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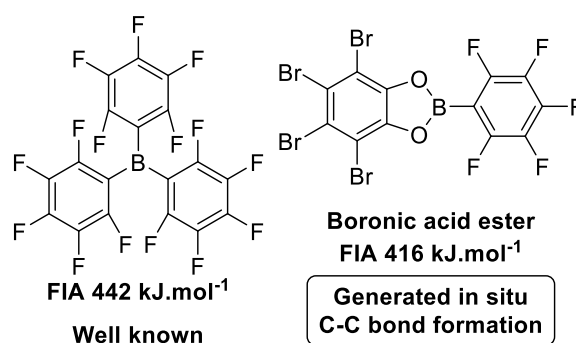
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From Building Blocks to Catalysts: The Underinvestigated Potential of Boronic Acid Esters.

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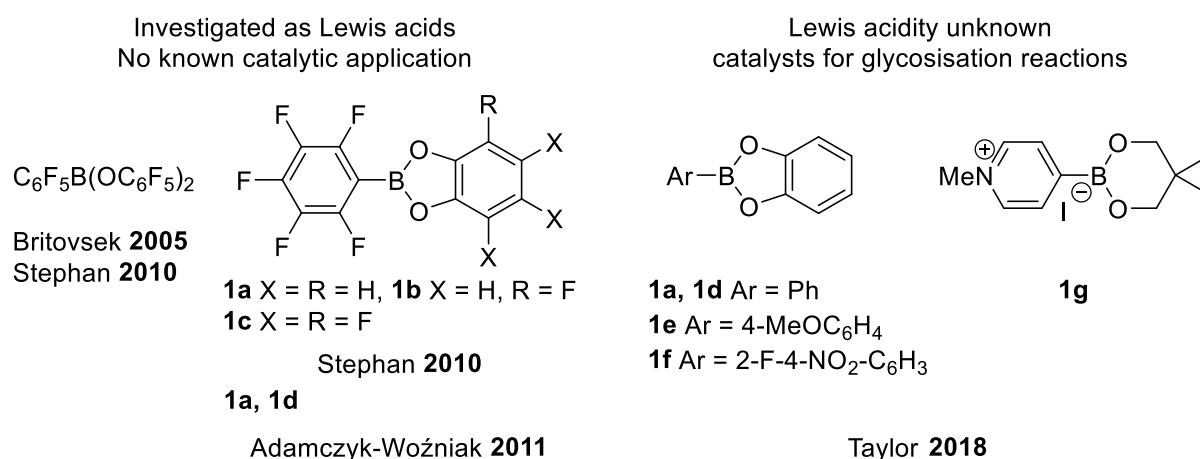
ABSTRACT Lewis acids are crucial in chemistry with applications in pharmaceuticals, agrochemicals, and materials science. In main-group chemistry, they offer alternatives to transition metals, prompting our study on halogenated boronic acid esters (BAEs). Although BAEs are well-known, their catalytic potential has been overlooked. Our investigation found their Lewis acidity superior to boron trifluoride and comparable to tris(pentafluorophenyl)borane. Additionally, their catalysis of the Sakurai allylation of aldehydes is documented, paving the way for future advancements.

INTRODUCTION

Since their conceptualization in 1923 by Gilbert N. Lewis, the eponymous acids have gained significant prominence in the field of organic chemistry due to their ability to promote specific reactions under mild conditions. As a consequence, their utilization is ubiquitous in pharmaceuticals, agrochemicals or advanced materials industry. In this context, main-group based Lewis acids represent a dynamic area of research dedicated to offering alternatives to transition metals to address concerns related to their availability, toxicity and carbon footprint. Halogenated triaryl boranes, known for decades, constitute an important group of boron derivatives, recognized for their strong Lewis acidity, stemming from the presence of a vacant

p-orbital on the boron atom.¹ However, one may counterbalance this versatility² with their sensitivity to air and moisture which can complicate both their synthesis and utilization. On the contrary, boronic acid esters (BAEs) are primarily regarded as fundamental building blocks (pinacol derivatives), given the significant advancements in the Suzuki-Miyaura cross-coupling method³, or as components of self-healing smart materials.⁴ A comprehensive review of the literature reveals that while their intriguing Lewis acidity has been subject to various degree of investigation⁵, their role as catalyst has been sparingly documented. As an example, Stephan reported that planar boronic acid esters **1a-c** (Figure 1) exhibited indications of forming frustrated Lewis pairs (FLPs) in the presence of PtBu₃ or PMes₃ (spectral data remained consistent with a Lewis acid unbound to the phosphine).⁶ However, when exposed to 4 atm of H₂, no reaction was observed. In 2018, Taylor investigated the use of pyridinium based boronic acid ester **1g** as catalyst for the glycosylation of 2-deoxysugars (Figure 1). In a closely related context, Hall and Moran reported that oxalic acid or perfluoropinacol, in combination with boronic acids, can promote the Friedel-Crafts reaction^{7b,c} or the Beckmann rearrangement.^{7d} As a result, the potential of these BAEs seemed overlooked⁸, prompting us to conduct a wider investigation into their Lewis acidity and catalytic properties.

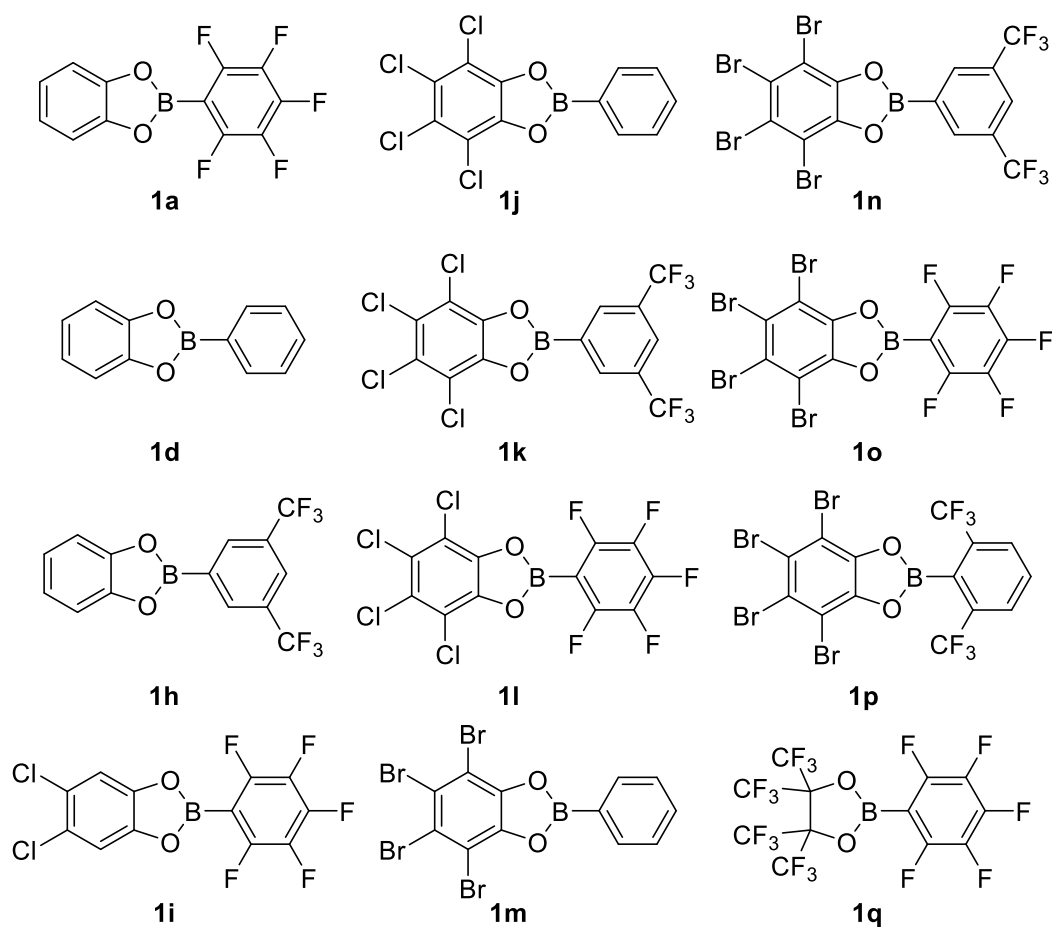
Figure 1. Lewis acidity of boronic acid esters and reported catalytic applications.



At the outset of this study, our focus was to evaluate the Lewis acidity of a variety of boronic acid esters, which were readily obtained by condensation of a diol and a boronic acid in the presence of molecular sieves as desiccant. A widely employed technique for the experimental evaluation of the Lewis acidity of a boron derivative involves the Gutmann-Beckett method.⁹ The procedure involves subjecting an excess of Lewis acid to triethylphosphine oxide (TEPO), and the resulting ³¹P NMR shift of the resultant adduct is then analyzed in correlation with the

Lewis acidity and quantified by its acceptor number (AN) ranging from 0 (in hexane) to 100 (in SbCl_5). Unsurprisingly, the boronate ester **1d** derived from unsubstituted benzene boronic acid and catechol gave an AN of 34.8 corresponding to a low Lewis acidity (Table 1). Interestingly, with pentafluoro (**1a**) and 3,5-trifluoromethyl phenylboronic acid (**1h**), the ANs rise to 76.9 and 71.2. In order to further increase the AN, we considered substitution at the catechol counterpart. With two chlorine atoms, **1i** recorded a AN of 83.1 which compared with the reported values of 84.0 for BF_3 and 81.8 for tris(pentafluorophenyl)borane (BCF).^{1a} Using tetrachlorocatechol (**1j-i**) led to an increased AN of 86.6 with pentafluorophenylboronic acid. A similar trend was noted with tetrabromocatechol (TBC) derivatives (**1m-p**), showcasing a peak AN of 87.1 for **1o**. Finally, when perfluoropinacol was used in place of a catechol derivative, an AN of 80.6 was obtained for **1q**. Those experimental results suggested high Lewis acidities for BAE **1i**, **1o** and **1q** in line with previously reported **1a-d**, BF_3 and BCF.

Table 1. Gutmann-Beckett scale and FIA for BAEs 2a-2l.



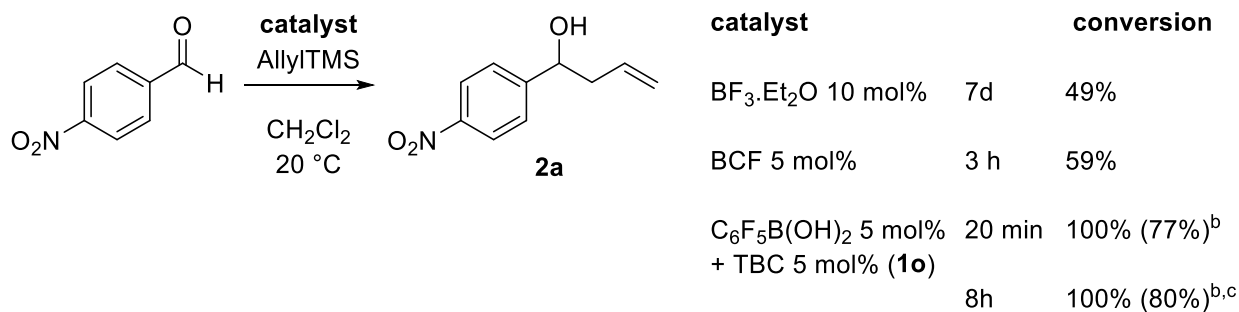
BAE	δ (ppm) ^a	AN ^b	FIA (kJ/mol) ^c
1a	75.7	76.9 (81.5) ^d	358.9
1d	56.7	34.8	308.6
1h	73.1	71.1	356.6
1i	78.5	83.1	390.1
1j	76.3	78.2	371.2
1k	79.2	84.6	414.6
1l	80.1	86.6	414.6
1m	76.5	78.6	376.0
1n	79.3	84.8	409.2
1o	80.3	87.1	416.0
1p	61.8	46.1	377.3
1q	77.4	80.6	418.9
BF ₃	(79.0)	(84.0) ^e	352.0 (346.2 ^f)
BCF	(78.0)	(81.8) ^e	442.4 (445.1 ^f)

Data from the literature in parentheses. ^a ³¹P NMR shift determined in the presence of triethylphosphine oxide in CDCl₃. ^b AN determined according to Gutmann-Beckett methodology. ^c FIA estimated as the $-\Delta H$ of the reaction $A + F^- \rightarrow AF^-$ using TMS⁺/TMSF as anchor. ^d AN value in C₆D₆ according to ref 6b. ^e AN value reported in CDCl₃ according to ref 1a. ^f FIA value reported in ref 11.

The Fluoride Ion Affinity (FIA) calculated at the ω WB97XD/def2-TZVPP level of theory¹⁰ aligns with the Gutmann-Beckett scale (Table 1). In this series, BAE **1o** demonstrates a FIA at 416.0 kJ/mol, preceded by **1q** at 418.9 kJ/mol, followed by **1k** and **1l** at 414.6 kJ/mol and **1n** at 409.2 kJ/mol. In summary, these values qualify those BAE as strong Lewis acids when compared to reference data for BF₃ (346.2 kJ/mol) and BCF (445.1 kJ/mol).¹¹ Of note, bis *ortho* substituted **1p** FIA (377.3 kJ/mol) did not correlate with the determined AN of 46.1. This discrepancy was attributed to the trifluoromethyl groups hindrance distinguishing a small fluoride ion from a larger Lewis base such a TEPO employed in the Gutmann-Beckett method. With these results in hand, we opted to explore the potential of BAEs as catalysts. We opted for the Hosomi-Sakurai allylation of aldehydes, an important reaction for generating homoallylic alcohols via C-C bond formation.^{12a} The reaction conditions typically require the use of strong oxyphilic Lewis acids such as TiCl₄, SnCl₄, BF₃.Et₂O or AlCl₃ in stoichiometric or greater quantities.^{2b} More recently, several strong Lewis acids were documented as efficient catalysts for Hosomi-Sakurai allylations.¹³ For comparison purpose, the allylation of 4-

nitrobenzaldehyde to alcohol **3a 2a** in the presence of 10 mol% of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was tested. The reaction was found sluggish, giving a low 49% conversion (^1H NMR monitoring) after one week at 20 °C (Scheme 1). In comparison, 5 mol% of the more efficient BCF achieved a 59% conversion of the starting aldehyde after 3 hours.

Scheme 1. Comparative Sakurai allylation between BF_3 and *in situ* formed **1o.^a**

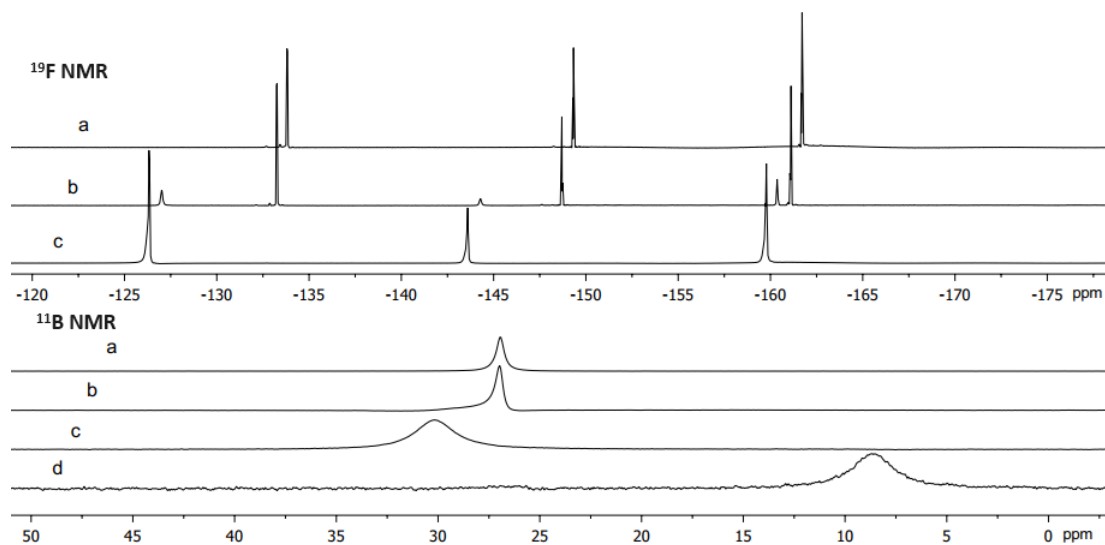


^aReaction conditions are as follows: $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (10 mol%), BCF (5 mol%) or $\text{C}_6\text{F}_5\text{B}(\text{OH})_2$ and TBC (5 mol%), AllylTMS (1.5 equiv), 4Å MS in CH_2Cl_2 , 20 °C. ^b Isolated yield. ^c Without molecular sieves.

Then we compared this result with **1o**, prepared *in situ* through the condensation of pentafluorophenylboronic acid and tetrabromocatechol in the presence of molecular sieves. With 5 mol% of **1o**, the reaction completed in 20 minutes, resulting in a 77% isolated yield. Intriguingly, the absence of desiccant significantly slowed the reaction but completion was still achieved within 8 hours (~5% conversion after 20 min). This last result led us to investigate the nature of the true catalyst in those reactions as a Brønsted acid catalysis could not be ruled out at this stage.¹⁴

Control reactions confirmed the ineffectiveness of pentafluorophenylboronic acid and tetrabromocatechol as active catalysts (almost no detectable conversion after 24 hours). Subsequently, we conducted a series of NMR experiments to track the formation of active species using ^{19}F and ^{11}B atomic probes. Pentafluorophenylboronic acid displayed diagnostic ^{19}F NMR signals at -132.7 (2F), -148.2 (1F), -160.6 (2F) ppm in CDCl_3 (Figure 2a, ^{19}F NMR). When of one equivalent of tetrabromocatechol was added and the sample shaken for 5 minutes, the formation of a new signals was observed at -126.4 (2F), -143.7 (1F), -159.8 (2F) ppm, accounting for 24% of the fluorinated species (Figure 2b, ^{19}F NMR). Then, a subsequent addition of 4Å molecular sieves completely shift the equilibrium toward the expected BAE **1o** (Figure 2c, ^{19}F NMR). ^{11}B NMR spectrum showed the formation of the BAE **1o** with a slight downfield shift (30.1 ppm, Figure 2c, ^{11}B NMR) relative to the free boronic acid (27.0 ppm, Figure 2a, ^{11}B NMR) by 3.1 ppm.

Figure 2. Active species in solution.

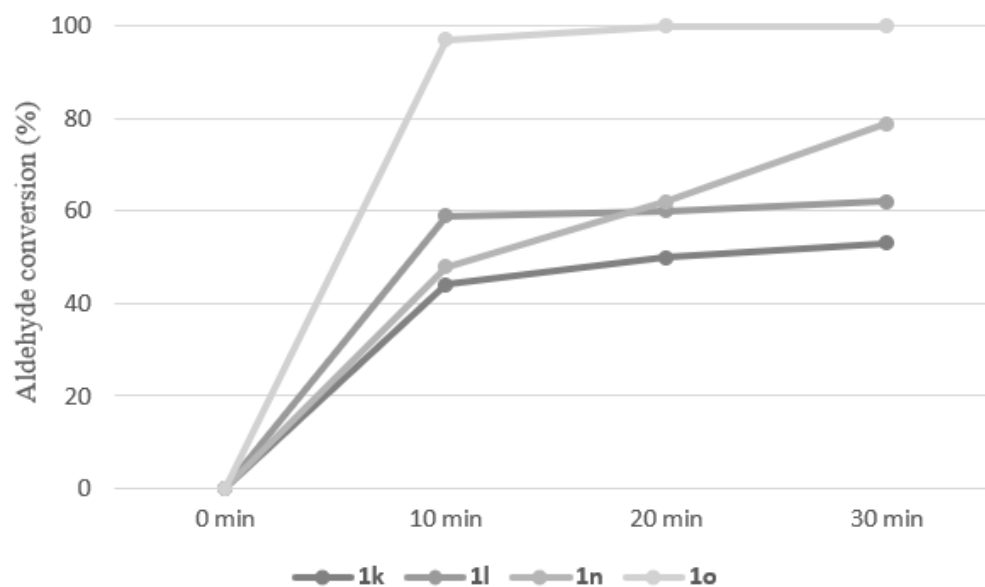


^a Experimental details: a) C₆F₅B(OH)₂ (0.05 mmol) in CDCl₃. b) tetrabromocatechol (0.05 mmol) was added, 5 mins. c) 100 mg 4Å MS was added, 5 mins. d) 4-nitrobenzaldehyde (2 equiv.) was added, 5 mins.

At this point, no signal indicating enhanced shielding was detected, implying the absence of sp³ hybridization in the boron atom. This implies that the water molecules produced during the condensation step were effectively removed by the molecular sieves and did not bind to **1o**. Furthermore, upon addition of a two-fold excess of 4-nitrobenzaldehyde, a new signal at 8.6 ppm (Figure 2d, ¹¹B NMR) was observed, in line with the formation of a Lewis adduct between **1o** and the aldehyde.¹⁵ Although the high Lewis acidity prevented the isolation of **1o** without partial hydrolysis to the boronic acid, a dichloromethane solution free from molecular sieves was eventually obtained using Schlenk techniques. Pleasingly, using this solution for the Sakurai allylation resulted in a similar reaction rate compared to the in-situ generation of **1o** in the presence of molecular sieves (88% conversion after 20 minutes).

Based on experimental evidence supporting the efficacy of Lewis acid catalysis, the comparative efficiency of the BAEs listed in Table 1 was evaluated. Monitoring the consumption of initial 4-nitrobenzaldehyde in ¹H NMR, against tetrachloroethane as an internal standard, revealed that even after 6 hours, BAEs **1c-1j**, **1m**, and **1q** exhibited low conversions (see supporting information). However, for the more active BAEs the reactivity order was clearly established as **1o** >> **1n** > **1l** > **1k** (see Figure 3).

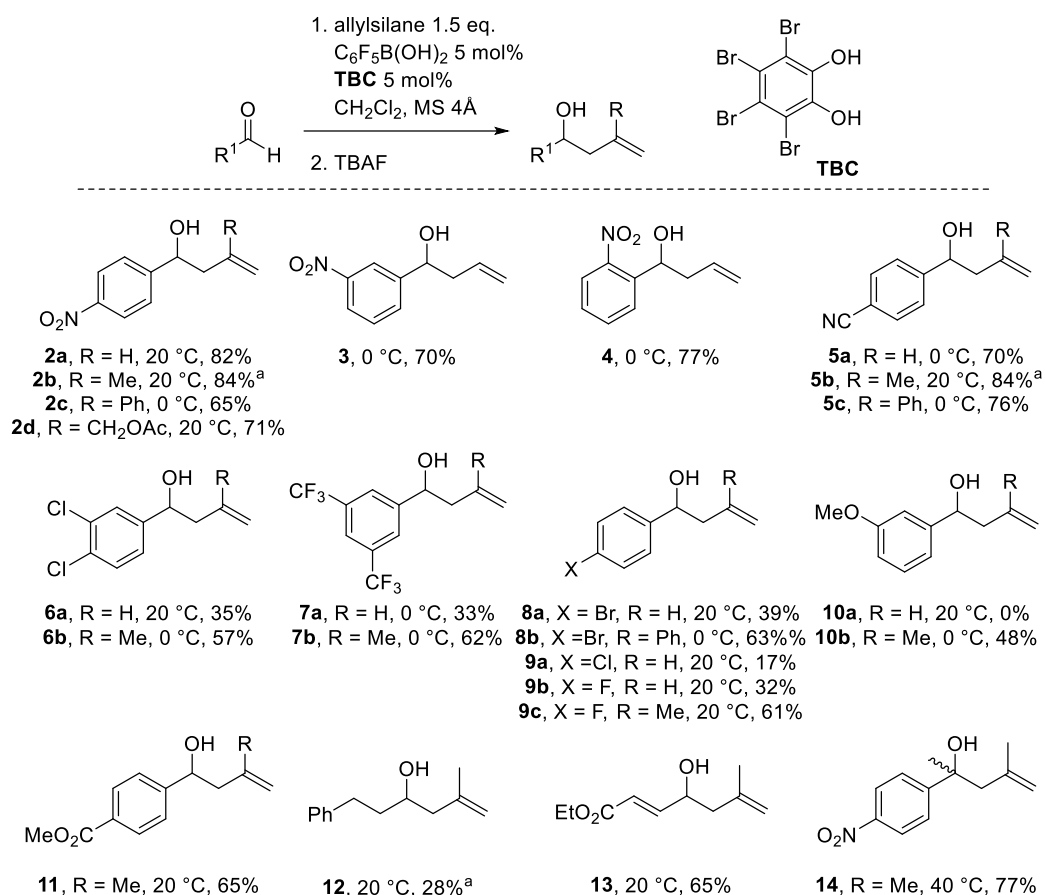
Figure 3. Allylation conversion monitored by ^1H NMR.^a



^a Reaction conditions see Scheme 1, footnote a. Conversion of 4-nitrobenzaldehyde determined by ^1H NMR.

A variety of benzaldehydes were investigated for conversion to the corresponding homoallylic alcohols (Scheme 2). Effective catalysis required the presence of electron-deficient aldehydes. Remarkably, the nitrile functional group was accommodated (**5a-5c**), despite its documented tendency to deactivate Lewis acids such as **BCF**.¹⁶ Several limitations of this methodology were identified. Specifically, 4-chlorobenzaldehyde and 3-methoxybenzaldehyde yielded poor results (17%, **9a**) or no product at all (**10a**). Additionally, aliphatic hydrocinnamaldehyde exhibited a low yield of 28%, despite a fast conversion (TLC monitoring). Unexpectedly, no side product was clearly identified with this substrate. Ultimately, the corresponding alcohol **14** was obtained in 77% yield from 4-nitroacetophenone after gentle heating at 40 °C.

Scheme 2. Scope of catalyzed Hosomi-Sakurai allylations.



^a C₆F₅B(OH)₂ 1 mol%, TBC 1 mol% were used.

In summary, our investigation into boronic acid esters involved quantifying their Lewis acidity, revealing their potential as catalysts in carbon-carbon bond formation reactions. The method involves the direct assembly of two commercially available bench-stable components under mild conditions without the recourse to glovebox. Further exploration aimed at enhancing Lewis acidity of BAEs and their application in organic synthesis will be reported in due time.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of ^1H and ^{13}C NMR spectra, atom coordinates and absolute energies of calculated structures.

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