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A masked diboron in Cu-catalysed borylation reaction: Highly regioselective formal hydroboration of alkynes for synthesis of branched alkenylborons

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The use of a masked diboron as a boron source in the presence of a Cu–*N*-heterocyclic carbene (NHC) catalyst enables alkyl-, aryl-, heteroatom- and silyl-substituted terminal alkynes to undergo α-selective formal hydroboration to give diverse branched alkenylboron compounds exclusively. Synthetic potential
10 of this α-selective hydroboration has been demonstrated by total synthesis of pharmaceutically significant bexarotene and LG100268.

The development of new methods for accessing regio- and stereodefined alkenylboron compounds has been one of the central subjects in chemical synthesis,[1] because it provides us a
15 convenient and potent entry to invaluable multisubstituted alkenes with controlled geometry through carbon–carbon bond-forming processes including Suzuki–Miyaura coupling,[2] the Petasis reaction,[3] transition metal-catalysed conjugate addition,[4] *etc.* One of the most straightforward approaches to alkenylboron
20 compounds would be hydroboration of alkynes,[5] and the anti-Markovnikov addition to terminal alkynes commonly occurs to provide linear alkenylboron compounds with high β-selectivity, regardless of the presence[6] or absence[7] of a transition metal catalyst (eqn (1)).

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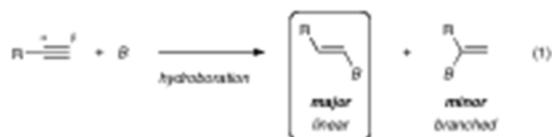
In marked contrast, selective access to branched alkenylboron compounds, regioisomers of linear ones, is narrow and laborious, because the existing procedures require multistep operation by use of preformed branched alkenyl anionic species[8] or halides.[9]
30 Although Miyaura[10a] and Hoveyda[10b] reported on direct synthesis of branched alkenylboron compounds via α-selective hydroboration of terminal alkynes using bis(pinacolato)diboron and a copper complex, these methods are still not versatile unfortunately, because of the confined substrate scope on
35 alkynes, the imperfect regioselectivity and the use of stoichiometric amounts of a copper complex (the former case). In view of the fact that 1,1-disubstituted alkenes are ubiquitous motifs in such biologically and pharmacologically significant molecules as apoatropine,[11] bexarotene,[12] dehydro-α-curcumene[13]
40 and isocombretastatin A-4[14] (Fig. 1), the development of catalytic and truly α-selective hydroboration of terminal alkynes with broad scope, which opens up a direct way to these valuable
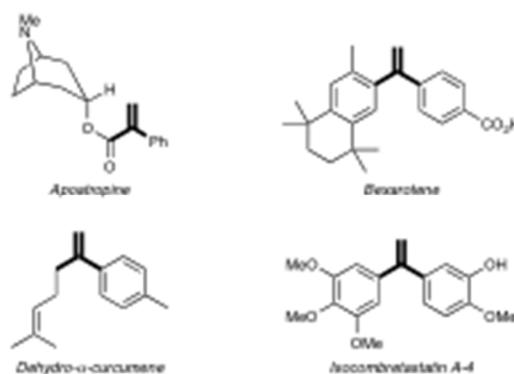
Fig. 1 Selected valuable compounds having a 1,1-disubstituted alkene
45 moiety.

classes of compounds, has been a long-sought goal.

We have recently devoted our attention to developing copper-catalysed borylation reactions of unsaturated carbon linkages[15] involving alkenes, alkynes and arynes by use of
50 bis(pinacolato)diboron as a boron source, and accomplished diborylation,[16a] borylstannylation[16b] and carboboration[16c] which enable previously inaccessible organoboron compounds to be synthesized efficaciously. The regiochemical outcomes of these reactions are definitively governed by mode of addition of a
55 borylcopper species, derived from (pin)B–B(pin) and a copper(I) complex, across the unsaturated C–C bonds, and anti-Markovnikov selectivities are usually observed with terminal alkynes (and alkenes) as depicted in Scheme 1. Similarly to the conventional uncatalysed hydroboration, one of the chief factors
60 affecting the orientation of the approaching borylcopper species should be the Lewis acidic character of the (pin)B moiety, which favours addition to the terminal carbons to generate more stable carbocationic transition state. We thus hypothesized that diminishing a Lewis acidity of a boron centre with appropriate
65 substituents may alter the regiochemical behaviour of a
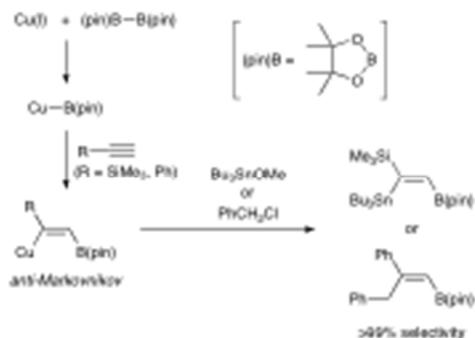
Scheme 1 Cu-catalysed borylstannylation and carboboration of terminal alkynes with *anti*-Markovnikov selectivity.

borylcopper species in the borylcupration step, leading to Markovnikov selectivity. Herein we report that the highly α-selective hydroboration of terminal alkynes with broad scope is achievable by use of a masked diboron[17] as a boron source under copper catalysis.

We first carried out the reaction of phenylacetylene with a diboron ((pin)B–B(dan)),[18] one of whose boryl moiety was masked with 1,8-diaminonaphthalene (dan),[19] in THF in the presence of a sterically congested *N*-heterocyclic carbene (NHC)-coordinated copper complex ((SIPr)CuCl, 2 mol%),[20] KO*t*Bu and MeOH,[21] and observed that the B(dan) moiety was introduced with exclusive α-selectivity to afford a branched borylstyrene (**1a**) in 81% yield (Table 1, entry 1). *ortho*- and *para*-Methoxy-substituted arylalkynes were also facilely convertible into the respective α-borylstyrenes (**1b** and **1c**) in excellent yields (entries 2 and 3), being in marked contrast to the Hoveyda's results that a mixture of α- and β-borylalkenes was produced (41:59 for *ortho*-methoxyphenylacetylene; 62:38 for *para*-methoxyphenylacetylene).[10b] Although a small amount of a linear borylalkene (**1'd**) was formed exceptionally in the reaction of *p*-CF₃-phenylacetylene, the selectivity for a branched one (**1d**) was still 95% (entry 4). It should be noted that the present hydroboration proceeded with the high degree of the α-selectivity, irrespective of steric and electronic properties of teminal alkynes employed, giving boryl-substituted aliphatic alkenes (**1e** and **1f**), silylalkene (**1g**) and allyl ether (**1h**) in high yields (entries 5–8). Furthermore, the high functional group compatibility of the reaction was demonstrated by use of 4-bromo-1-butyne, leaving the C–Br bond intact (**1i**, entry 9), and the reaction was applicable to 1,7-octadiyne, both of whose triple bonds underwent the α-selective hydroboration to give diborylation product **1j** (entry 10).

Synthetic utility of the α-selective formal hydroboration has been demonstrated by total synthesis of bexarotene (**4**), being used to treat cutaneous T-cell lymphoma (Scheme 2).[12] Thus, a branched borylalkene (**1k**) was available as the sole product in 97% yield by the formal hydroboration of the respective arylalkyne, where only 0.1 mol% catalyst loading was enough for excellent conversion and regioselectivity. Unmasking of the B(dan) moiety of **1k** under acidic conditions provided **2**,[22] whose C–B(pin) bond was coupled with methyl 4-iodobenzoate in the presence of a palladium catalyst to afford **3**. Hydrolysis of the ester moiety of **3** finally gave bexarotene (**4**) in 60% overall yield (4 steps, based on the alkyne). Similarly, the cross-coupling of **2**

Table 1 Scope of Cu-catalysed α-selective hydroboration of terminal alkynes.

Entry	Product	Yield/%[a]	α:β[b]
1	**1a**	81	>99:1
2	**1b**	99	>99:1
3	**1c**	92	>99:1
4	**1d**	67	95:5
5	**1e**	92	>99:1
6	**1f**	79	>99:1
7	**1g**	99	>99:1
8	**1h**	99	>99:1
9	**1i**	99	>99:1
10[c]	**1j**	95	>99:1

[a] Isolated yield. [b] Ratio of products determined by ¹H NMR. [c] Reaction carried out with half the molar of an alkyne.

with ethyl 6-chloronicotinate produced a 78% yield of diarylalkene (**5**).[23] Subsequent cyclopropanation with a sulfoxonium ylide, followed by hydrolysis of the resulting diarylcyclopropane (**6**) furnished LG100268 (**7**),[24] a high affinity,
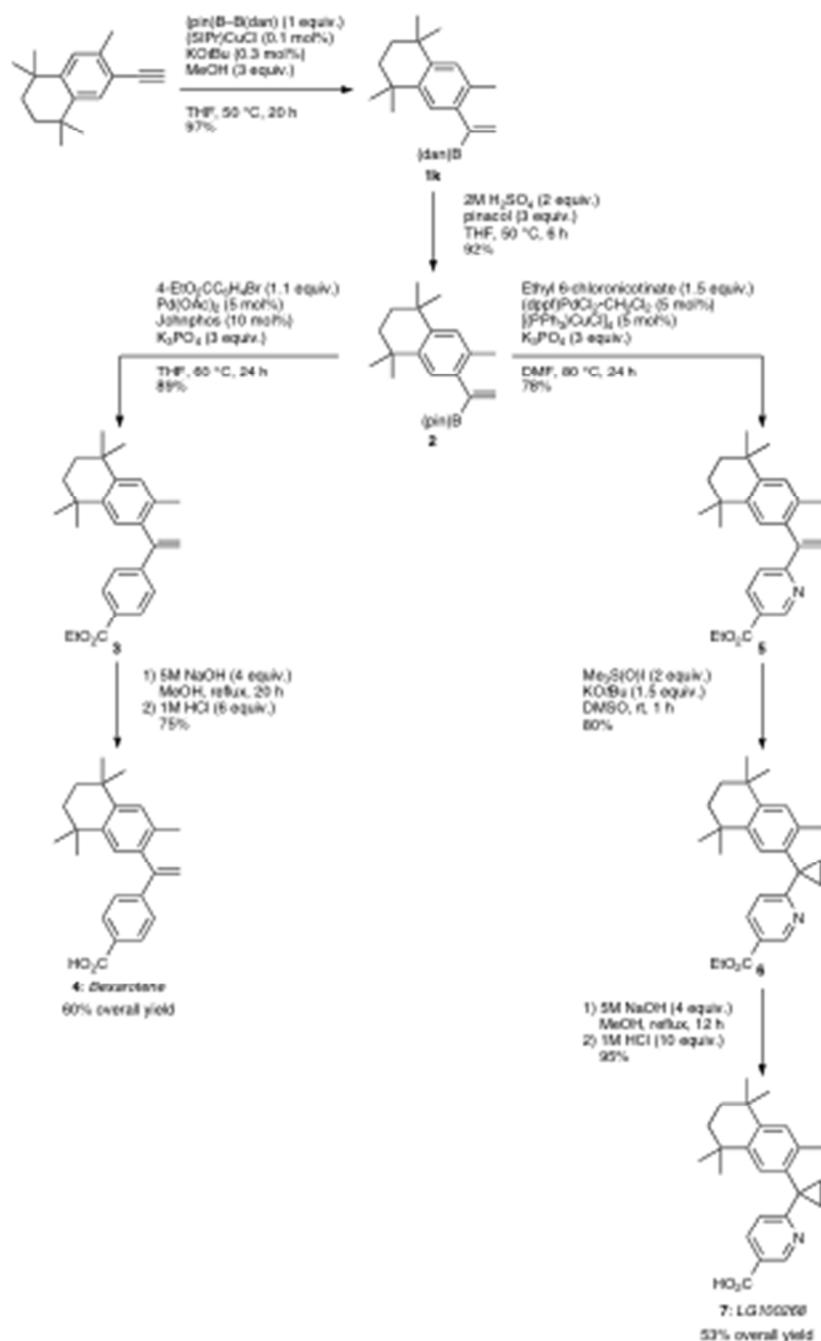
Scheme 2 Total synthesis of bexarotene and LG100268.

selective retinoid X receptor (RXR) agonist, in 53% overall yield (5 steps, based on the alkyne).

The present hydroboration would be triggered by exclusive formation of a borylcopper species, Cu–B(dan), which can be rationally explained by selective interaction between the Lewis acidic B(pin) moiety of (pin)B–B(dan) and the alkoxy moiety of Cu–OR in σ-bond metathesis step. Subsequent insertion of an alkyne into the Cu–B(dan) bond which generates a β-borylalkenylcopper species, followed by protonation with MeOH provides the hydroboration product with regeneration of Cu–OR (Scheme 3). Owing to the diminished Lewis acidity of the masked B(dan) moiety[19] in Cu–B(dan), the interaction between an incoming terminal alkyne and the boron centre, which may be a contributory factor of anti-Markovnikov-type (β-selective) addition through more stable carbocationic transition state (*vide supra*),[25] would be negligible in the borylcupration step. Therefore the orientation of Cu–B(dan) should simply be controlled by steric repulsion between a substituent on alkynes and the bulkier copper moiety, which results in the sole introduction of the B(dan) moiety into the internal carbon of terminal alkynes.

In conclusion, we have developed the first general α-selective hydroboration by combining a masked diboron and (SIPr)CuCl catalyst, that leads to the direct and potent method for
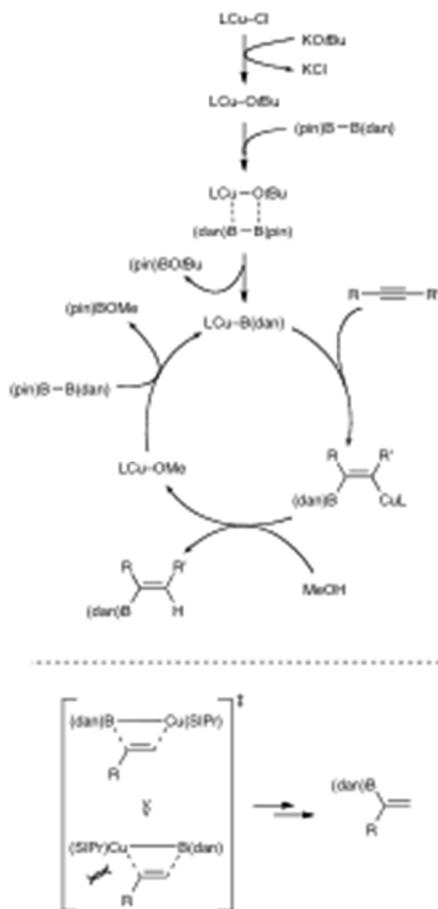
Scheme 3 Catalytic cycle for the Cu-catalysed hydroboration of alkynes.

synthesizing diverse branched borylalkenes, irrespective of electronic and steric nature of terminal alkynes employed. The resulting branched borylalkene has proven to be synthetically useful for fabricating pharmacologically significant compounds such as bexarotene and LG100268. Further studies on borylation reactions using a masked diboron under copper catalysis as well as on mechanistic details are in progress.

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