Aluminium-Catalyzed C(sp)–H Borylation of Alkynes

Dominic R. Willcox+, Daniel M. De Rosa+, Jack Howley, Abigail Levy, Alan Steven, Gary S. Nichol, Carole A. Morrison, Michael J. Cowley,* and Stephen P. Thomas*

Abstract: Historically used in stoichiometric hydroalumination chemistry, recent advances have transformed aluminium hydrides into versatile catalysts for the hydroboration of unsaturated multiple bonds. This catalytic ability is founded on the defining reactivity of aluminium hydrides with alkynes and alkenes: 1,2-hydroalumination of the unsaturated π-system. This manuscript reports the aluminium hydride catalyzed dehydroborylation of terminal alkynes. A tethered intramolecular amine ligand controls reactivity at the aluminium hydride centre, switching off hydroalumination and instead enabling selective reactions at the alkyne C–H α-bond. Chemoselective C–H borylation was observed across a series of aryl- and alkyl-substituted alkynes (21 examples). On the basis of kinetic and density functional theory studies, a mechanism in which C–H borylation proceeds by s-bond metathesis between pinacolborane (HBpin) and alkyne aluminium intermediates is proposed.

Alkyne hydroalumination is a textbook application of main group species for organic synthesis.[1] The intermediate alkyln aluminium compounds are rarely isolated, but rather treated in situ with electrophiles to give functionalized alkenes.[2] Recently, we[3] and others[4] have rendered these reactions catalytic and increased the breadth of aluminium catalysis beyond Ziegler–Natta processes, reduction (Meerwein-Ponndorf-Verley) and Lewis acid catalysis.[5]

Aluminium-catalyzed hydroboration combines the prototypical alkyne hydroalumination with a turnover step that uses pinacolborane (HBpin) to provide boronic esters and regenerate the aluminium hydride catalyst. However, these reactions were limited to the preparation of alkenyl- and alkyl boronic esters.[3,4] We thus sought to develop Al–C bond forming reactivity of aluminium hydrides that is not based on hydroalumination, and open aluminium catalysis to the synthesis of other classes of boronic esters.[6] Particularly promising in this regard was the work of Roesky and Zhu, who reported an Al/N frustrated Lewis pair for the stoichiometric dehydrogenative aluminiation of heterocycles and alkynes.[7]

Here, we report an aluminium-catalyzed dehydrogenative C–H borylation. Using the in situ generated tethered Lewis pair catalyst 1a, we “switch off” alkyne hydroalumination to favour C–H aluminiation. The resulting alkynyl aluminium species react with HBpin to provide alkynyl boronic esters and regenerate the aluminium hydride. This C–H borylation is complementary to the typical reactivity of transition metal catalysts with HBpin and alkynes, which overwhelmingly results in hydroboration.[8]

To favour dehydrogenative C–H aluminiation over hydroalumination, we designed the aluminium dihydride 1a by adapting principles from previously reported aluminium- and boron-based intramolecular FLPs.[7,9] Our hypothesis was that the rigid aromatic backbone bearing a “hard” amine donor

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:

https://doi.org/10.1002/anie.202106216.

© 2021 The Authors. Angewandte Chemie International Edition published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.
orthogonal to the aluminium centre would increase the basicity of the aluminium hydrides, and quench the Lewis acidity of the aluminium centre.

A boron analogue of the aluminium dihydride 1a reacts with alkynes by hydroboration,[8] reflecting the low barrier for that reaction (compared to deprotonation). We carried out preliminary DFT calculations [B97XD/6-311 + + G(d,p)] to examine the relative barriers to alkylene hydroalumination and dehydrogenation C–H aluminol. Computationally, the anilino-ligand of the alane 1a provides substantial energetic discrimination between the two pathways, with the activation barrier for hydroalumination being 9.1 kcal mol⁻¹ higher than that predicted for C–H aluminol (Scheme 1, c).

The prediction of good discrimination between the two possible pathways encouraged us to seek experimental verification. We have previously used alkylalanes and HBpin to generate catalytically-active aluminium hydrides under reaction conditions.[9] Adopting the same concept, we prepared the dimethylalane 1b in 54% yield by reaction of 2-lithio-N,N-dimethylalane with Me₂AlCl, as a precursor to the dihydride 1a.

The dimethylalane 1b is a pre-catalyst for C–H borylation of alkynes, generating dihydride 1a in situ. Reaction of 1-ethyl-4-fluoro-benzene with HBpin in the presence of dimethylalane 1b (10 mol %) gave only trace amounts of alkynyl boronic ester 3 at room temperature (Table 1). At higher temperatures, we observed formation of alkynyl boronic ester 3 (30%), dihydrogen and significant hydroboration (entries 2 and 3). That alkylene hydroboration was competitive with C–H borylation seemed at odds with the predicted large barrier to hydroalumination by 1a (Scheme 1, c). Furthermore, Roesky and Zhu reported high selectivity for dehydrogenative aluminol of alkynes with a related aluminium dihydride.[7] They postulated that the hydroboration product could instead be the result of hidden BH₃-catalyzed hydroboration.[10] Monitoring the reaction of 1b with HBpin by ³¹B NMR spectroscopy revealed signals attributable to BH₃ (SI section 2.3). The same was observed when monitoring catalytic reactions.

To suppress the unwanted reaction of BH₃ with the substrate, we investigated the addition of dienes as BH₃ traps (see SI section 2.2). Reaction in the presence of 0.1 equivalents of 1,5-cyclooctadiene (COD) showed the formation of cyclooctetynyl-B₉-BBN, and increased selectivity for the C–H borylation product (72:20, Table 1, entry 4). Using 1 equivalent of COD further improved the yield and selectivity (entry 5). 1.5-Hexadiene[11] gave the greatest selectivity (entry 6, see also SI section 2.2).

Control reactions confirm pre-catalyst 1b is needed for C–H borylation. Reactions in the absence of 1b led only to recovery of starting materials. The bifunctional alane-amine structure of 1a/1b is required for C–H borylation: neither PhAlMe₂ alone nor in combination with an external amine (N,N-dimethylaniline) are active for catalytic C–H borylation.

We next examined the substrate scope of the Al-catalyzed C–H borylation (Table 2). Ortho-, meta-, and para-substituted aryalkynes 3b–d showed equal reactivity and selectivity for C–H borylation over hydroboration. Anisole and aniline derivatives 3f,g, competing Lewis bases, did not perturb reactivity or selectivity. Reaction of alkyne 3h proceeded to give the diborylated species. A CF₃ group led to substantially reduced reactivity (3i), which was not observed for aryl chloride or fluoride substituents (3j,k). Chemoselectivity was maintained with a thiophene-substituted alkyne 3l and an internal alkene 3o. Ethynylcyclopropane 3q reacted without observable ring-opening, and the trimethylsilyl group in 3r was retained. An alkyl alkyne 3s, thiol ether 3t and ether 3u were all tolerated with no substitution or elimination observed. The synthetic utility of the alkynyl boronic esters was demonstrated by Carboni-Lindsey reaction with a 1,2,4,6-tetrazine[12] to give a pyridazine 4 and BH₃-catalyzed hydroboration to give a diborylated alkene 5[10a].

Under reaction conditions there are two possibilities for generating the active aluminium dihydride catalyst 1a from the dimethyl pre-catalyst 1b. Al/B exchange with two equivalents of HBpin would generate 1a and MeBpin.[3] Alternatively, deprotonation of the alkyne by 1b would generate methane[13] and a bis(alkynyl)aluminium compound which could enter the catalytic cycle after Al/B exchange.

Using 19F NMR spectroscopy, we monitored the reaction of 4-fluorophenylacetylene 2k with HBpin in the presence of 10 mol % pre-catalyst 1b at 80°C (Scheme 2). In the initial stages of the reaction, alkynyl consumption and product formation were rapid. After this initial period, the rate of reaction decreased. In the first 10 minutes, approximately 10% of the substrate was consumed, corresponding to the formation of 10% of borylated product (Scheme 2). The total consumption of substrate during the initial period was always equivalent to the catalyst loading (see SI 8.2). Accompanying this, we observed the generation of CH₄ by ¹H and ¹³C NMR spectroscopy, and MeBpin in the ¹BNMR spectrum. Using D₄-4-fluorophenylacetylene d₂-2k, DCH₃ was observed. The simultaneous observation of methane and MeBpin suggests two concurrent pathways for pre-catalyst activation. We thus examined in turn the stoichiometric reactivity of the dimethylalane pre-catalyst 1b with alkynyl and HBpin.
Reaction of pre-catalyst 1b with excess phenylacetylene rapidly generated the tris-acetylide species 6, which was structurally characterized (Scheme 3, a). The formation of the tris-acetylide 6 results from protonolysis of all Al–C bonds in 1b, generating methane and N,N-dimethylaniline, which coordinates to the aluminium centre. Under catalytic conditions this would generate methane (as observed) and an alkynyl-aluminium species which would then undergo Al/B exchange with HBpin to generate the product 3a. Treatment of the tris-acetylide 6 with HBpin gave alkynyl boronic ester 3a in a reduced yield (39%). The tris-acetylide 6 is not catalytically active, presumably because the dimethyl-aniline unit is no longer covalently attached to the aluminium centre.

With HBpin, pre-catalyst 1b gave the adduct 7 at room temperature, indicated by the observation of a signal in the $^{11}$B NMR spectrum at $\delta = 6.0$ (d, $J_{B/C}H = 135$ Hz). Crystallography revealed coordination of the amine of 1b to the boron centre of HBpin. The aluminium centre is maintained as four-coordinate by coordination of an HBpin oxygen. Heating 7 to 80°C generated MeBpin; we infer corresponding formation of the Al-H functionality. When 7 is heated in the presence of alkylene, rapid formation of borylated alkyne 3, MeBpin and CH$_4$ occurs, as observed in catalysis (Scheme 3, b).

Based on these observations, we propose that catalyst activation occurs through two distinct and concurrent pathways to give the common Al-H catalyst 1a. In pathway (a), Al/B exchange with HBpin generates MeBpin and Al-H functionality. In pathway (b), deprotonation of the alkyne by 1b generates methane and alkynyl-aluminium species which can undergo Al/B exchange with HBpin, generating product and the Al-H catalyst 1a (Scheme 3, c). Both of these pathways were found to be viable by DFT calculations, with pathway (a) having a much higher barrier to activation (28.7 kcal mol$^{-1}$) compared to the alkyne-deprotonation pathway (b) (18.7 kcal mol$^{-1}$) (Figure 1).

From our initial kinetic study, it is clear that catalyst activation generates product more rapidly than under steady-state conditions. Thus, alkyne deprotonation by the dimethyl aluminium pre-catalyst 1b than the tris-acetylide 6.
Dihydride catalyst 1a, in line with the expected reactivity differences of alkyl- and hydrido-aluminium compounds. 

Dividing the reaction into two phases, we determined rates for the initiation phase with rate $k_1$ and “turnover” phase with rate $k_2$. Using time-normalization kinetics, the order of the reaction in each component was determined for the “turnover” phase ($k_2$) (Scheme 4, a). The reaction was found to be 1st order with respect to alkyne, and 2nd order with respect to catalyst, suggesting the active catalyst 1a exists in solution largely as a dimer, $[1a]_2$, which is reacting directly with alkyne in the rate-limiting step.

Consistent with the presence of an oligomeric catalyst species under reaction conditions, attempts to isolate the dihydride 1a (by reaction of 2-lithio-N,N-dimethylaniline with H$_2$AlCl), gave a tetrameric aluminium species 8. The alane 8 is formally a tetramer of 1a (i.e. the molecular formulae of 8 and 4[1a] are the same). The tetramer 8 can be considered a hydride-bridged dimer of an AlH$_3$ adduct of

**Scheme 3.** (a) Formation and reactivity of tris(phenylacetylide) aluminium-N,N-dimethylaniline 6. (b) Formation and reactivity of 1b-HBpin adduct 7. (c) Proposed catalyst activation pathways. Thermal ellipsoids shown at 50% probability level. Hydrogen atoms except $\mathbf{B}$ omitted. [a] Yield determined by comparison to N,N-dimethylaniline. 

**Scheme 4.** (a) Reactant orders from variable time normalization analysis (VTNA). (b) Kinetic isotope effect with D-4-fluorophenylacetylene $d_2$-2k and DBpin.

---

**Figure 1.** DFT-computed free energies for the two possible catalyst activation pathways of 1a. (Energies calculated at oB97X-D/6-311 + + G(d,p) on oB97X-D/6-31 + G(d,p)-optimised structures).
a bis(anilino)aluminium hydride (Figure 2). Each aluminium centre in the tetramer 8 is 5-coordinate. The tetramer 8 is catalytically competent for dehydrogenative alkyne hydroboration, though a significant level of hydroboration was observed, presumably catalyzed by AlH₃ released from the tetramer 8. Using DFT \( \{\omega B97XD/6-311++G(d,p)\} \), we calculated the relative energies of the catalyst 1a, dimeric catalyst \([1a]_2\), \([anilino]_2\text{AlH-AlH}_3\), and its hydride-bridged dimer 8. All four compounds were within 4.4 kcalmol\(^{-1}\) of each other (see SI 9.5).

\[ \text{Scheme 5} \] Proposed catalytic cycle.

Returning to the kinetic studies, we sought preliminary evidence for the operative catalytic mechanism beyond the catalyst activation stage. We determined kinetic isotope effects in the “turnover” phase of the reaction (i.e. \( k_1 \)) using both DBpin and \( D-4\)-fluorophenylacetylene \( (d/-2k) \), substituting each reagent in turn and then both together (Scheme 4, b). Both the B–H and C–H bond KIE values are small \( (k_{\text{H}}/k_{\text{D}} = 1.5; C–H 1.4) \). \(^3\)H NMR spectra during these experiments excluded isotopic scrambling between starting materials as an explanation for the small isotope effects.

We can readily exclude \( \text{o-bond} \) metathesis of \( \text{Al–C} \) and \( \text{B–H} \) bonds as the rate-limiting step in the \( \text{C–H} \) borylation of alkenes by the catalyst 1a since: i) the reaction is zero order in HBpin and, ii) \( k_{\text{H}}/k_{\text{D}} (\text{B–H}) \), at 1.5, is substantially smaller than expected for a process in which \( \text{O-bond} \) metathesis is rate-limiting. We instead explain the observed value of \( k_{\text{H}}/k_{\text{D}} (\text{B–H}) \) as a \( \text{Al-H/Al-D} \) isotope effect, since HBpin generates Al-H functionality during activation and in the catalytic cycle (see below).

The reaction is second order in the pre-catalyst 1b and first order in the alkynyl substrate. These measurements indicate that the rate-limiting step is deprotonation of the alkynyl C–H and that this is effected a dimeric aluminium species, for example, \([1a]_2\) (see SI 9.5). The small \( k_{\text{H}}/k_{\text{D}} (\text{C–H}) \) value, at 1.4, is typical for asynchronous deprotonation during the rate-limiting step. The inferred (see above) \( k_{\text{H}}/k_{\text{D}} (\text{Al-H}) \) of 1.5 is of the correct magnitude for a primary isotope effect (predicted value 2.1, see SI S8.4) and indicates that at least one Al–H bond is broken during this process.

With the combined evidence, we propose a catalytic cycle (Scheme 5) in which dimeric catalyst \([1a]_2\) deprotonates the alkynyl to form the zwitterionic acetylide 9, necessitating cleavage of a bridging Al–H bond. Subsequent H₂ elimination precedes Al/B exchange which occurs by \( \text{o-bond} \) metathesis (as during catalyst activation), regenerating the bridged aluminium dihydride \([1a]_2\).

As main group compounds continue to find increasing use as catalysts, chemists will need new strategies to control reactivity at the main-group centre, mirroring the journey to establish ligand design principles in transition-metal chemistry. Here, we have shown how a pendant amine functionality can alter the preference of aluminium for hydroalumination of alkenes and instead enable selective catalytic functionalization of the C–H \( \text{o bonds} \). Our findings suggest new principles for ligand design in the growing field of aluminium-catalyzed functionalization. We are currently undertaking a detailed mechanistic study to establish the precise nature of the catalytic cycle in this reaction.

\section*{Acknowledgements}

S.P.T. thanks the Royal Society for a University Research Fellowship (URF/R/191015). D.R.W. and S.P.T. thank the Royal Society for funding a PhD studentship (RGF/EA/180218). M.J.C., S.P.T. and D.M.D.R. thank AstraZeneca, the EPSRC and CRITICAT CDT for funding a PhD studentship (EP/LO161419/1). We acknowledge the EaStCHEM Research Computing Facility and the Edinburgh Compute and Data Facility for access to software and high-performance computing resources. This project has received funding from the European Research Council (ERC) under the European Union’s Horizon 2020 research and innovation programme (grant agreement no. ERC-2016-STG-716315).
Conflict of Interest

The authors declare no conflict of interest.

Keywords: aluminium · borylation · catalysis · main-group chemistry · o-bond metathesis

Aluminium-Catalyzed C(sp)–H Borylation of Alkynes

The aluminium hydride catalyzed dehydroborylation of terminal alkynes is reported. By using a tethered-intramolecular-amine Lewis base as a ligand at the aluminium hydride centre the reactivity is controlled. Hydroalumination is switched off and selective reactions at the alkyne C–H α-bond are enabled.