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Breaking the dichotomy of reactivity *vs.* chemoselectivity in catalytic S_N1 reactions of alcohols†

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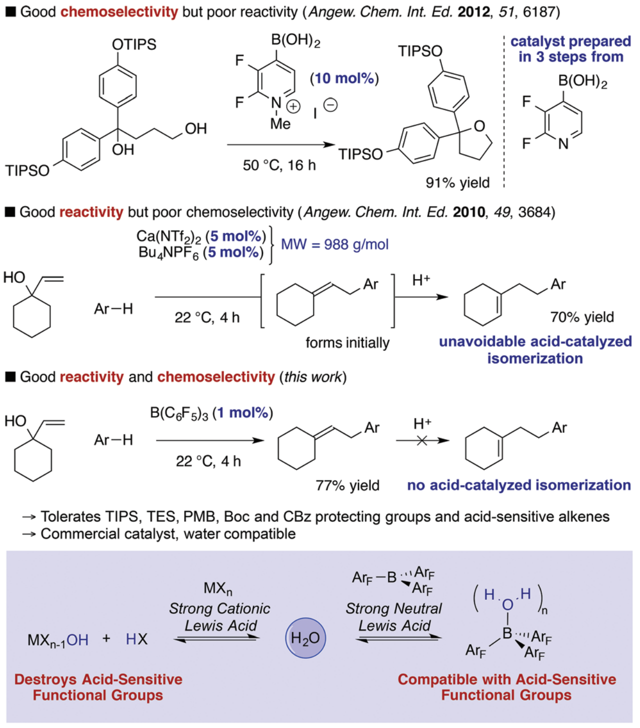
The inability to decouple Lewis acid catalysis from undesirable Brønsted acid catalysed side reactions when water or other protic functional groups are necessarily present has forced chemists to choose between powerful but harsh catalysts or poor but mild ones, a dichotomy that restricts the substrate scope of dehydrative transformations such as the direct S_N1 reaction of alcohols. A systematic survey of Lewis and Brønsted acids reveals that the strong non-hydrolyzable Lewis acid $B(C_6F_5)_3$ leads to highly chemoselective alcohol substitution in the presence of acid-sensitive alkenes, protecting groups and other functional groups without the typical compromise in reaction rates, substrate scope and catalyst loading.

Introduction

Chemoselectivity is a critical but often ignored parameter that affects the utility of any reaction. The inability to decouple Lewis acid catalysis from undesirable Brønsted acid catalysed side reactions[1] when water or other protic functional groups are necessarily present has forced chemists to choose between powerful but harsh catalysts or poor but mild ones, a dichotomy that restricts the substrate scope and utility of dehydrative transformations. This undesirable compromise is perhaps best illustrated by the synthetic limitations of the direct catalytic S_N1 reactions of alcohols, a powerful and nearly ideal set of "green" dehydrative transformations.[2–4] On one hand, cationic Lewis acid catalysts, such as metal chlorides, triflates or perchlorates, activate a wide variety of π-activated alcohols at low catalyst loadings, but also hydrolyse to release strong Brønsted acids that isomerize sensitive alkenes[4j] or cleave alkyl and aryl silyl ethers at or near room temperature.[5] On the other hand, deliberate efforts to develop chemoselective catalysts, such as electron-poor boronic acids[6] or weak Brønsted acids,[7] have resulted in severely limited alcohol scope for intermolecular reactions, sluggish reaction rates and the requirement for high catalyst loadings (Scheme 1). The identification of a catalyst for alcohol substitution that combines the paradoxical properties of robust, general reactivity with superior functional group compatibility would open up new synthetic applications for this powerful transformation in complex molecule synthesis. $B(C_6F_5)_3$,[8] a commercially available strong non-hydrolyzable neutral Lewis acid whose hydrates undergo rapid ligand exchange,[9] possesses a combination of properties that may offer a practical solution to this general problem. $B(C_6F_5)_3$



Scheme 1 The dichotomy of reactivity *vs.* chemoselectivity in catalytic S_N1 reactions of alcohols.

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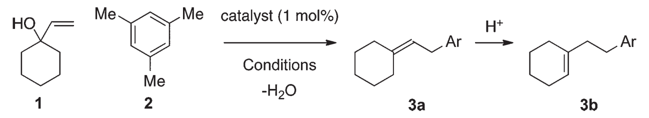
is typically exploited in catalysis under inert atmospheres and rigorously dry conditions.[10] Like many strong Lewis acids, $B(C_6F_5)_3$ has been shown to enable dehydrative reactions of alcohols,[11] but the absence of a systematic comparison of reactivity and chemoselectivity profiles with other catalysts has obscured potential advantages. Herein, we demonstrate that $B(C_6F_5)_3$ possesses an attractive chemoselectivity and reactivity profile compared to established Brønsted and Lewis acids in direct S_N1 reactions of alcohols in the presence of acid-sensitive alkenes and protecting groups, breaking the traditional dichotomy between reactivity and chemoselectivity and opening up new synthetic potential for this important class of transformations.

Results and discussion

Our initial investigations began by studying the Friedel–Crafts reaction of allylic alcohol **1** with mesitylene **2** to give exocyclic alkene **3a**, which can undergo an undesirable further isomerization in the presence of Brønsted acid to give the thermodynamically favorable endocyclic alkene isomer **3b** (Table 1). Reactions were studied at 80 °C and at room temperature to best resolve differences in chemoselectivity and reactivity, respectively. A survey of common strong Brønsted acids at 1 mol% catalyst loading under a common set of conditions after 1 h reaction time at 80 °C revealed that all mediate the Friedel–Crafts reaction accompanied by extensive olefin isomerization (entries 2–5). Weaker Brønsted acids avoid olefin isomerization at the cost of attenuated reactivity (entry 6). For cationic Lewis acids, significant olefin isomerization occurs in all cases (entries 7–12), even for "water stable"[12] $Yb(OTf)_3$ (entry 13). Weaker neutral Lewis acids such as electron-poor boronic acids and triphenylborane were unable to mediate the transformation at the given catalyst loadings (entries 14–15, see Table S1† for a more extensive screen). $B(C_6F_5)_3$ was the most efficient of all catalysts surveyed yet showed little isomerization to **3b** (entry 16). Furthermore, just 1 mol% of $B(C_6F_5)_3$ at room temperature gives 60% yield of **3a** after 1 h and 77% after 4 h without any detectable **3b** (entries 17–18). In contrast, strong Brønsted acids show slower reaction rates compared to $B(C_6F_5)_3$ and cause olefin isomerization even at 22 °C (entries 19–20). Weaker Brønsted acids such as TFA did not furnish a detectable quantity of **3a** under the same conditions (entry 21). The different outcomes for BF_3 and $B(C_6F_5)_3$ are particularly noteworthy since they possess comparable Lewis acidities according to the Gutmann–Beckett and Childs methods.[13] Likewise, though the pK_a of monohydrated $B(C_6F_5)_3$ has been found to be comparable to H_2SO_4 in MeCN,[9b] the two produce markedly different degrees of isomerization. Thus, the combination of reactivity and chemoselectivity of $B(C_6F_5)$ is unique among the surveyed Lewis and Brønsted acids.

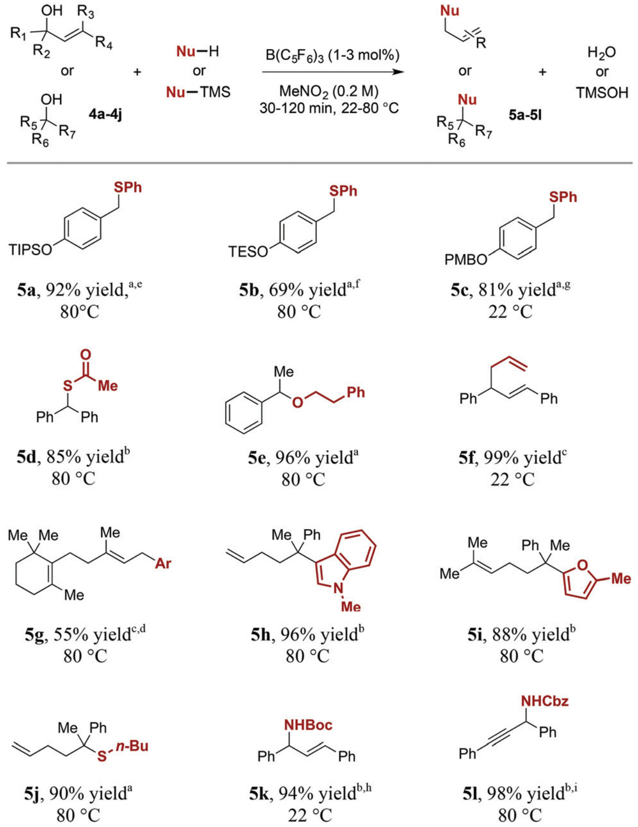
Table 1 A comparison of catalysts for alcohol activation in the absence of Brønsted acid-catalyzed olefin isomerization



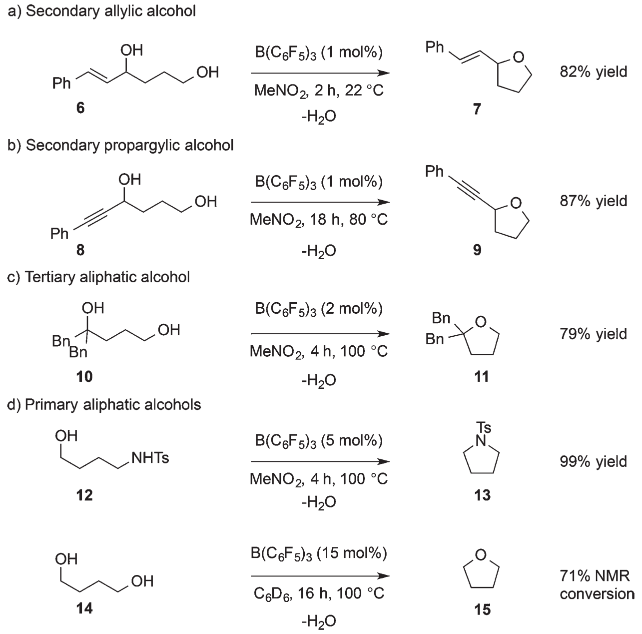
Entry	Catalyst	T (°C)	Yield[a] 3a + 3b [%]	Ratio (3a : 3b)
1	None	80	<5	N/A
2	TfOH	80	77	1 : 10
3	HBF_4	80	88	1 : 9
4	H_2SO_4	80	78	1 : 5
5	*p*-TsOH	80	74	4 : 1
6	TFA	80	68	≥20 : 1
7	$Ca(NTf)_2/Bu_4NPF_6$	80	74	1 : 9
8	$Bi(OTf)_3$	80	83	1 : 12
9	$Sc(OTf)_3$	80	83	1 : 9
10	BF_3·THF	80	82	1 : 10
11	$FeCl_3$	80	82	1 : 3
12	$AuCl_3$	80	85	6 : 1
13	$Yb(OTf)_3$	80	62	4 : 1
14	$B(C_6F_5)(OH)_2$	80	<5	N/A
15	BPh_3	80	<5	N/A
16	$B(C_6F_5)_3$	80	92	≥20 : 1
17	$B(C_6F_5)_3$	22	60	≥20 : 1
18[b]	$B(C_6F_5)_3$	22	77	≥20 : 1
19	TfOH	22	47	2 : 1
20	*p*-TsOH	22	32	≥20 : 1
21	TFA	22	<5	N/A

Conditions: 1.0 equiv. **1** (0.2 M in $MeNO_2$), 3.0 equiv. **2**, 1 h. [a] Isolated yield after silica gel chromatography. [b] Reaction time of 4 h.

Examples of catalytic carbocation generation from alcohols in the presence of acid-labile silyl protecting groups are rare, particularly above ambient temperatures. Recently, Hall and co-workers reported a boronic acid-catalyzed cyclodehydration of a highly biased bis-benzylic alcohol bearing a TIPS-protected phenol at 50 °C, a group that otherwise cleaves under Brønsted acid-catalyzed conditions (Scheme 1, top).[6e] To gauge functional group compatibility in a relatively more challenging intermolecular reaction using $B(C_6F_5)_3$, we examined the coupling of protected 4-hydroxybenzyl alcohols with thiophenol at 80 °C, though room temperature was also sufficient (Scheme 2, **5a–5c**). TIPS-protected phenol **5a** is formed smoothly in 92% yield after 1 h with no detectable cleavage of the silyl ether. To test the limits of compatibility, TES-protected phenol product **5b** ($\approx 10^4$ times more labile than TIPS) is isolated intact in 69% yield at 80 °C. Furthermore, the more facile activation of alcohols compared to ethers can be exploited to achieve selectivity when benzylic ethers and benzylic alcohols are both present on the same substrate. PMB-protected benzylic alcohol **4c** converts to **5c** in 81% yield without cleavage of the PMB-ether simply by carrying out the reaction at room temperature over 4 h. Numerous other acid-sensitive alcohols, nucleophiles or products persist under conditions that might otherwise be expected to lead to decomposition (Scheme 2, **5d–5l**). Thioacetic acid reacts efficiently with a benzylic alcohol at 2 mol% catalyst loading to give **5d** without observable hydrolysis despite heating in the presence of a stoichiometric quantity of water. To our knowledge, this is the first time that thioacids and alcohols are dehydratively coupled without the use of near-stoichiometric quantities of activating agents[14] or a large excess of nucleophile. Direct



Scheme 2 Intermolecular $B(C_6F_5)_3$-catalyzed alcohol substitution in the presence of acid-labile protecting groups or acid-sensitive functionalities. Reaction conditions: 1 equiv. alcohol (0.2 M in $MeNO_2$), 1.1–3.0 equiv. nucleophile. Isolated yield after silica gel chromatography. [a]1 mol %. [b]2 mol%. [c]3 mol%. [d]Ar = 2,4,6-mesityl. [e]TIPS = triisopropylsilyl. [f]TES = triethylsilyl. [g]PMB = *para*-methoxybenzyl. [h]Boc = *tert*-butoxycarbonyl. [i]Cbz = carboxybenzyl.



Scheme 3 $B(C_6F_5)_3$-catalyzed dehydrative cyclizations.

etherification between 1- and 2-phenylethanol at 80 °C leads cleanly to elimination-prone ether **5e**, a compound described by Hartwig and coworkers to decompose in the presence of catalytic TfOH at 70 °C.[1b] Friedel–Crafts alkylation of complex terpene derivatives containing tri- and tetra-substituted olefins occurs in good yield to give **5g** without subsequent alkene hydroarylation or isomerization. *N*-Methylindole and 2-methylfuran couple with alkenols in the absence of acid-catalyzed decomposition at 80 °C to give **5h** and **5i**, respectively. Thiols react cleanly with alkenols to give **5j** without any detectable thiol–ene "click" reaction or acid-catalyzed hydrothiolation of the alkene moiety. Finally, Boc and Cbz groups are stable under the reaction conditions.

$B(C_6F_5)_3$ performs exceptionally well compared to established mild boronic acid cyclodehydration catalysts (Scheme 3).[6e] Though 10 mol% of a boronic acid catalyst was reportedly unable to cyclize isomer **6**, it is accomplished readily at room temperature with 1 mol% $B(C_6F_5)_3$ in just 2 h. Secondary propargylic alcohol **8** is cyclized to 2-alkynyl tetrahydrofuran **9** in 87% yield without an additional pre-activation step.[15] Tertiary aliphatic alcohol **10** forms 2,2-dialkyltetrahydrofuran **11** in 79% yield after 4 h, a ten-fold reduction in catalyst loading and four-fold reduction in time compared to 2,3-difluoro-4-methylpyridiniumboronic acid catalyst under otherwise identical conditions.[6e] Cyclizations of primary aliphatic alcohols, which typically undergo cyclodehydrations only with stoichiometric dehydrating agents or in the presence of superacids at high temperatures (>160 °C), are facile at 100 °C, presumably operating by an S_N2-type mechanism. For example, hydroxytosylamide **12** cyclizes to pyrrolidine **13** in nearly quantitative yield, a reaction previously accomplished only by stoichiometric pre-activation.[16] Similarly, cyclodehydration of 1,4-butanediol **14** to THF **15** is carried out under milder conditions than existing homogeneous or heterogeneous processes.[17,18]

Mechanistic experiments that discriminate between Lewis and Brønsted acid catalysis are not straightforward in reactions that produce water, given the complex equilibria between many potential species. Nevertheless, the different reactivity and chemoselectivity profile of $B(C_6F_5)_3$ compared to strong Brønsted acids such as *p*-TsOH ($pK_a = 8.6$[19]) suggests that the borane monohydrate ($pK_a = 8.4$[9b]) is not present in significant quantities under the reaction conditions or possesses an attenuated kinetic acidity. It is not possible at this time to distinguish between Lewis acid-catalysis or Brønsted acid catalysis arising from borane hydrates.[20]

Conclusion

In summary, $B(C_6F_5)_3$ displays the opposing qualities of a powerful yet gentle catalyst for the dehydrative substitution of alcohols and breaks the traditional dichotomy between reactivity and chemoselectivity in catalytic dehydrative reactions. Diverse π-activated and aliphatic alcohols are displaced with a wide range of nucleophiles without isomerization or cleavage of acid-sensitive groups under low catalyst loadings and in the absence of rigorously dried solvents or an inert atmosphere, providing a highly practical method for an important class of transformations. We anticipate that the unique chemoselectivity profile of strong neutral Lewis acids such as $B(C_6F_5)_3$ will be of broad utility in synthesis when Lewis acid catalyzed transformations must be carried out in the presence of water or other protic functional groups.

Acknowledgements

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