Unsymmetrical Diarylmethanes by Ferroceniumboronic Acid Catalyzed Direct Friedel–Crafts Reactions with Deactivated Benzylic Alcohols: Enhanced Reactivity due to Ion-Pairing Effects

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ABSTRACT: The development of general and more atom-economical catalytic processes for Friedel-Crafts alkylations of unactivated arenes is an important objective of interest for the production of pharmaceuticals and commodity chemicals. Ferroceniumboronic acid hexafluoroantimonate salt (**1**) was identified as a superior air- and moisture-tolerant catalyst for direct Friedel-Crafts alkylations of a variety of slightly activated and neutral arenes with stable and readily available primary and secondary benzylic alcohols. Compared to the use of classical metal-catalyzed alkylations with toxic benzylic halides, this methodology employs exceptionally mild conditions to provide a wide variety of unsymmetrical diarylmethanes and other 1,1-diarylalkane products in high yield with good to high regioselectivity. The optimal method, using the bench-stable ferroceniumboronic acid salt **1** in hexafluoroisopropanol as co-solvent, displays a broader scope compared to previously reported catalysts for similar Friedel-Crafts reactions of benzylic alcohols, including other boronic acids such as 2,3,4,5-tetrafluorophenylboronic acid. The efficacy of the new boronic acid catalyst was confirmed by its ability to activate primary benzylic alcohols substituted with destabilizing electron-withdrawing groups like halides, carboxyesters, and nitro substituents. Arene benzylation was demonstrated on a gram-scale at up to 1M concentration with catalyst recovery. Mechanistic studies point toward the importance of the ionic nature of the catalyst and suggest that factors other than the Lewis acidity (pKa) of the boronic acid are at play. A S_N1 mechanism is proposed where ion-exchange within the initial boronate anion affords a more reactive carbocation paired with the non-nucleophilic hexafluoroantimonate counteranion.

Introduction

Transformations of arenes and heteroarenes are at the core of the production of pharmaceutical agents and commodity chemicals. The classical Friedel-Crafts procedure for alkylation of arenes, as originally reported in 1877,[1] employs a stoichiometric amount of strong Lewis acid (e.g., $AlCl_3$, $FeCl_3$) to activate an alkyl halide and form a reactive carbocation as the electrophile.[2] Many alkyl halides, including benzylic chlorides, pose a safety hazard as toxic lachrymator chemicals that hydrolyze readily to generate irritating haloacid gas (HX) as a by-product. These reaction conditions, which prevailed for more than a century, are far from ideal from the standpoint of atom-economy and green chemistry. It is therefore not surprising that the *ACS Green Chemistry Institute Pharmaceutical Roundtable* has identified Friedel-Crafts reactions as one of the top research priorities.[3] Specifically, there is a need for more direct and atom-economical procedures employing a catalytic amount of activator with more stable and less toxic electrophiles like alcohols.[4] The use of readily accessible benzylic alcohol derivatives in Friedel-Crafts alkylations of arenes is of great interest for its potential as a simple and direct route to access diaryl- and triarylmethane products. Both classes of diaryl- and triarylmethane products have found numerous applications as pharmaceutical and agrochemical agents (Figure 1).[5]

A number of cross-coupling methods exist for synthesizing diarylmethane products using, for the most part, benzylic and arene substrates that are both embedded with activating groups. Although this C–C bond-forming strategy can assure a high regioselectivity, it requires the preparation of activated substrates as well as expensive transition metal catalysts.

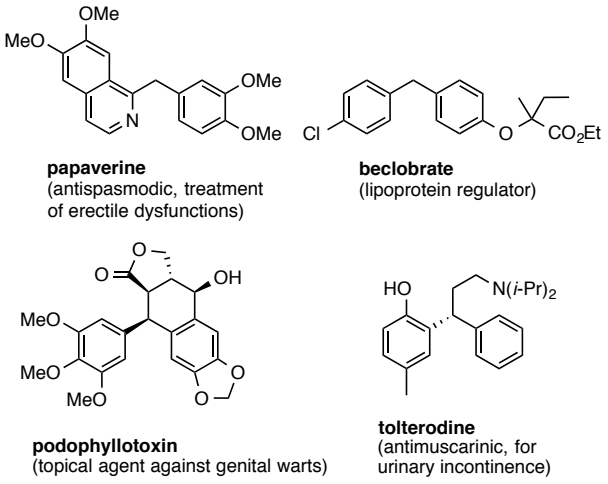


Figure 1. Examples of biologically active diarylmethane and diarylalkane compounds.

As exemplified by the work of Georgiou and co-workers with a benzylic bromide (Figure 2a),[6] the use of benzylic halides and pseudo-halides in the Suzuki-Miyaura cross-coupling of arylboronic acids constitutes a viable approach.[7] Molander and co-workers successfully coupled benzylic trifluoroborate salts with aryl triflates (Figure 2b).[8] The analogous Negishi coupling can also be achieved (Figure 2c),[9,10] as well as Kumada-Corriu and related cross-coupling processes.[11] Barluenga and co-workers reported a metal-free method for the preparation of diarylmethane products between hydrazones and arylboronic acids (Figure 2d).[12] More recently, efforts have been made to eliminate activating groups. Thus, methods using the catalytic C–H activation of arenes followed by coupling with benzylic halides have been reported, however most of these methods employ structurally limited substrates engineered with directing groups and they tend to require high reaction temperatures.[13]

The Friedel-Crafts benzylation of arenes under the classical reaction conditions using benzylic chlorides and strong Lewis acids, typically $AlCl_3$, has been thoroughly studied by Olah and co-workers (Figure 3a).[14] Recently, a method for in situ activation of benzylic alcohols with a stoichiometric amount of a fluorination reagent was reported.[15] A number of other attractive methods employing various alcohol derivatives as non-halogenated substrates, such as ether and ester derivatives, were also reported.[16] For example, Bode and co-workers recently described the use of benzylic hydroxamates and a stoichiometric amount of boron trifluoroborate as a remarkably effective method for the benzylation of neutral and deactivated arenes with a wide range of compatible functional groups on both substrates.[17] Although these methods do bypass the use of toxic benzylic halides, they often require a super-stoichiometric amount of Lewis acid and generate by-products resulting from release of the activating group. These procedures are thus less atom-economical compared to the use of alcohols, where water would be generated as the only by-product.

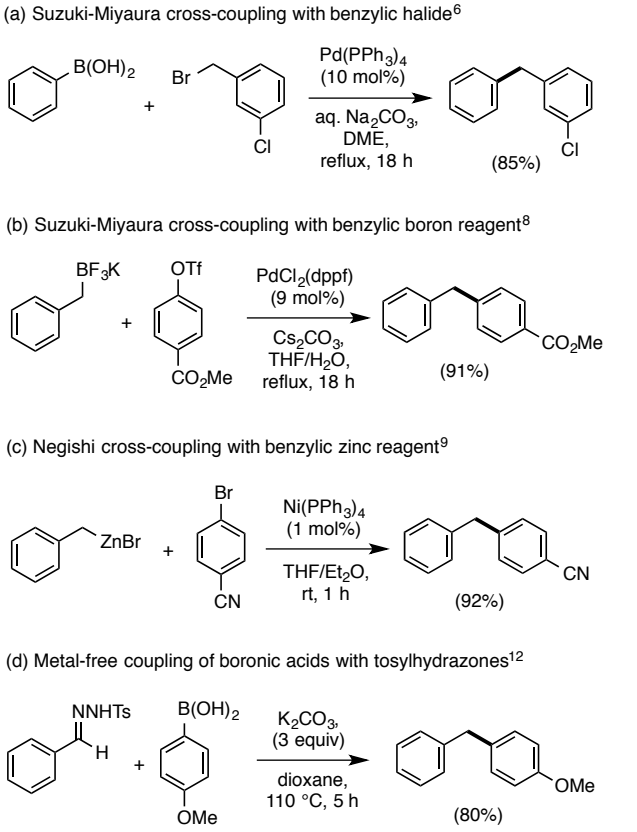


Figure 2. Examples of methods for the preparation of diarylmethane products using two activated substrates.

It is only in the past decade, however, that successful efforts to replace benzylic halides and harsh Lewis acids have appeared, spearheaded by the report of a scandium triflate catalyzed benzylation of activated arenes with benzylic alcohols (Figure 3b).[18] Subsequently, a number of other metal-catalyzed procedures were developed for direct Friedel-Crafts alkylations with benzylic alcohols, including $FeCl_3$,[19] $PtCl_4$,[20] $Bi(OTf)_3$,[21] $HAuCl_4$,[22] $Ca(NTf)_2$,[23] and other catalysts and variants.[24] Remarkable advances were described by Beller and co-workers with the use of 10 mol% of iron trichloride[19] or platinum (IV) chloride[20] in direct Friedel-Crafts benzylations of neutral and activated arenes with primary benzylic alcohols, whereas Rueping and co-workers identified bismuth triflate as a catalyst that can be employed in lower loadings (Figure 3b).[21] Most of these procedures, however, require a large excess of arene used essentially as a solvent, and often at high temperatures. Moreover, the demonstrated scope of substrates is generally limited to arene and benzylic alcohol substrates, mostly secondary alcohols, that are functionalized with simple activating substituents.

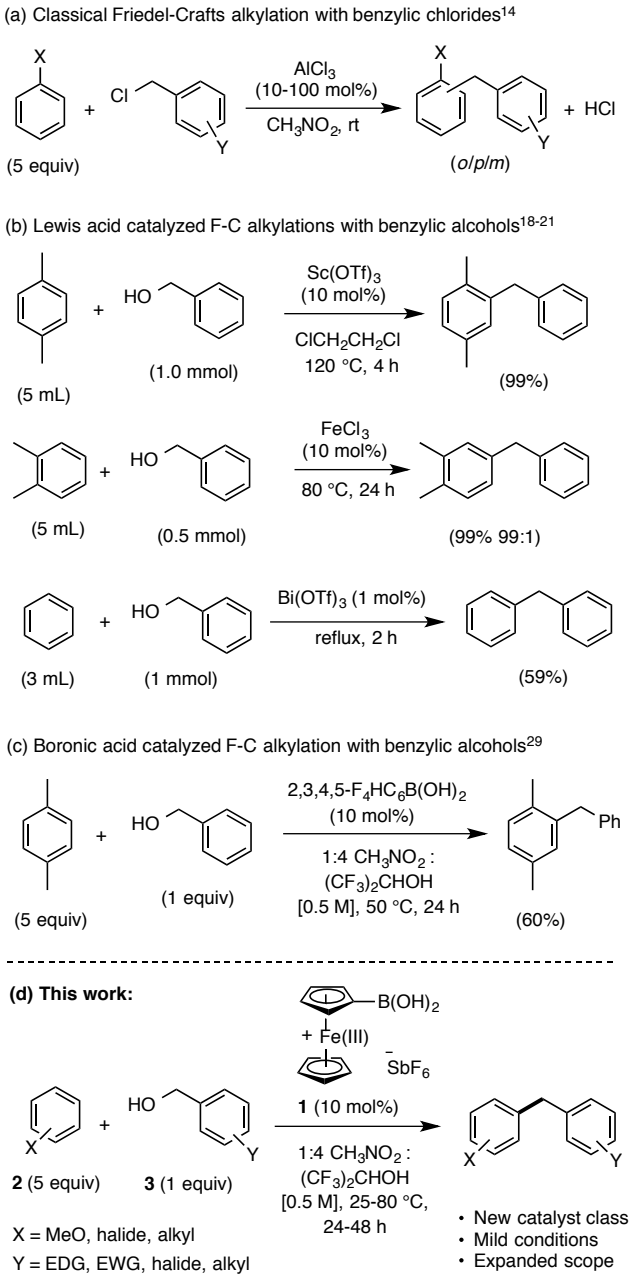


Figure 3. Friedel-Crafts reactions with primary benzylic halides and alcohols.

Boronic acid catalysis is emerging as a promising metal-free alternative for activating free carboxylic acids and alcohols as substrates in a variety of reactions.[25,26] Arylboronic acids are stable and safe compounds that can form covalent bonds with alcohols in a reversible manner. The resulting transient boronates can impart a mild electrophilic activation of the hydroxyl group to facilitate the complete or partial ionization of the C–O bond leading to a putative carbocation intermediate.[27] Moreover, compared to the use of strong Brønsted acids, boronic acids exhibit a wider functional group tolerance due to their mildly acidic character (pKa 5-9).[28] McCubbin and co-workers were first to report on the catalytic activation of alcohols with boronic acids by using the highly Lewis acidic pentafluorophenylboronic acid in regioselective Friedel-Crafts reactions of allylic and activated benzylic alcohols with activated, electron-rich arenes or heteroarenes. Recently, we reported the use of tetrafluorophenylboronic acid as a superior catalyst in Friedel-Crafts allylations and benzylations of neutral arenes.[29] Although secondary benzylic alcohols reacted smoothly at room temperature, the reaction of benzyl alcohol as a prototypic primary alcohol with both meta and ortho xylene was more difficult and afforded moderate yields of products (Figure 3c). The preparation of diarylmethane products by Friedel-Crafts benzylation is particularly challenging when using neutral arenes of moderate nucleophilicity and primary benzylic alcohols functionalized with electronically deactivating substituents that destabilize the benzylic carbocation intermediate. In such cases, undesired polyalkylation or alkylation of the alcohol substrate can become a predominant side-reaction. Here, we demonstrate that the ionized form of ferroceneboronic acid, the ferroceniumboronic acid hexafluoroantimonate salt **1**, is a significantly more powerful activator of electronically deactivated primary benzylic alcohols and can catalyze Friedel-Crafts alkylations of a wide range of neutral arenes functionalized with various substituents that confer synthetic usefulness to the products (Figure 3d). Studies were also conducted to address the reaction's mechanism and the origin of the catalyst's efficacy, which likely functions through a novel ion-exchange mechanism that takes advantage of the ionic nature of catalyst **1**.

Results and Discussion

Optimization of reaction conditions with catalyst 1

Previous work on boronic acid catalyzed activation of alcohols uncovered a general trend where superior activation was achieved with arylboronic acids of a lower pKa.[26j,29] This trend, however, does not always hold true and special effects may operate depending on the nature of the ortho substituent. For example, despite its significantly higher pKa, tetrafluorophenylboronic acid was found to be a superior catalyst in Friedel-Crafts allylations compared to pentafluorophenylboronic acid.[29] From this perspective, the possibility for anomalous reactivity led us to consider arylboronic acids of a different structural nature. In particular, we surmised that charged boronic acids could promote an ion-exchange process that would increase the lifetime or the reactivity of carbocations. The possibility of exchanging the trihydroxyboronate counteranion formed in the ionization of benzylic alcohols with normal boronic acids (eq. 1), through replacement with a non-nucleophilic anion (X^-, eq. 2), could mitigate the back-reaction reverting the carbocation to the starting alcohol (Figure 4a). This search led us to ferroceneboronic acid and its oxidized Fe(III) congener, the ferrocenium boronic acid salt **1**, which can be prepared according to literature procedures (Figure 4b).[30] The hexafluoroantimonate salt (**1**) is easily obtained by treating an acetone solution of commercially available ferroceneboronic acid with $AgSbF_6$,

followed by a filtration to remove metallic silver and leave a filtrate that provides a bench-stable dark-blue powder after evaporation and drying. Using cyclic voltammetry, Moore and Wayner measured the pKas of ferroceneboronic acid and the corresponding ferrocenium salt to be 10.8 and 5.8, respectively.[31] The pKa of the ferrocenium boronic acid, thus, is close to the value of 6.0 for 2,3,4,5-tetrafluorophenylboronic acid,[29] so it was deemed a good candidate for evaluation as a catalyst for direct Friedel-Crafts alkylations with primary benzylic alcohols.

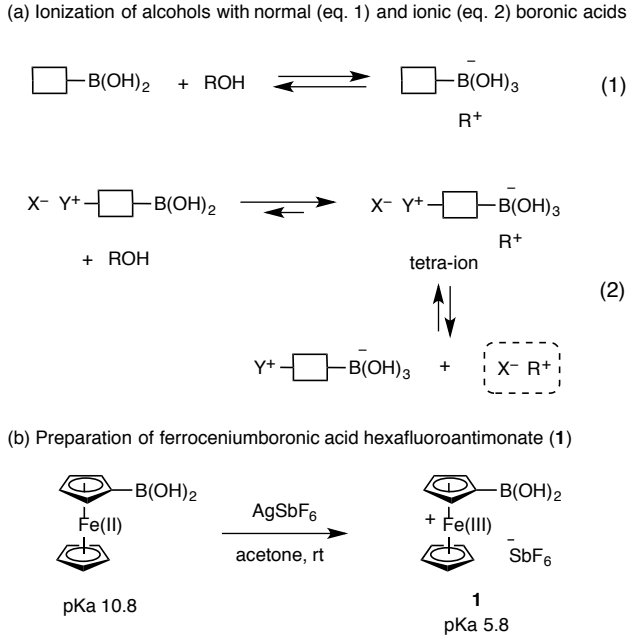
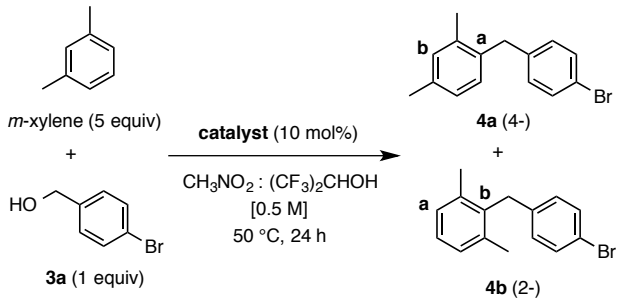


Figure 4. (a) Concept of ion-exchange with ionic boronic acids. (b) Preparation of ferrroceniumboronic acid salt **1**.

The initial evaluation of catalysts was performed using the alkylation of m-xylene (**2a**) with 4-bromobenzyl alcohol (**3a**) under previously reported conditions with a 4:1 mixture of hexafluoroisopropanol and nitromethane as the solvent at a temperature of 50 °C (Table 1).[29] Our previous best catalyst, 2,3,4,5-tetrafluorophenylboronic acid, and ferroceneboronic acid both failed to activate alcohol **3a** and produce the diarylmethane isomers **4** (entries 1-2). To our satisfaction, the ferroceniumboronic acid salt **1** provided a high yield of **4a** and **4b** under the same conditions (entry 3). We then examined the effect of the solvent mixture. As observed previously,[29] the reaction was sensitive to the proportions of hexafluoroisopropanol and nitromethane, with a 4:1 mixture being preferable in order to optimize product yield (entries 3-4). A lower yield was obtained when the reaction was conducted at a higher concentration (entry 5) or at ambient temperature (entry 6).

Table 1. Optimization of Friedel-Crafts benzylation with catalyst 1.



entry	catalyst	solvent ratio	T (°C)	yield (%)	a:b
1	2,3,4,5-$F_4HC_6B(OH)_2$	1:4	50	0	
2	$CpFe(II)CpB(OH)_2$	1:4	50	0	
3	$CpFe(III)CpB(OH)_3(SbF_6)$ (**1**)	1:4	50	87	78:22
4	**1**	1:2	50	71	78:22
5[a]	**1**	1:4	50	74	78:22
6	**1**	1:4	rt	14	75:25

[a] 1M concentration

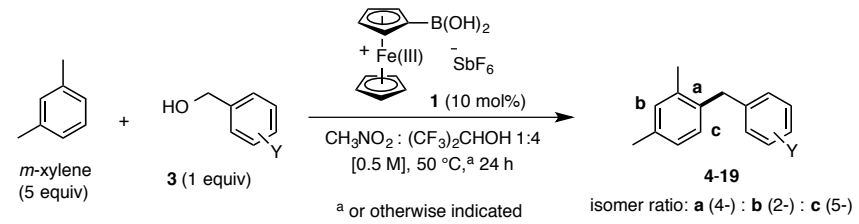
Examination of substrate scope

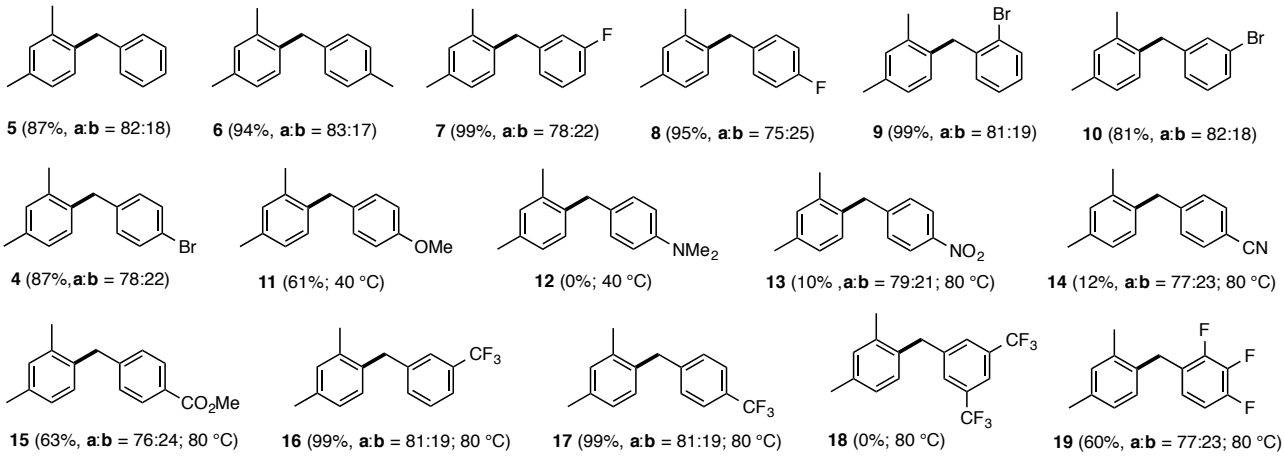
The generality of the reaction was studied under the optimal conditions of Table 1 (entry 3). Using m-xylene as a model neutral arene, we first examined the nature of the benzylic alcohol and the reaction's compatibility with various substituents and functional groups (Figure 5).

Benzylic alcohols containing an electronically neutral arene core or others with slightly deactivating substituents such as fluoride or bromide led to high yields of products **4**-**10** at or below 50 °C. The use of bromide substituents is particularly attractive in view of derivatizing the resulting products (e.g., **4**, **9**-**10**) using cross-coupling chemistry. Although 4-methoxylbenzyl alcohol reacted efficiently to yield **11** at 40 °C, the 4-dimethylamino analogue failed to afford product **12**. A possible reason for this failure could be protonation or H-bonding of the aniline substituent by the HFIP solvent (pKa = 9.3), which would effectively inhibit the mesomeric stabilization of the benzylic carbocation provided by the nitrogen atom. Although benzylic alcohols with strongly electron-withdrawing substituents such as nitro and cyano provided only a low yield of the desired products (e.g., products **13** and **14**), it is remarkable that the catalyst was effective with other substrates bearing highly deactivating substituents like a carboxyester (product **15**), or trifluoromethyl (products **16**-**17**). A temperature of 80 °C was required but these conditions did not lead to side reactions and very high yields of products were obtained. It is noteworthy that the nature of the benzylic alcohol had little effect on the regioselectivity of the reaction. Not surprisingly, due to unfavorable steric effects, substitution between the two methyl groups of m-xylene was discouraged thus the 4-substituted products

(**a**) were isolated preferentially over the 2-substituted products (**b**) with selectivities greater than 3:1. This level of selectivity is very similar to that obtained in classical Friedel-Crafts benzylations with benzylic halides,[14] indicating that all of these variants are controlled mainly by the properties of the arene substrate, and that a common carbocation intermediate is produced regardless of the electrophilic precursor. The use of p-xylene as a substrate allowed us to further examine the scope of the benzylic alcohol without the complication of forming regioisomers (Figure 6). Thus, various benzylic alcohols substituted with methyl or halide substituents, including multiply substituted ones, reacted successfully (products **20**-**28**). Other heteroatom-substituted diarylmethanes such as **29** and **30** can be produced. Remarkably, catalyst **1** is capable of activating 4-nitrophenylbenzyl alcohol to afford a moderate yield of product **31** at 80 °C. The successful formation of product **32** further highlights the great reactivity of catalyst **1**. In this example, the benzylic alcohol substituted with a *para* carboxyester was successfully activated by catalyst **1** to afford **32** under conditions where 2,3,4,5-tetrafluorophenylboronic acid failed entirely. The scope of this methodology is particularly attractive from the viewpoint of medicinal chemistry for its applicability to benzylic alcohols decorated with fluoride (products **21**-**25**, **28**) and trifluoromethyl substituents (product **33**). No product **34** (or **18**, Figure 5) was isolated from the use of 3,5-bis(trifluoromethyl)benzyl alcohol, thus indicating the reaction's limits with respect to carbocation stability. On the other hand, a naphthylmethanol was a suitable reagent (product **35**).

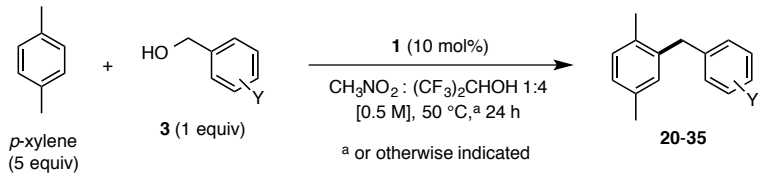
Figure 5. Scope of primary benzylic alcohols with m-xylene as the arene nucleophile.[a]

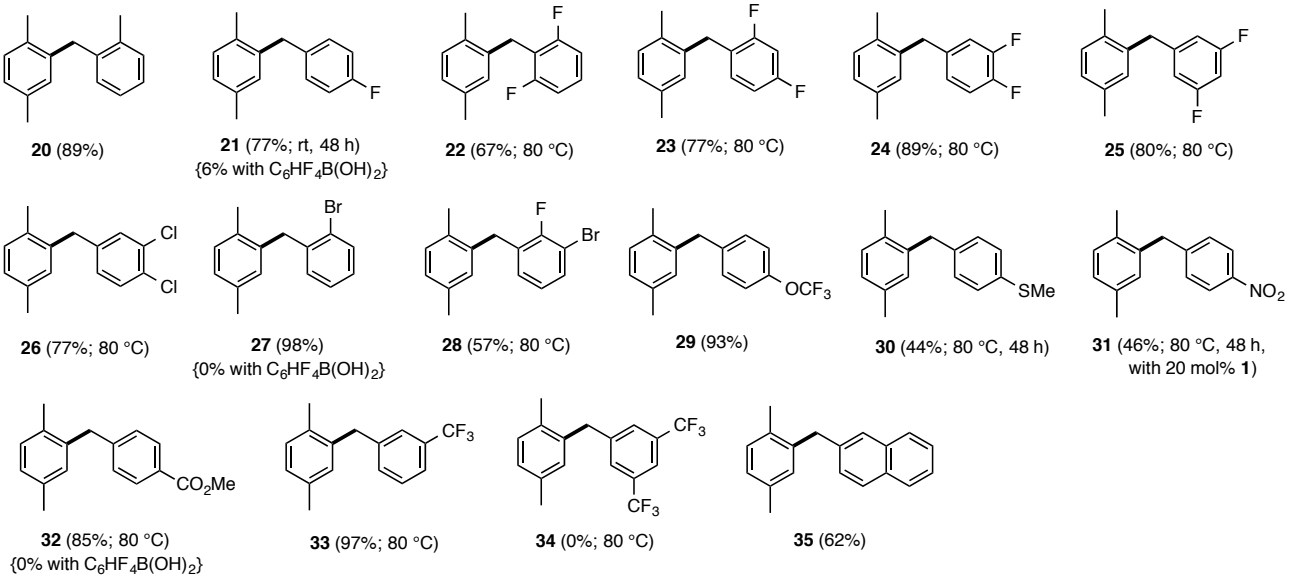




[a] Reaction scale: 0.5 mmol of alcohol. Reported yields are isolated yields of combined regioisomers. Isomer ratios were measured by ^{1}H NMR. For products 7, 9, 10, 13-17, 19, less than 6% of the 5-substituted isomer **c** was obtained. Some regioisomers are not separable (see Supporting Information).

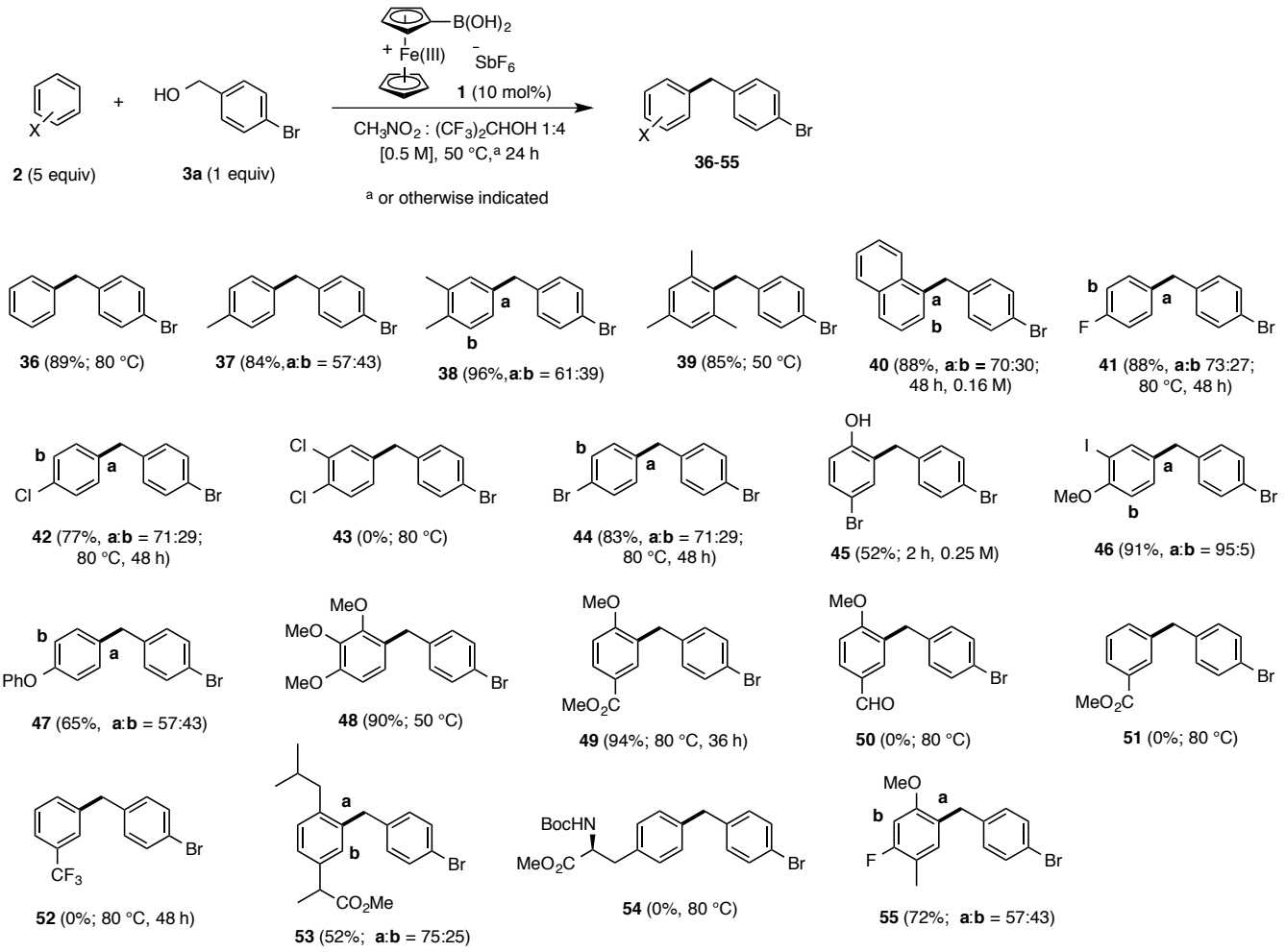
Figure 6. Scope of primary benzylic alcohols with p-xylene as the arene nucleophile.[a]





[a] Reaction scale: 0.5 mmol of alcohol (1.0 mmol for 21 and 32). Reported yields are isolated products as single isomers.

Figure 7. Scope of arenes with 4-bromobenzyl alcohol as the electrophile.[a]

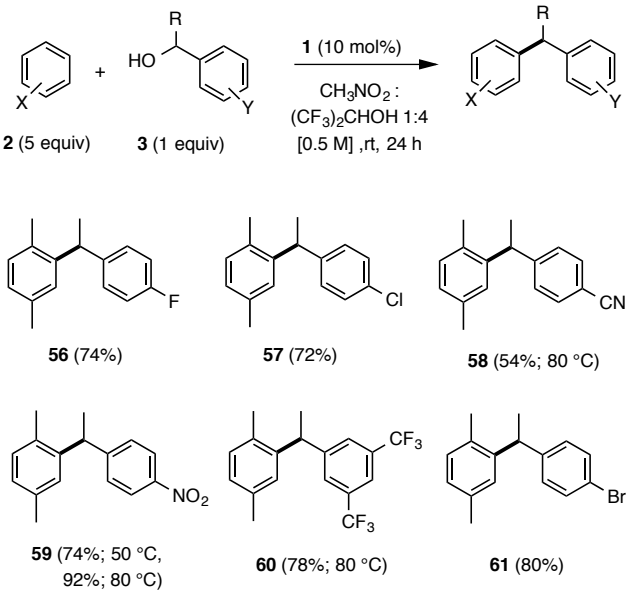


[a] Reaction scale: 0.5 mmol of alcohol (except for preparation of **45**, **46**, **49**, **53**: 0.25 mmol). Reported yields are isolated yields of combined regioisomers. Isomer ratios were measured by ^{1}H NMR. Some regioisomers are not separable (see Supporting Information)

The scope of possible arene nucleophiles was examined by using 4-bromobenzyl alcohol as a prototypical benzylating agent (Figure 7). Thus, relatively poor nucleophiles like benzene, toluene, o-xylene, trimethylbenzene, and naphthalene as well as halide-substituted arenes reacted efficiently at 80 °C to afford the respective products **36**-**42, 44**. These *o*/*p*-directing deactivating substituents led to the expected mixture of regiosomeric products **a**/**b**. The reaction conditions tolerate a free phenol (product **45**). Although fluorobenzene was successful in affording product **41**, strongly deactivated arenes such as dichlorobenzene, methyl benzoate, and trifluoromethylbenzene failed to afford the respective products **43, 51, 52**. The catalyst's efficiency is probably not at fault in these difficult examples resulting in complicated mixtures where the alcohol was consumed. It is more likely that the nucleophilicity of the arene has reached a threshold where the benzylic alcohol reacts as a nucleophile with its own carbocation intermediate to form undesired oligomeric products. Although 4-methoxybenzaldehyde was too unreactive to give the desired product **50**, the corresponding carboxyester afforded product **49** in high yield at 80 °C. Other multiply substituted arenes were tested. Ibuprofen methyl ester was successfully reacted to afford product **53** in moderate yield. In contrast, the expected product **54** was not observed from an attempted benzylation of Boc-Phenylalanine methyl ester, which was recovered unreacted probably due to inhibition of the catalyst by the aminoester unit.[32] A trisubstituted polyfunctionalized arene was successfully reacted to give product **55**.

As exemplified by the formation of products **56**-**61**, it is not surprising that secondary alcohols are suitable benzylating reagents (Figure 8). The additional stabilization provided by a secondary carbocation permits the use of strongly deactivated arene units such as 3,5-bis(trifluoromethyl)phenyl units that failed when employed as part of a primary benzylic alcohol (cf. **34**, Figure 6).

Figure 8. Scope of secondary benzylic alcohols with p-xylene as the arene nucleophile.[a]



[a] Reaction scale: 0.5 mmol of alcohol. Reported yields are isolated yields of single isomers.

There are two possible disconnections that can be devised towards planning the synthesis of an unsymmetrical 1,1-diarylmethane product using a Friedel-Crafts benzylation. If one approach fails as a result of challenging electronic considerations, such as the need to use a poorly nucleophilic arene, there is a possibility that the alternate disconnection is more favorable. This complementarity can help to increase the scope of potentially accessible products. For example, whereas product **43** could not be made by combining 1,2-dichlorobenzene with 4-bromobenzyl alcohol (cf. Figure 7), the alternate disconnection using bromobenzene and 3,4-dichlorobenzyl alcohol does produce **43** in good yield, albeit with moderate regioselectivity (Eqs. 1-2, Figure 9). Likewise, trifluoromethylbenzene is too poorly nucleophilic to react with the carbocation of 2,5-dimethylbenzyl alcohol but the alternate combination smoothly afforded the desired product **33** in 97% yield (Eqs. 3-4, Figure 9).

Additional experiments were designed to address the practicality of this method and the robustness of catalyst **1**. Satisfactorily, a gram-scale reaction with a 3-month old batch of catalyst **1** provided a near-quantitative yield of product **62** with 60% recovery of the catalyst (Eq. 1, Fig. 10). Cognizant of the relatively high cost of HFIP as a co-solvent, we were glad to find that the same reaction can be achieved in high yield under conditions that favor solvent savings at a high concentration of 1.0 M (Eq. 1, Fig. 10). This new method was applied to the preparation of a pharmaceutical agent, beclobrate, which was obtained in high yield from the direct alkylation of an alkoxybenzene derivative with 4-chlorobenzyl alcohol (Eq. 2, Figure 10).

Figure 9. Preparation of unsymmetrical 1,1-diarylmethanes using alternate disconnections.

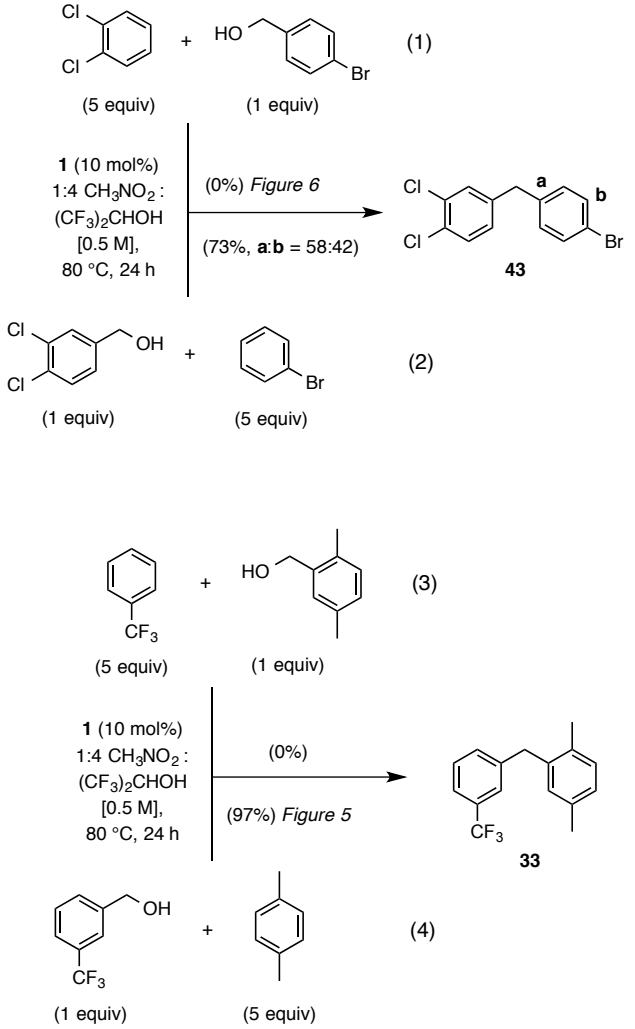
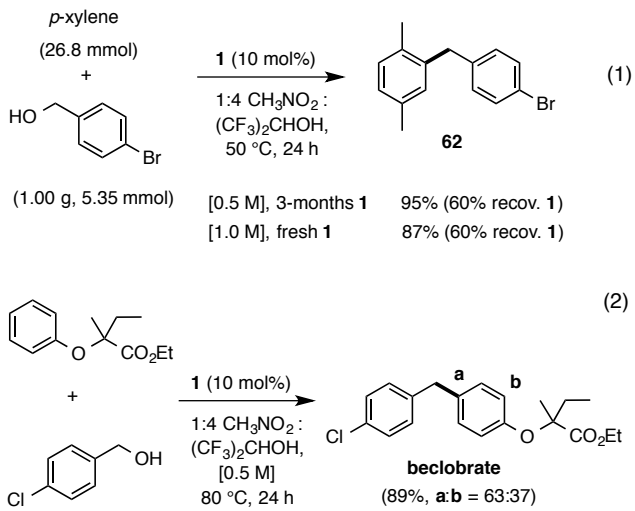


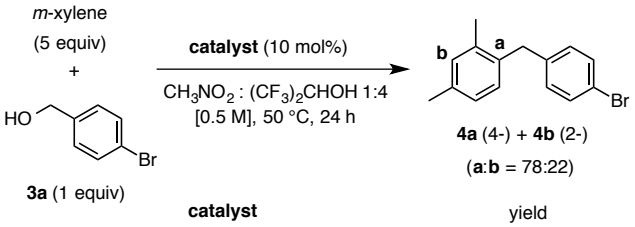
Figure 10. Gram-scale reaction (eq. 1) and beclobrate preparation (eq. 2).



Study of the nature and reactivity of catalyst 1

The special structure and ionic nature of ferroceniumboronic acid catalyst **1** along with its surprising efficiency raise many questions. Although it is characterized by a pKa of 5.8 that is similar to that of 2,3,4,5-tetrafluorophenylboronic acid, catalyst **1** is clearly much more reactive and it sustains a broader scope of arenes and benzylic alcohols compared to 2,3,4,5-tetrafluorophenylboronic acid and other methods using catalysts such as $FeCl_3$ and $Bi(OTf)_3$.[19,21] For example, not only is 2,3,4,5-tetrafluorophenylboronic acid impotent in promoting the formation of product **4** (Table 1, entry 1), it also fails to yield **27** and **32** (Figure 6) under the same conditions that led ferroceniumboronic acid hexafluoroantimonate (**1**) to afford these products in high yields.

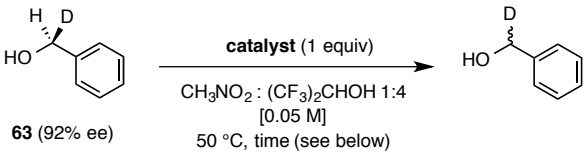
Our first line of investigation was directed at identifying which features of catalyst **1** that are responsible for its exceptional reactivity. In light of the known ability of Fe(III) salts such as $FeCl_3$ to catalyze Friedel-Crafts reactions of benzylic alcohols, we designed a number of control experiments to assess the relative roles of the Fe(III) metal and the free boronic acid in the catalytic reactivity of catalyst **1** (Scheme 1). Thus, compared to the reference yield of 87% obtained with **1**, the ferrocenium salt devoid of a boronic acid group provided a low yield of 15%. The pinacolate derivative of catalyst **1** also led to a lower yield. As shown with a control run using molecular sieves, it is likely that adventitious partial hydrolysis to the boronic acid is responsible for this low activity. Catalyst **1** is inactive in the presence of molecular sieves that would promote the formation of boronic anhydrides. Clearly, a free boronic acid is much preferred for promoting the exchange with alcohol substrates and form a transient hemiboronate. On the other hand, as shown in Table 1, the corresponding ferrocene precursor of **1**, $CpFe(II)CpB(OH)_2$, is not an active catalyst. Thus, from all these results it is apparent that both the Fe(III) ion and a free boronic acid are critical components of catalyst **1**. Because $AgSbF_6$ is inactive (Scheme 1), a solitary role for the antimonate anion as well as the adventitious formation of HF can both be ruled out. As mentioned above, the cationic Fe(III) ion with its considerable electron-withdrawing effect lowers the pKa of boronic acid **1** by five units compared to the neutral ferroceneboronic acid. The possibility that catalyst **1** acts merely as a Brønsted acid can be ruled out by the lack of activity of boronic acids of similar pKa (c.f., 2,3,4,5-$F_4HC_6B(OH)_2$, Table 1) and also by the absence of reaction with strong protic acids such as trifluoroacetic acid (pKa –0.3), with or without water (Scheme 1).

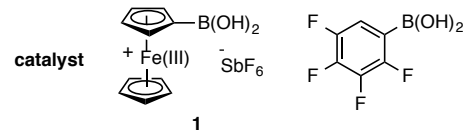


catalyst	yield
$[CpFe(III)CpB(OH)_2]^+ SbF_6^-$ (**1**)	87
$[CpFe(III)Cp]^+ SbF_6^-$	15
$[CpFe(III)CpBpin]^+ SbF_6^-$	45
$[CpFe(III)CpBpin]^+ SbF_6^-$ + 4A m.s.	27
1 + 4A m.s.	0
$Ag^+ SbF_6^-$	0
CF_3CO_2H	trace
CF_3CO_2H + H_2O (20 mol%)	trace

Scheme 1. Control experiments examining the importance and the role of the boronyl unit of catalyst **1**.

The substrate scope of the reaction provides strong support for an S_N1 reaction mechanism over an S_N2 substitution mechanism. For example, whereas the primary alcohol bis-3,5-bis(trifluomethyl)benzyl alcohol cannot form product **34** (cf. Figure 6), a secondary benzylic analogue that provides better stabilization of a carbocation intermediate successfully led to product **59** (cf. Figure 8). This hypothesis is further supported by a study on the stereochemical fate of optically enriched deuterated primary benzylic alcohol **63** (Scheme 2). When activated with a stoichiometric amount of catalyst **1** in the absence of an arene nucleophile, the optical activity of **63** was found to fade with time (according to ^1H NMR analysis of the resulting Mosher ester, see Supporting Information). This result indicates that a primary carbocation is formed, and that it is formed reversibly. Not surprisingly, 2,3,4,5-tetrafluorophenylboronic acid, which is not a very effective activator for the arylation of primary benzylic alcohols (cf. Table 1), was unable to epimerize alcohol **63** under the same reaction conditions at 50 °C.

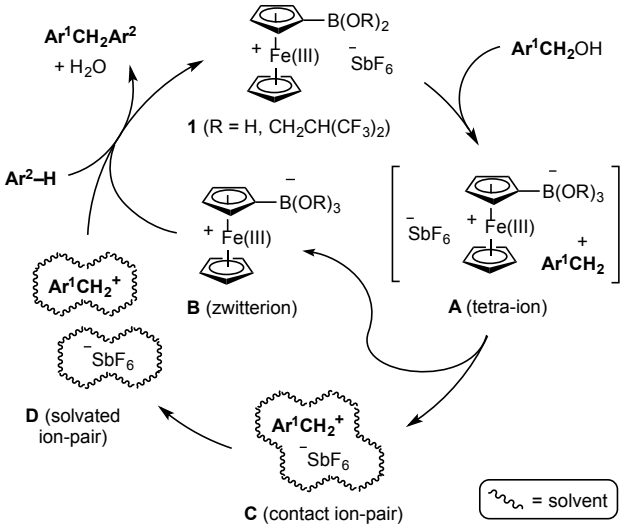




time: 15 min	75% ee	92% ee
30 min	63% ee	92% ee

Scheme 2. Ionization of optically enriched, deuterated alcohol **63**.

Altogether, these results indicate that catalyst **1** is a powerful activator of primary benzylic alcohols and does so by full ionization to provide a solvated primary carbocation. Although the role of HFIP is likely that of a highly polar co-solvent that facilitates the formation and solvation of carbocations,[33] the possibility of generating a highly acidic hexafluoroisopropoxyboronic ester cannot be excluded (R = $CH_2CH(CF_3)_2$) in Scheme 3). Because the pKa of **1** is similar to that of 2,3,4,5-tetrafluorophenylboronic acid, its structure surely provides additional benefits. We suggest that the ionic nature of catalyst **1** and the non-coordinating hexafluoroantimonate counteranion lead to a ion-exchange process where the expected tetra-ionic species **A** breaks down to form two intimate ion pairs, **B** and **C** (Scheme 3). The non-nucleophilic antimonate anion is conducive to favor a solvent separated ion pair (**D**) that leaves a more reactive carbocation intermediate. The obvious influence of the arene nucleophile, as seen from the substrate scope of Figure 7, is consistent with electrophilic substitution as being the rate-determining step (i.e., formation of the π or σ complex)[34] requiring the appropriate reactivity matching of the carbocation's electrophilicity with an arene of sufficient nucleophilicity.[35] In this scenario, the hexafluoroantimonate counteranion facilitates the reaction by raising the energy of the carbocation compared to a boronate counteranion (i.e., **A** in Scheme 3).



Scheme 3. Proposed catalytic cycle and mode of activation for catalyst **1**.

Conclusion

We have disclosed a new boronic acid catalyst, ferroceniumboronic acid hexafluoroantimonate salt (**1**), as a superior air- and moisture-tolerant catalyst for direct Friedel-Crafts alkylations of a diverse selection of slightly activated and neutral arenes with readily available primary and secondary benzylic alcohols. Compared to the use of classical metal-catalyzed alkylations with toxic benzylic halides, this method employs exceptionally mild conditions to provide a wide variety of unsymmetrical diarylmethanes and other 1,1-diarylalkane products in high yield with good to high regioselectivity. The optimal reaction conditions, using the bench-stable ferroceniumboronic acid salt **1** in hexafluoropropanol as co-solvent, provide a broader scope of substrates compared to previously reported catalysts for similar Friedel-Crafts procedures with benzylic alcohols, including $FeCl_3$, $Bi(OTf)_3$, and other boronic acids such as 2,3,4,5-tetrafluorophenylboronic acid. The efficacy of the new boronic acid catalyst was confirmed by its ability to activate primary benzylic alcohols substituted with destabilizing electron-withdrawing groups like halides, carboxyesters, and nitro substituents. Arene benzylations were demonstrated on a gram-scale at up to 1 M concentration with recovery of the catalyst. Mechanistic studies point toward the importance of the oxidized cationic nature of catalyst **1** and suggest that factors other than the Lewis acidity (pKa) of the boronic acid are at play. A S_N1 mechanism is proposed where ion-exchange takes place with the boronate anion to afford a more reactive carbocation paired with the non-coordinating hexafluoroantimonate counteranion.

Boronic acid catalysis is emerging as a new strategy to effect direct catalytic transformations of functional groups that are otherwise difficult to achieve with current approaches. This work on a novel class of metalocene boronic acid catalysts, with a new mode of activation taking avantage of ion-pairing, opens up new possibilities for achieving direct transformations of alcohols.

ASSOCIATED CONTENT

SUPPORTING INFORMATION.

Experimental details, analytical and spectral reproductions for the prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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ABBREVIATIONS

Cp, cyclopentadienyl; NMR, nuclear magnetic resonance; THF, tetrahydrofuran.

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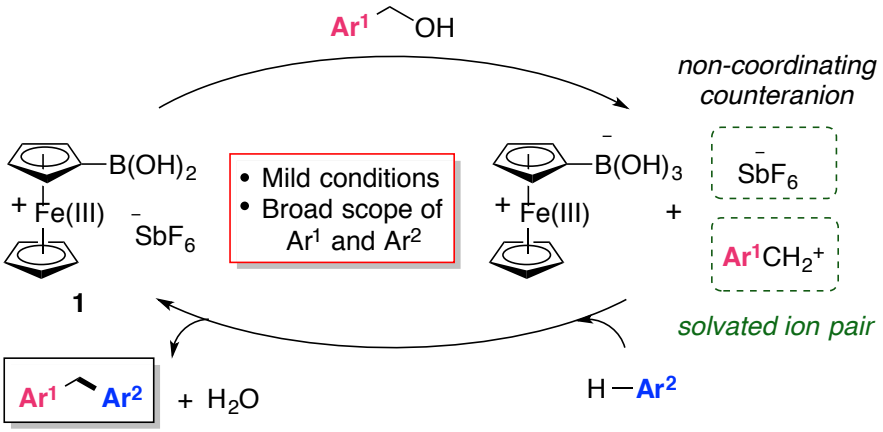
Ar1 OH
non-coordinating counteranion
B(OH)2
+ Fe(III)
SbF6
1
• Mild conditions
• Broad scope of Ar1 and Ar2
B(OH)3
+ Fe(III)
+
SbF6
Ar1CH2+
solvated ion pair
Ar1 Ar2
+ H2O
H—Ar2