate was completely converted into the corresponding β-boryl aldehyde (Table 2, entry 1). Significantly, the reaction time decreased from 6 h to 1 h. However, MeOH seems to be necessary under those new reaction conditions, because the reaction is not completed in its absence and the chemoselectivity decreases to 63% of the desired product.

IPrCuOMe was also active in a series of related substrates (Table 2, entries 2 and 3), although the conversion significantly diminished in the β-boration of phenylcinnamate and required longer reaction times for quantitative conversions (Table 2, entry 4). However, the 1,4 B-addition was also predominant in all these cases. Because of the beneficial effect of the alkoxy moiety on the copper complex we prepared the analogous IPrCuO^{t}Bu complex[11] and used it for catalytic purposes. Improved catalytic activity and chemoselectivity with IPrCuO^{t}Bu was observed in the β-carbon of crotonaldehyde and phenylcinnamate (Table 2, entries 5 and 6). In the presence of a quarter of the catalyst loading, the reaction was completed within 20 min, and gave excellent yield and chemoselectivity for the β-organoboronate derivative (Table 2, entry 7).

Table 2 IPrCuOR′-catalysed the base-free β-boration of crotonaldehyde with B_2pin_2[a]

Entry	R	IPrCuOR′	Conv. (%)[b]	 (%)[b]
1	Me	IPrCuOMe	99	84
2	Et	IPrCuOMe	99	86
3	Pr	IPrCuOMe	99	95
4	Ph	IPrCuOMe	19	90
5	Me	IPrCuO^{t}Bu	99	90
6	Ph	IPrCuO^{t}Bu	43	95
7[c]	Me	IPrCuO^{t}Bu	99	90

[a] Standard conditions: Substrate/Cu complex = 0.5/0.01, 1.1 eq. of bis(pinacolato)diborane (B_2pin_2), 2 eq. MeOH, THF, 90 °C, 1 h. [b] Determined by ^{1}H NMR. [c] Catalyst loading 0.5 mol%, 20 minutes.

Two significant advantages were observed when alkoxy copper(I) complexes were used: higher catalytic activity and higher chemoselectivity. Both trends can be seen in Fig. 1, which compares activity and chemoselectivity within 80 minutes of reaction. A similar acceleration of the hydroboration of vinylarenes in the presence of AcO^- as counterion in the catalyst [Rh(OAc)(cod)]$_2$/DPPB (1,4-bis(diphenylphosphino)butane) has recently been reported, providing the most powerful and practical approach to date.[12]

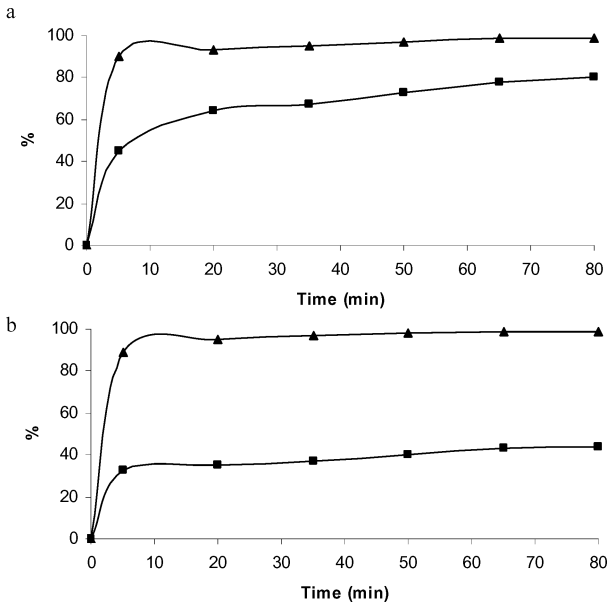
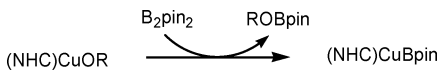


Fig. 1 Catalytic profiles for β-boration of crotonaldehyde with IPrCuO^{t}Bu (▲), and [IPrCu(NCCH$_3$)]BF$_4$ (■). (a) % conversion and (b) % chemoselectivity for 1,4 B-addition.

Our current understanding of this transformation suggests that in the absence of base, the precursor of catalyst (NHC)CuOR could react with the bis(pinacolato)diboron to promote a Cu-boryl intermediate (Scheme 3). Hou *et al.*[8] have recently reported that IPrCuO^{t}Bu transmetallates arylboronic esters to afford the corresponding arylcopper complex. However, no reaction was observed between IPrCuCl and the borane unless the base KO^{t}Bu was added to the media. In our study, the alkoxy group seems to be crucial in favouring the heterolytic cleavage of the diboron, transmetallating and stabilizing the second boryl unit as ROBpin.



Scheme 3 Postulated transmetallation step.

Finally, and under the standard conditions of Table 2, we studied the β-boration of more hindered α- and β-substituted α,β-unsaturated aldehydes (Fig. 2). While 3-methylcrotonaldehyde proceeded in a similar way to crotonaldehyde, the α-substituted substrates (*trans*-2-methyl-2-butenal, *trans*-methyl-2-pentenal) did not convert even after 16 h of reaction. Only 1-cyclohexene-1-carboxaldehyde provided a slight conversion with quantitative

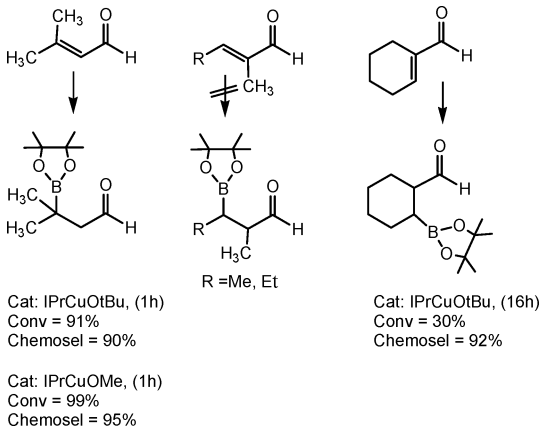


Fig. 2 Catalytic β-boration of α- and β-substituted α,β-unsaturated aldehydes.

chemoselectivity towards the desired product as a diastereoisomeric mixture, within 16 h. The steric properties of the substrate seem to have a considerable influence on the reaction outcome.

In conclusion, we have found a new strategy for the (NHC)Cu-mediated chemoselective β-boration of α,β-unsaturated aldehydes with bis(pinacolato)diboron. In the absence of base, the (NHC)CuOR catalyst precursors (where OR = OMe, O^{t}Bu) transformed quickly into their corresponding β-organoboronate derivatives. These precursors are very stable synthons for use in organic synthesis. We are currently studying the asymmetric version of this reaction by modifying copper complexes with chiral NHC ligands.

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