Copper-catalyzed addition of diboron reagents to α,β-acetylenic esters: efficient synthesis of β-boryl-α,β-ethylenic esters†

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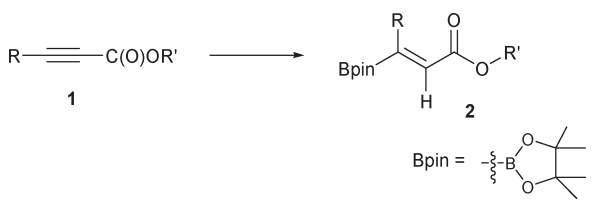
The efficient copper-catalyzed addition reaction of bis(pinacolato)diboron to α,β-acetylenic esters has been developed, which produces the corresponding β-borylated-α,β-ethylenic esters in high yields under mild reaction conditions.

Vinylboronates are versatile organic synthetic intermediates that have been widely used in various carbon–carbon bond forming reactions.[1] While simple vinylboronates can be easily accessed by either conventional[2] or metal-catalyzed hydroboration of alkynes,[3] a general preparation method for electron deficient vinylboronates, *i.e.* β-borylated-α,β-ethylenic carbonyl compounds, is still lacking; only β-boryl acrylates are available by a multi-step procedure of hydroboration of propiolic acid esters with alkylboranes, followed by conversion of the products to the stable pinacol boronates.[4] In the case of β-substituted propiolic acid esters, it was reported that the regioselective introduction of a boronate group at the β-position is not possible due to steric effects.[5]

Given that electron deficient β-borylated-α,β-ethylenic carbonyl compounds have recently exhibited interesting synthetic potential as reactive dienophiles in cycloadditions[4b,6] and radical acceptors,[7] in addition to their wide applications in cross coupling reactions,[1,8] the development of a general and efficient preparation method for these highly functionalized compounds is required.

Recently, we have reported an efficient copper-catalyzed conjugate addition of bis(pinacolato)diboron (B_2pin_2) to α,β-ethylenic carbonyl compounds that produced the corresponding saturated alkyl boronic esters.[9] We were intrigued by the possibility of utilizing this reaction for the addition reaction with α,β-acetylenic esters (**1**) to obtain β-borylated-α,β-ethylenic esters (**2**) (Scheme 1). We report here the first example of catalytic and stereoselective preparation of **2** that is efficiently catalyzed by a copper-chelating bisphosphine complex in the presence of methanol.



Scheme 1 Synthetic route to β-borylated-α,β-ethylenic carbonyl compounds from alkyno esters **1**.

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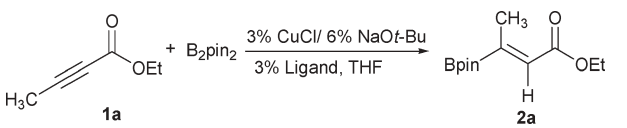
In our initial experiments, we investigated the boron addition reaction of ethyl 2-butynoate (**1a**) by employing a catalytic amount of copper salt and ligand in the presence of B_2pin_2 in THF. We initially chose DPEphos[10] or Xantphos[10] as the ligand on the basis of their efficiency in the β-boration of ethyl crotonate[9a] and examined a range of reaction conditions.

As shown in Table 1, the reaction without the methanol additive showed no appreciable conversion at room temperature (entry 1). Increasing the reaction temperature to 70 °C resulted in moderate conversion and isolated yield (entry 2). However, addition of the alcohol to the reaction mixture led to an enhanced rate of reaction at room temperature and the reactions with either DPEphos or Xantphos proceeded with good conversion (entries 3 and 4). The *syn* addition product, (*Z*)-**2a**[8] was exclusively formed. Xantphos ligand performed better than DPEphos ligand, as the reaction with DPEphos proceeded with incomplete conversion and concurrent production of a small amount of the diboration product (**2a′**). Another bidentate phosphine ligand, dppf, was tried, but it gave inferior results and formed a large amount of the β,β-diborylated product[11] (entry 6).

With an optimal reaction protocol using Xantphos ligand and methanol as an additive in the presence of 1.1 equivalents of B_2pin_2,[12] the copper-catalyzed β-boration of various α,β-acetylenic esters was examined (Table 2). Both primary (**1b**, **1d**) and secondary alkyl substituted acetylenic esters (**1c**) proceeded smoothly within the reaction time to provide the addition products with excellent stereoselectivity in high yield (entries 1–3). Ester **1e**, derived from the corresponding protected propargyl alcohol, was

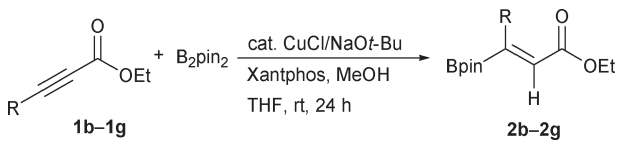
Table 1 Optimization of catalytic addition of B_2pin_2 to ethyl 2-butynoate (**1a**)



Entry	Ligand	Additive (equiv.)	Temp./°C	Time/h	Conv. (%)[a]	Yield (%)[b]
1	DPEphos	—	rt	14	No rxn	—
2	DPEphos	—	70	18	64	51
3	DPEphos	MeOH (2)	rt	6	93	81[c]
4	Xantphos	MeOH (2)	rt	6	100	86
5	Xantphos	MeOH (1)	rt	24	100	85
6	dppf[d]	MeOH (2)	rt	14	90	—[e]

[a] Conversion was determined on the basis of consumed starting material by GC analysis. [b] Isolated yields of **2a**. [c] 2% of diborylated product (**2a′**) was formed. [d] dppf = 1,1-bis(diphenylphosphino)-ferrocene. [e] **2a** : **2a′** = 3.3 : 1.

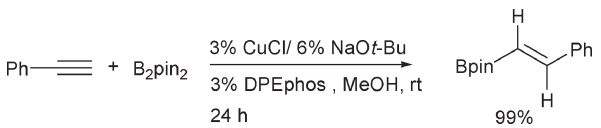
Table 2 Copper-catalyzed β-boration of α,β-acetylenic esters[a]



1b–1g 2b–2g

Entry	Substrate	R	Product	Yield (%)[b]
1	**1b**	*n*-C_6H_{13}	(*Z*)-**2b**	93
2	**1c**	Cyclohexyl (Cy)	(*Z*)-**2c**	99
3	**1d**	Cy–CH_2	(*Z*)-**2d**	88
4[c]	**1e**	THPO–CH_2	(*Z*)-**2e**	77
5[d]	**1f**	*t*-Bu	(*E*),(*Z*)-**2f**	71
6[e]	**1g**	H	(*E*)-**2g**	65

[a] Reaction conditions: 3 mol% CuCl, 6 mol% NaO*t*-Bu, 3 mol% Xantphos, 2 equiv. MeOH with 1.1 equiv. B_2pin_2 in THF at room temperature. Reaction time is not optimized. [b] Isolated yield of borylated product (**2**). [c] **2e** : protodeboronated product = 87 : 13 by GC and NMR analysis. [d] A mixture of (*E*)- and (*Z*)-isomers (66 : 34) was obtained. [e] 90% conversion.



Scheme 2 Addition reaction with phenylacetylene.

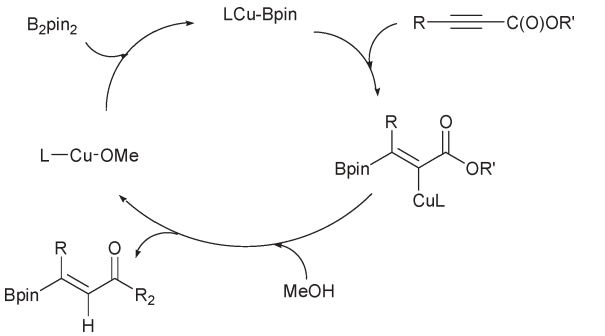
reacted to give the desired borylated product **2e** along with formation of the protodeboronated product[13] under the reaction conditions (entry 4).

In general, the addition reaction was shown to be highly stereoselective, affording the product of *syn* addition to the triple bond almost exclusively except for the *tert*-butyl substituted ester **1f**. When R was *t*-Bu, mixtures of (*E*)- and (*Z*)-isomers were obtained (entry 5).[14] This loss in stereoselectivity presumably results from the equilibration of copper enolates[15] generated by the addition of copper boryl species to the ester. Although ethyl propiolate **1g** gave lower conversion compared with other β-substituted substrates examined, it afforded the *syn* addition product in reasonable yield (entry 6).

In order to examine if an electron withdrawing group is a requisite for the reaction, we investigated the addition reaction with phenylacetylene (Scheme 2). While a simple aliphatic alkyne, 1-octyne, was not reactive, phenylacetylene gave the addition product[2b] in high yield with DPEphos ligand.

A possible catalytic cycle for the β-boration of α,β-acetylenic esters is shown in Scheme 3. A phosphine ligated copper boryl complex conjugatively adds to the ester and the resulting copper enolate reacts with MeOH to yield the protonated product and a copper alkoxide, which regenerates the active catalyst with B_2pin_2.

In summary, we have developed an efficient procedure for the conjugate addition of bis(pinacolato)diboron to α,β-acetylenic esters based on a copper–phosphine catalyst, which provides a route to stereoselective synthesis of β-borylated-α,β-ethylenic esters. Studies are under way to extend the application of the boron derivatives to organic synthesis.



Scheme 3 A proposed catalytic cycle.

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