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Aluminum-hydride catalyzed hydroboration of alkynes

Alessandro Bismuto,^[a] Stephen P. Thomas*,^[a] Michael J. Cowley*^[a]

Abstract: The aluminum-catalyzed hydroboration of alkynes is reported using either commercially available aluminum hydride DIBAL-H (H-AIⁱBu₂) or bench stable Et₃Al-DABCO as the catalyst and H-Bpin as both the boron reagent and stoichiometric hydride source. Mechanistic studies reveal a unique mode of reactivity where the reaction is proposed to proceed by hydroalumination and σ -bond metathesis between the resultant alkenyl aluminum species and HBpin acting to drive turnover of the catalytic cycle.

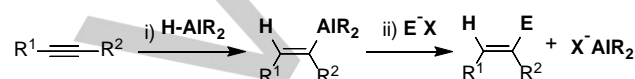
Transition metal catalysis has revolutionized synthetic chemistry. However, the increasing need for sustainable chemical processes has led to a drive to replace transition metals with earth abundant, non-toxic and environmentally benign alternatives. Main group elements offer many of these properties, and are increasingly useful catalysts for synthetic transformations.^[1,2] In particular, the reductive functionalization of unsaturated polar bonds (C=O, C=NR, etc.) with silicon and boron reagents is well-established using both s- and p-block based catalysts.^[3–8] Although aluminum compounds find use as Lewis acid catalysts and stoichiometric hydride reagents,^[9] there is a dearth of applications in wider catalysis.

Hydroalumination offers a controlled method to functionalize alkenes and alkynes.^[9–12] The stoichiometric reaction of alanes with alkynes gives alkenyl aluminum reagents, which can be functionalized by treatment with electrophiles.^[9] These reactions offer a powerful method for the stereoselective preparation of alkenes, but are not ideal. The requirement for stoichiometric amounts of inherently air- and moisture sensitive alanes makes hydroalumination chemistry hazardous and wasteful. There is a clear need for novel methodologies which avoid the direct handling of alanes, and allow substoichiometric amounts of alane to be used.

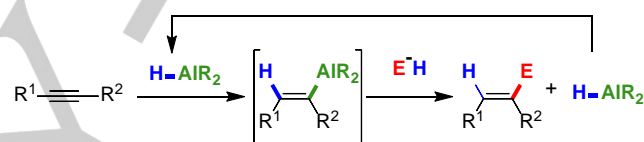
We envisaged a new class of catalytic hydrofunctionalization reactions in which hydroalumination was the first step of a catalytic cycle, and where turnover is achieved by simultaneous alkene functionalization and aluminum hydride regeneration (Scheme 1, Concept). In this way, stoichiometric quantities of aluminum hydride reagents would be avoided. Instead, treatment of an alkenyl aluminum species with a suitable hydride source would trigger σ -bond metathesis to give the functionalized alkene, whilst concurrently regenerating the Al-H bond, enabling catalytic turnover (stoichiometric transmetalation from boron to aluminum is well established).^[13–16] We thus identified borane reagents as possible reaction partners, and

potential hydride source. Ideally a readily available, air- and moisture-stable hydride source would be used. Transmetalation of alkenyl aluminum species with pinacol borane (HBpin), which fulfils these criteria, would result in the formation of synthetically useful alkenyl boronic esters. Here, an aluminum hydride would be generated using a substoichiometric amount of alkyl aluminum reagent with pinacol borane acting as the stoichiometric hydride source and hydrofunctionalization reagent.

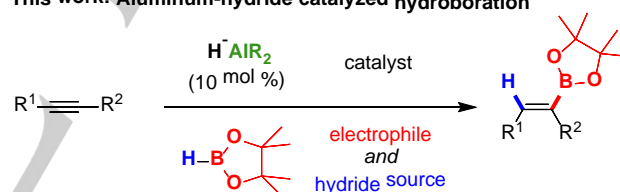
Established reactivity: Stoichiometric alkyne functionalization



Concept: *In situ* Al-H regeneration



This work: Aluminum-hydride catalyzed hydroboration

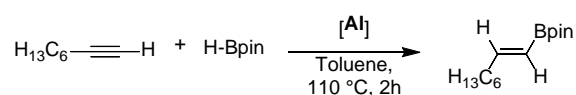


Scheme 1. i) Established hydroalumination chemistry; ii) Proposed catalysis concept; functionalization and regeneration of alane; iii) this work: aluminum-hydride catalyzed hydroboration.

We began by investigating the catalytic activity of commercially available dialkyl aluminum hydride reagents in the presence of HBpin and 1-octyne to establish if our concept would lead to a viable process.^[17] Using diisobutylaluminum hydride (10 mol %) as the catalyst gave the terminal boronic ester with complete control of regiochemistry for the linear hydroboration product in good yield (Table 1, entry 1), demonstrating that an aluminum hydride was capable of catalyzing alkyne hydroboration and showing that our catalytic concept was valid.

We next trialed trialkyl aluminum reagents as catalyst precursors. Use of these inexpensive and readily available reagents would require an initial transmetalation event to trigger catalysis by exchange of H from HBpin to AlR₃ to generate the active HAIR₂ catalyst. Triethyl- and trimethyl aluminum both successfully catalyzed the hydroboration of octyne to give the linear alkenyl boronic ester in 59% and 23% yields, respectively (entries 2 and 3).

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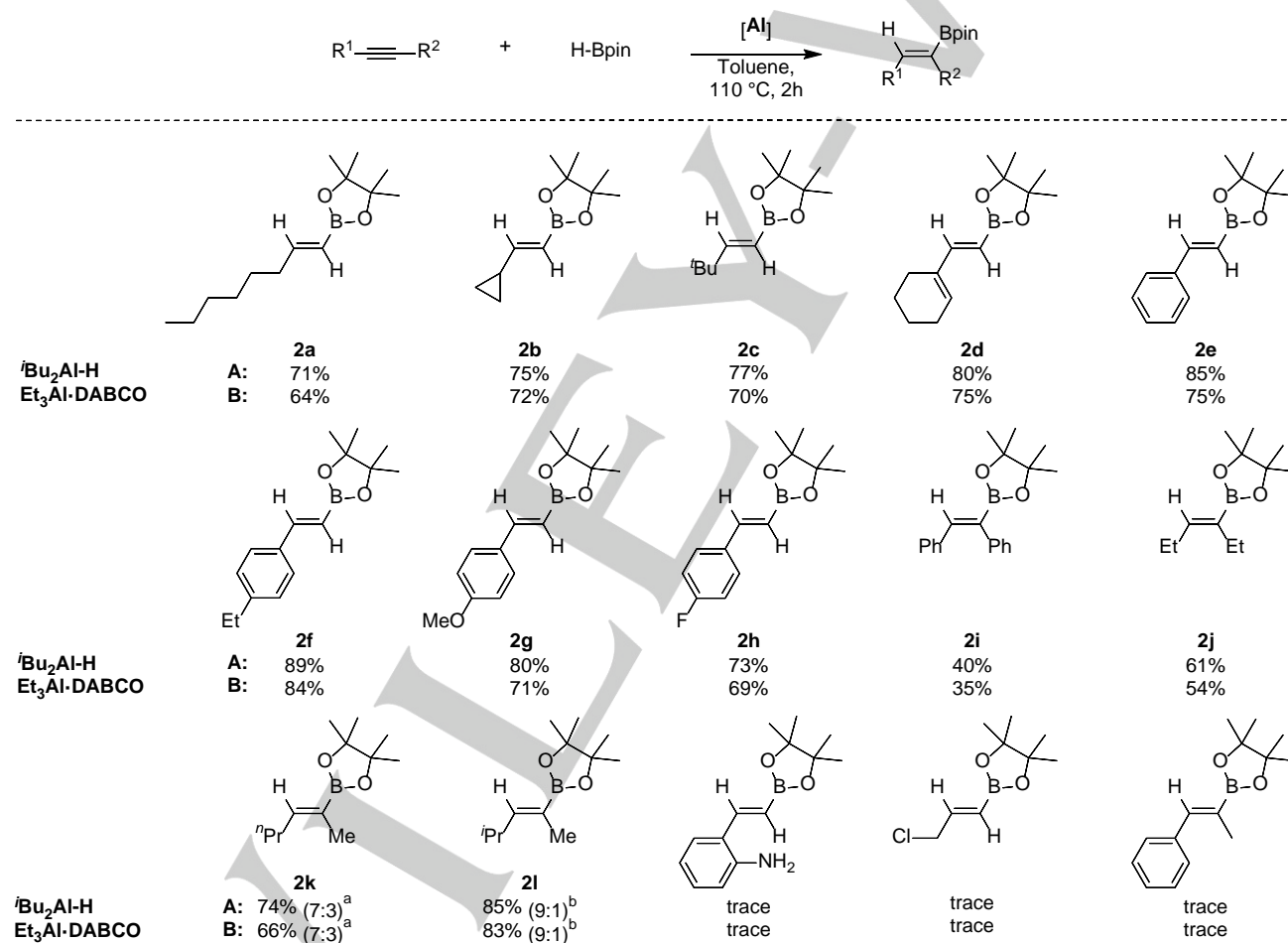
Table 1. Results of catalyst screening.

Entry	Catalyst (10 mol %)	Yield (%)
1	^t Bu ₂ Al-H	73
2	AlEt ₃	59
3	AlMe ₃	23
4	Et ₃ Al·DABCO	72
5	(Me ₃ Al) ₂ ·DABCO	36

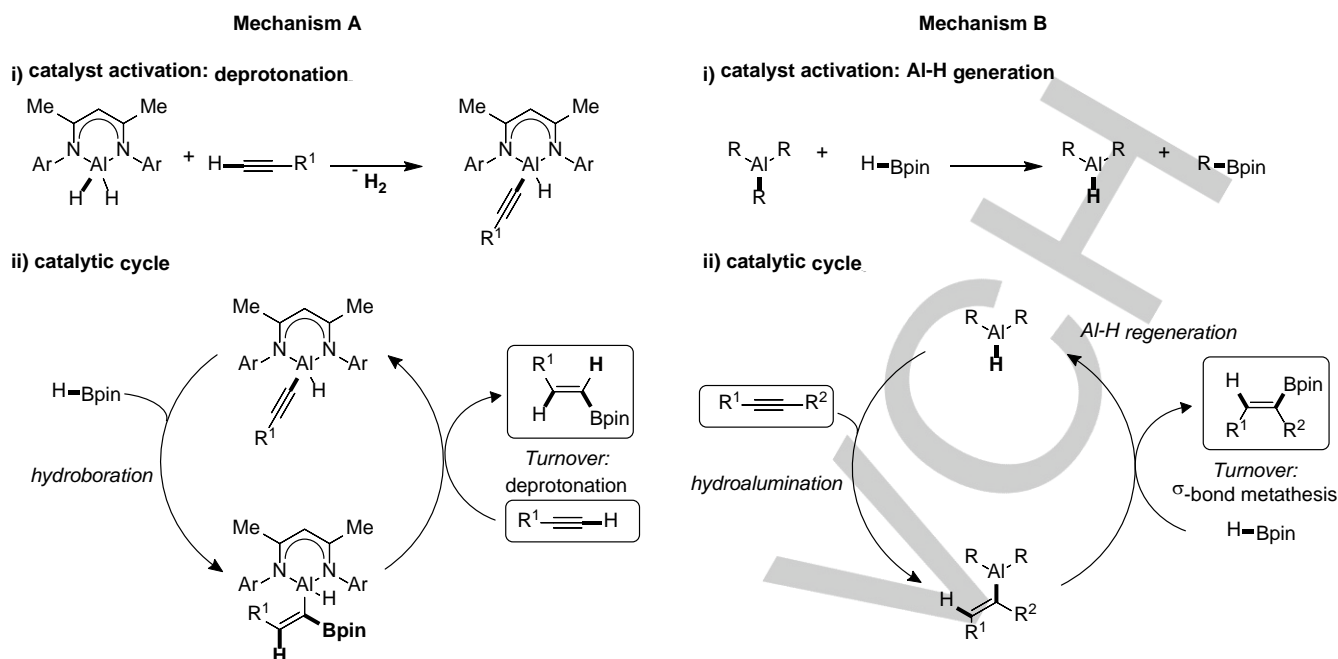
Reaction conditions: catalyst (0.015 mmol, 10 mol %), 1-octyne (0.15 mmol) and HBpin (0.22 mmol, 1.5 eq.) in 0.60 mL toluene-*d*₆, heated to 110 °C for 2 h. Yields determined by ¹H NMR of the reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

In order to increase the operational simplicity of our catalytic hydroboration, we trialed commercially available (Me₃Al)₂·DABCO (entry 5) and Et₃Al·DABCO (entry 4), prepared from DABCO and Et₃Al.^[17] Both of these bench-stable solids successfully catalyzed the hydroboration reaction, with the triethyl aluminum analogue adduct giving excellent catalytic activity.

Using our optimized conditions of 10 mol % aluminum catalysts, ^tBu₂AlH or Et₃Al·DABCO, and 1.2 equivalent of HBpin (see SI for detailed results concerning reaction time and temperature) we next explored the substrate scope of our method. Terminal alkyl- and aryl-substituted alkynes all underwent successful hydroboration (Scheme 2, **2a-2h**). Alkyl substituent steric parameters had little effect on catalyst activity with primary (**2a**), secondary (**2b**) and tertiary (**2c**) groups showing equal reactivity. The chemoselective hydroboration of alkynes was achieved in the presence of an alkene (**2d**).



Scheme 2. Substrate scope for aluminum-hydride catalyzed alkyne hydroboration. **A:** isolated yield using DIBAL-H (10 mol%), toluene, 2h, 110 °C; **B:** isolated yield using AlEt₃·DABCO (10 mol%), toluene, 110 °C. ^{a,b} **2k** and **2l** were obtained as mixture of regioisomers in the ratios indicated.



Scheme 3. Conceivable mechanisms for aluminum-hydride-catalyzed hydroboration. Mechanism **A** proposed by Roesky and co-workers for the operation of the NacNacAlH_2 catalyst.^[20] Mechanism **B** is consistent with the observations reported here.

Variation of the electronic character of the alkyne aryl substituent again showed that equal catalyst activity was achieved with both catalysts across arenes bearing either electron-donating (**2g**) and or electron-withdrawing (**2h**) substituents. Finally, we explored reactions of the more challenging disubstituted alkynes, which are not hydroborated by other aluminum systems.^[20] Symmetrical alkynes with both aryl- (**2i**) and alkyl substituents (**2j–2l**) underwent hydroboration with both aluminum catalysts in good to moderate yields. Even unsymmetrical disubstituted alkynes could be converted to the vinylic boronic esters with moderate to good regioselectivity using both aluminum catalysts (**2k**, **2l**). It is worth noting that across all 15 substrates, both ${}^t\text{Bu}_2\text{Al-H}$ and $\text{Et}_3\text{Al-DABCO}$ showed equal catalytic activity, which strongly suggests a shared mode of operation.

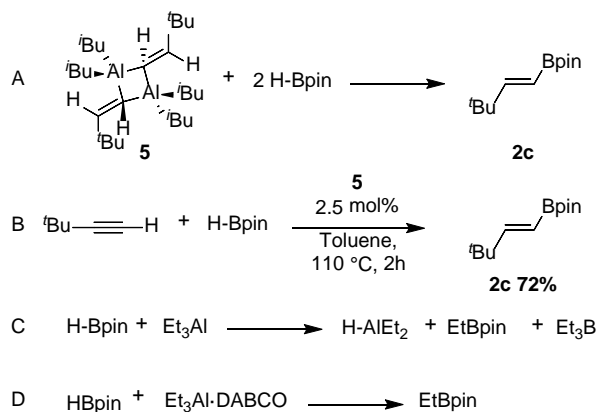
With a broad picture of substrate scope established, we sought experimental confirmation of the mechanism underpinning aluminum-catalyzed hydroboration. Yang, Parameswaran, and Roesky have reported the catalytic hydroboration of alkynes by a *N,N*-bis-2,6-diisopropylphenyl diketiminato (NacNac) supported aluminum dihydride.^[20] Based on a computational study, they suggested a mechanism which proceeds by an initial deprotonation of the alkyne substrate by the aluminum hydride resulting in the production of H_2 (Scheme 3, A). The rate-determining step in this mechanism was predicted computationally to be the protonation of the borylated alkenyl group at the aluminum center by the incoming terminal alkyne, with an activation barrier of $45.3 \text{ kcal mol}^{-1}$.^[21] Although this mechanism is a possibility for the NacNacAlH_2 system, it cannot explain the ability of ${}^t\text{Bu}_2\text{Al-H}$ and $\text{Et}_3\text{Al-DABCO}$ to hydroborate internal alkynes. Furthermore, when we monitored the catalytic hydroboration of ${}^t\text{BuC}\equiv\text{CH}$ with HBpin in a sealed system by ${}^1\text{H}$ NMR spectroscopy, we did not observe any

production of H_2 , which suggests that Mechanism **A** may not be operating under our reaction conditions.

We considered an alternative mechanism whereby initial alkyne hydroalumination is followed by σ -bond metathesis with HBpin , in which the alkenyl substituent undergoes transmetalation from aluminum to boron, regenerating the aluminum hydride. In order to determine which mechanism was operating in our hydroboration we undertook a series of mechanistic investigations (Scheme 4). Treatment of the isolated alkenyl aluminum species **5**^[22] with HBpin formed the borylated alkene **2c** (Scheme 4, A). The alkenyl aluminum species **5** is also an active catalyst for the alkyne hydroboration (Scheme 4, B). These observations confirm the crucial C-B bond-forming step occurs by transmetalation with concomitant Al-H regeneration, showing that the hydroalumination reaction is integral to the catalytic cycle. When we performed catalytic hydroboration with either deuterated alkyne (${}^t\text{BuC}\equiv\text{CD}$) or pinacolborane- d_1 , the stereochemistry of the products was consistent with the hydroalumination-based process in mechanism B. Thus, when ${}^t\text{BuC}\equiv\text{CD}$ was borylated with HBpin , the ${}^t\text{Bu}$ and deuterium substituents were observed in a *cis* orientation to each other. When ${}^t\text{BuC}\equiv\text{CH}$ was treated with DBpin , we again observed a *cis* arrangement of deuterium and Bpin , entirely consistent with the proposed σ -bond metathesis step. This stereochemistry is consistent with hydroalumination (Mechanism B, step 1) but cannot exclude hydroboration of an alkynyl aluminum (Mechanism A), which would result in the same stereochemistry. However, under stoichiometric or catalytic conditions using ${}^t\text{Bu}_2\text{Al-H}$ and ${}^t\text{BuC}\equiv\text{CD}$ we did not observe formation of H-D.^[17]

A final question concerns the generation of the aluminum hydride catalyst in cases where $\text{Et}_3\text{Al-DABCO}$ is the catalyst precursor. Monitoring the reaction of AlEt_3 with 1 equivalent of

HBpin by ^{11}B NMR spectroscopy, we observed immediate formation of EtBpin, alongside Et_3B (Fig. S2). This indicates that the aluminum hydride functionality is delivered by alkyl/hydride exchange from aluminum to boron. Indeed, in the ^1H NMR spectra of these mixtures, the characteristic aluminum hydride resonance for $\text{Et}_2\text{Al-H}$ is observed at $\delta = 3.54$.



Scheme 4. Mechanistic studies. A) Treatment of isolated alkenyl aluminum compound **5** with HBpin to give **2c**. B) Catalytic competence of **5**. C) Reaction of Et_3Al with HBpin. D) Reaction of Et_3Al -DABCO with HBpin.

The role of added base in the catalytic systems is complex. The exchange behavior of alanes AlX_3 and boranes BY_3 generates mixtures of the 'crossover' alanes and boranes (e.g. $\text{AlX}_n\text{Y}_{3-n}$, $\text{BY}_n\text{X}_{3-n}$).^[15,16] Treatment of Et_3Al with HBpin results in mixtures of boranes including EtBpin and Et_3B (Fig S2). However, in the presence of DABCO, Et_3B formation is suppressed and EtBpin is the only boron-containing product observed (Fig S3). Consistent with this, treatment of the alkenyl alane **5** with HBpin results in significant quantities of trialkylborane. Performing the same reaction in the presence of DABCO suppresses trialkylborane formation. The major function of added base thus appears to be to prevent decomposition of the aluminum catalyst. Under catalytic conditions, even in the absence of added base (using tBu_2AlH as the catalyst), we did not observe any formation of trialkylboranes.

In summary, we have exploited hydroalumination and Al/B exchange to enable the aluminum-hydride-catalyzed hydroboration of alkynes. Bench-stable (Et_3Al -DABCO) and commercially available (HAl^iBu_2) aluminum catalysts can be used. The method is highly stereoselective, proceeding with *syn* addition of HBpin and good regioselectivity for unsymmetrical alkynes. Mechanistic studies show that hydroboration proceeds by initial hydroalumination, followed by Al/B exchange, regenerating the aluminum hydride. We are currently working to extend the range of catalytic hydrofunctionalization reactivity available through this new concept.

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Keywords: aluminium • hydroboration • catalysis • main group • mechanism

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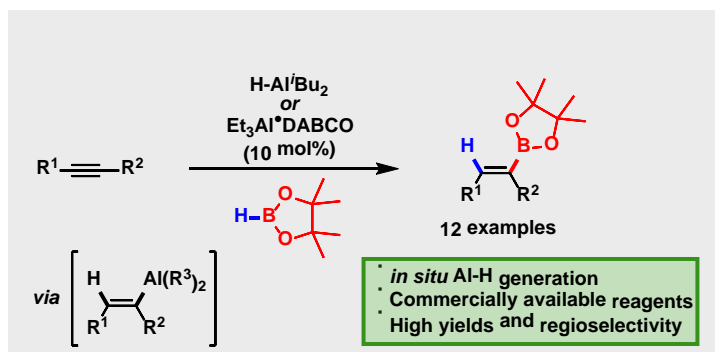
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