



Organocatalyzed Friedel–Crafts arylation of benzylic alcohols

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ABSTRACT

Electron-rich aromatic and heteroaromatic rings are functionalized directly with a variety of benzylic alcohols under mild conditions. The reaction is catalyzed by commercially available pentafluorophenylboronic acid, which is stable under ambient conditions and recoverable. The reaction itself is highly atom economical and produces water as the only byproduct. A Friedel–Crafts mechanism is proposed.

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Di-, tri-, and tetraarylmethanes are important substructures in a variety of substances with biological relevance¹ as well as diverse classes of functional materials.² They are generally prepared via reaction of a nucleophilic aryl species (**1**), with an electrophilic benzyl derivative (**2**, Scheme 1). Classical methods typically rely on either the use of harshly acidic reagents, often in stoichiometric quantities,³ or pre-activation of the nucleophile and/or electrophile.^{4,5} Both of these general approaches produce significant amounts of waste in the form of salt byproducts, and the latter often requires non-trivial preparation of starting materials.

Direct catalytic substitution of aromatic C–H bonds via Friedel–Crafts (FC)-type reactions is an attractive alternative, since it eliminates the need for pre-activation of the aromatic species and significantly reduces the waste generated in the coupling process.

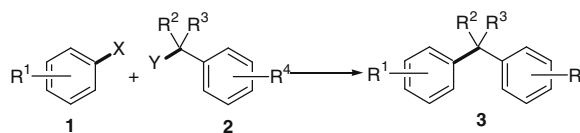
The ideal FC reaction would employ a benzylic alcohol as the electrophile, and therefore generate water as the only byproduct. This has recently been achieved with a variety of conventional Lewis acids,⁶ Bronsted acids,⁷ and transition-metal complexes.⁸ Although these methods have significant advantages over traditional FC reactions (i.e., the nature of the leaving group), there are several areas in need of improvement, including a somewhat limited substrate scope, the harsh acidity of many Bronsted and Lewis acid catalysts, and the often high cost and toxicity of transition-metal-based catalysts.

Diversely substituted aryl boronic acids are inexpensive and widely available, primarily due to their use as coupling partners in the Suzuki–Miyaura reaction.⁹ They possess several useful properties, including air and moisture stability, high solubility in organic solvents, and a Lewis acidic boron atom, which can be modulated by ring substituents.¹⁰ Despite this, there are only sporadic reports of their use as catalysts.¹¹

We have recently described the arylboronic acid-catalyzed FC reactions of allylic alcohols with a variety of electron-rich aromatics and heterocycles.¹² Herein we wish to report on an extension of this reaction to include a second class of π -activated substrates, benzylic alcohols.

We began by screening a variety of electron-rich aromatic heterocycles and carbocycles (**4–10**) in reactions with di- and triphenyl methanol (**2a** and **b**) under conditions established previously for related substrates (Table 1).¹² We were pleased to observe that in all cases, Diphenyl methanol underwent clean reaction with aromatic substrates **4–9** in excellent to quantitative yields to afford triaryl substitution products **4a–9a**. In the case of **10**, the reaction did not reach completion (starting materials recovered, entry 13). However, by changing the solvent to toluene, high conversion and yield of **10a** were achieved (entry 14). We attribute the difference in yields to the higher temperature achieved in refluxing toluene.¹³ In all cases, a single isomer of the desired product was recovered, with no evidence of the formation of other possible regioisomers.

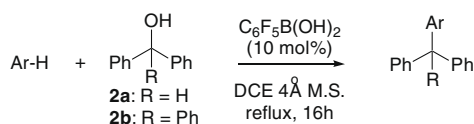
Disappointingly, reactions of our aromatic substrates with triphenyl methanol (**2b**) were less successful. Those that involved five-membered heterocycles (**4**, **5**, and **8**) performed well, affording the corresponding tetraaryl methanes (**4b**, **5b**, and **8b**) in near-quantitative yields (entries 2, 4, and 10). However, all the six-membered carbocyclic derivatives (**6**, **7**, **9**, and **10**) failed to react (entries 6, 8, 12, and 15) under the specified conditions, with quantitative recovery of the starting materials. We attribute the marked



Scheme 1. Benzylic coupling for the formation of diarylmethanes.

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Table 1
Synthesis of aryl diphenyl- and aryl triphenylmethanes



Run	Ar-H	2	Product	Yield (%) ^a
1		2a	4a: R = H	93
2	4	2b	4b: R = Ph	99
3		2a	5a: R = H	85
4	5	2b	5b: R = Ph	90
5		2a	6a: R = H	99
6	6	2b	6b: R = Ph	0
7		2a	7a: R = H	76 ^b
8	7	2b	7b: R = Ph	0
9		2a	8a: R = H	94
10	8	2b	8b: R = Ph	98
11		2a	9a: R = H	87
12	9	2b	9b: R = Ph	0
13		2a	10a: R = H	60
14 ^c	10	2a	10a: R = H	82
15	10	2b	10b: R = Ph	0

^a Isolated yield.

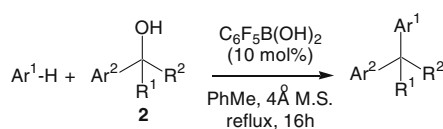
^b 12% of disubstituted product was isolated in addition.

^c Reaction run in refluxing PhMe.

difference in reactivity between the 5- and 6-membered nucleophiles to differences in steric bulk. The presumed carbocation (vide infra) formed from the departure of the hydroxide-leaving group in **2b** is crowded significantly by the three phenyl groups, which may be difficult for the bulkier substituted six-membered ring nucleophiles to access. Electronic factors may be a contributing factor in some cases: The triphenyl methane carbocation is also significantly more stable than the corresponding diphenyl methane carbocation, which may render it unreactive to poorer nucleophiles.

Having established the scope of the reaction of various aromatic nucleophiles with simple di- and tri-arylmethanes, we turned our attention to the reaction of these nucleophiles with a selection of functionalized mono- and diaryl-methanols (Table 2). Reaction of pyrrole **5** with electron-rich methoxy diaryl methane **2c** afforded

Table 2
Scope of reaction with benzylic alcohols



Run	ArH	X	Product (X): yield (%) ^a
1	5	2c	5c: 74
2	5	2d	0
3	6	2e (X = H)	0
4	4	2f (X = OH)	4f: 76
5	6	2g	6g: 95
6	8	2h (X ¹ = OMe, X ² = OH)	8h: 94
7	8	2i (X ¹ = H, X ² = OH)	8i: 67
8	8	2j (X ¹ = H, X ² = OMe)	8j: 81
9	10	2k	10k: 89
10	8	2l	8l: 54
11	8	2m	8m: 48
12	8	2n (R ¹ = R ² = Me)	8n: 72 ^b
13	8	2o (R ¹ -R ² = (CH ₂) ₅)	8o: 55 ^c

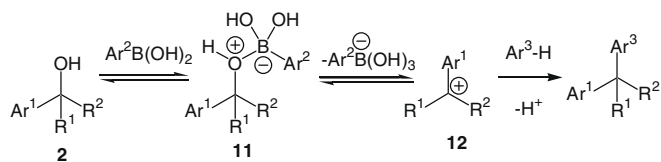
^a Isolated yields.

^b 23% of 1-methylstyrene was isolated in addition.

^c 36% of 1-phenylcyclohexene was isolated in addition.

triarylmethane **5c** in good yield (entry 1). In contrast, electron-poor diarylmethanol **2d** failed to react with furan **8** under the same conditions. This suggests that the stability of the diarylcarbocation is critical to the success of this reaction and the presence of even moderately electron-withdrawing groups is sufficiently destabilizing to prevent the reaction from occurring.

Similarly, 1-phenylethanol **2e** failed to react under the specified conditions (entry 3), which suggests that a single unsubstituted



Scheme 2. Proposed mechanism.

phenyl ring affords insufficient stabilization of the carbocation intermediate. However, increasing the electron density by incorporation of a free phenol in **2f** allows the reaction with indole **4** to proceed smoothly to completion to afford **4f** in good yield (entry 4). Naphthyl derivative **2g** was also an effective electrophile, and afforded **6g** in high yield upon reaction with **6** (entry 5). We attribute the success of this substrate (cf. **2e**, entry 3) to the increased electron density of naphthalene relative to benzene. Electron-rich benzylic alcohols, including methoxy phenol **2h**, phenol **2i**, and methoxy benzene **2j** all performed well in the reaction with **8** (entries 6–8). They afforded furan derivatives **8h**, **8i**, and **8j**, respectively, in good yields. The success of the reaction in the presence of free phenols (entries 4, 6, and 7) demonstrates the further advantage that protecting groups are not required.

We next tested brominated derivatives **2k** and **2l** in combination with **10** and **8**, respectively, with some success (entries 9 and 10). High yield of the coupled product **10k** and moderate yield of **8l** were obtained. We attribute the somewhat reduced yields in these cases (cf. entries 6 and 7) to a decrease in electron density due to the electronegative bromine atoms. These products have the advantage of allowing for further derivatization of the aryl bromides. Similarly to phenols, free amines are well tolerated under these conditions (entry 11).

Finally, we tested the coupling of tertiary alcohols **2n** and **2o** with **8**, to afford **8n** and **8o**, respectively, in modest yields, with some formation of the elimination products observed (entries 12 and 13).

Our results for this reaction are consistent with the mechanistic proposals reported previously for a similar process.¹² The decreased reactivity (or lack thereof) of alcohol substrates leading to relatively unstabilized carbocations suggests that the formation of such intermediates is integral to the reaction. We therefore propose a Friedel–Crafts mechanism, involving S_N1 substitution (Scheme 2). Complexation of the arylboronic acid to benzylic alcohol **2** results in the formation of ate species **11**. This enhances the leaving group ability of the hydroxide, resulting in a heterolytic cleavage to form resonance-stabilized carbocation **12**. This undergoes nucleophilic attack by the aromatic nucleophile, followed by a conventional Friedel–Crafts mechanism to afford the product. The resulting arylborate is in equilibrium with the arylboronic acid and water, which is removed in situ by the molecular sieves, regenerating the active catalytic species.

In summary, we have developed a mild, organocatalyzed method for the synthesis of a variety of tetra- and tri-aryl methanes. The reaction is also amenable to the preparation of electron-rich diaryl-methanes with potential medicinal applications. The process is highly atom economical, employing a recoverable catalyst and producing water as the only byproduct. Preliminary results are consistent with those of an S_N1/Friedel–Crafts mechanism. Extension of the scope of this reaction, as well as detailed mechanistic studies is ongoing in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.151.

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- In the related reaction of electron-rich aromatics with allylic alcohols, toluene and dichloroethane were found to be equally suitable at room temperature. See Ref. 12.