Arene Functionalization

DOI: 10.1002/ange.201105380

# Friedel–Crafts Benzylation of Activated and Deactivated Arenes**

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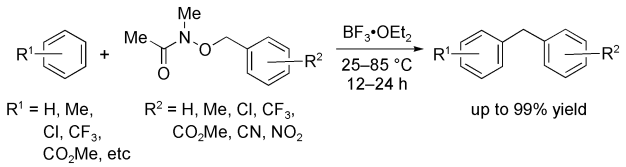
The Friedel–Crafts alkylation of aromatic compounds is a versatile method for C–C bond formation from unactivated C–H bonds.[1] Despite the power and historical importance of Friedel–Crafts reactions, the poor reactivity of deactivated aromatic compounds, the difficultly of employing even modestly deactivated alkyl halides, and complications from the aluminum by-products have encouraged the development of new aromatic transformations. In the current era, new reactions for regio- and chemoselective direct functionalization of arenes through C–H bond activation, largely based on transition metal catalysis, have revolutionized the preparation of aromatic derivatives.[2,3] Despite these advances, there remains an unmet synthetic need for refinements to the more economical Friedel–Crafts reaction to improve its substrate scope, operational simplicity, and sustainability, particularly for substitutions of electron-deficient substrates.[4] Herein we document a new approach to Friedel–Crafts benzylations that operates with both electron-deficient electrophiles and nucleophiles, proceeds under mild, simple conditions, and does not require the use of aluminum or other metal reagents or catalysts (Scheme 1). Importantly, this method allows for the selective mono-*meta*-functionalization of electron-deficient nucleophiles with electron-poor electrophiles.[5]




***Scheme 1.*** $BF_3{\cdot}OEt_2$-promoted Friedel–Crafts benzylation.

A recent advance in Friedel–Crafts alkylations[6] of aromatic substrates is the discovery that metal salts including $TeCl_4$,[7] $Sc(OTf)_3$,[8] $FeCl_3$,[9] $Bi(OTf)_3$,[10] and $HAuCl_4$[11] promote the coupling of activated benzyl alcohols and halides with arenes. Other researchers have employed heterogeneous catalysts, such as zeolites, to Friedel–Crafts reactions.[12] These improvements both reduce the reliance on toxic organohalides and decrease the environmental impact of Friedel–Crafts reactions. In most cases, however, these advances are limited to highly activated primary or secondary benzylic substrates, the use of electron-rich nucleophiles, such as anisoles, or intramolecular reactions. The textbook Friedel–Crafts benzylation of even simple arenes, such as chlorobenzene or benzoic esters, has seen little improvement in its 135 year history.

The key to our improvement of the Friedel–Crafts alkylation is the selective activation of a *N*-methyl hydroxamic acid[13] leaving group with $BF_3{\cdot}OEt_2$, an inexpensive and easily handled Lewis acid. Friedel–Crafts reactions using this approach are cleaner, more selective, and more easily executed than traditional methods. This research stemmed from our recent finding that mixed hydroxamate acetals are superior substrates for $BF_3{\cdot}OEt_2$-promoted cross-coupling reactions with organotrifluoroborates to give dialkyl ethers with outstanding regioselectivity.[14] Our mechanistic studies suggested that the improved reactivity and conditions were achieved by the ability of the boron-chelated hydroxamate to serve as a reversible leaving group—a process that allows controlled generation of the reactive oxonium cation. We anticipated that this strategy would be applicable to other reactions proceeding via carbocation intermediates and selected the Friedel–Crafts alkylation for initial investigations.

Our studies began with a survey of reactions and conditions for the alkylation of toluene with *para*-chlorobenzyl hydroxamate **1**.[15] As desired, the use of $BF_3{\cdot}OEt_2$ (4 equiv) at room temperature gave the benzylation product **3** as a mixture of regioisomers in excellent yield (Table 1, entry 1). Similar results were obtained using only 2 equivalents of $BF_3{\cdot}OEt_2$ (Table 1, entry 2). The reaction workup was operational friendly; aqueous extraction removed the $BF_3{\cdot}OEt_2$ and hydroxamic acid without difficulty to obtain the pure product after evaporation of the organic solvent. As expected, catalytic reactions were not effective, likely due to chelation of the $BF_3{\cdot}OEt_2$ by released hydroxamate, an effect that sequesters the $BF_3{\cdot}OEt_2$ after the reaction. This is beneficial under non-catalytic conditions, as it prevents the formation of side products. In contrast, a number of other Lewis or protic acids including $HBF_4$ (Table 1, entry 5), $B(OH)_3$ (Table 1, entry 6), $ZnCl_2$ (Table 1, entry 7), $Mg(acac)_2$ (Table 1, entry 8), and $Cu(OAc)_2$ (Table 1, entry 10) proved ineffective. $FeCl_3$ and $AlCl_3$ were viable reagents but led to more complicated workup and the formation of side products (Table 1, entries 11 and 12).[16] Experiments in the absence of additive (Table 1, entry 14) and with 0.1 equivalents of $FeCl_3$ (Table 1, entry 13) did not afford product and confirmed that the reactions were not promoted by trace metal impurities. The reactions could also be performed with

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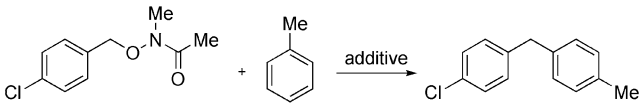
[**] This work was supported by ETH Research Grant ETH-12 11-1. We thank the ETH Zürich Mass Spectrometry Service for spectroscopic data, Aaron Dumas for helpful discussions, and Cam-Van Thi Vo for a preliminary study.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201105380.

***Table 1:*** Additive screening of Friedel–Crafts benzylation.[a]




1 2 3

| Entry | Additive | Equiv | *T* [°C] (*t* [h]) | Yield [%][b] (ratio)[c] |
|---|---|---|---|---|
| 1 | $BF_3{\cdot}OEt_2$ | 4 | 25 (13) | 99 (55:43:2) |
| 2 | $BF_3{\cdot}OEt_2$ | 2 | 25 (22) | 99 (55:43:2) |
| 3 | $BF_3{\cdot}OEt_2$ | 0.1 | 25 (24) | n.r. |
| 4[d] | $BF_3{\cdot}OEt_2$ | 4 | 40 (18) | 80 (54:43:3) |
| 5 | $HBF_4{\cdot}OEt_2$ | 4 | 25 (24) | traces (n.d.) |
| 6 | $B(OH)_3$ | 4 | 50 (24) | n.r. |
| 7 | $ZnCl_2$ | 4 | 50 (24) | n.r. |
| 8 | $Mg(acac)_2$ | 4 | 50 (24) | n.r. |
| 9 | TMSCl | 4 | 25 (24) | n.r. |
| 10 | $Cu(OAc)_2$ | 4 | 50 (24) | n.r. |
| 11 | $AlCl_3$ | 1 | 25 (5) | 83 (48:45:7) |
| 12 | $FeCl_3$ | 4 | 25 (12) | 75 (50:45:5) |
| 13 | $FeCl_3$ | 0.1 | 80 (24) | n.r. |
| 14 | no additive | – | 50 (24) | n.r. |

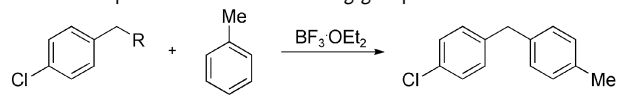
[a] Conditions: *para*-chlorobenzyl hydroxamate **1** (0.4 mmol), toluene (**2**; 4 mL) and additive. [b] Yields of isolated products. [c] Ratio of regioisomers determined by GC/MS. [d] Toluene (**2**; 1.6 mmol), $CH_2Cl_2$ (4 mL).

only 4 equivalents of toluene in $CH_2Cl_2$ by raising the temperature to 40 °C (Table 1, entry 4).

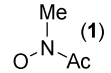
We confirmed the unique ability of the hydroxamate leaving group to be activated by $BF_3{\cdot}OEt_2$ and give clean Friedel–Craft reactions by examining the other benzylating agents (Table 2). Only trace amounts of product could be observed with benzyl alcohol (Table 2, entry 2) or acetate (Table 2, entry 3), and no reaction occurred with benzyl methyl ether or *para*-chlorobenzyl chloride at room temperature (Table 2, entries 4 and 5). It should be noted that most other recent reports on improved Friedel–Crafts reactions require the more activated secondary benzylic chlorides.[6]

The optimized conditions were applied to three classes of aromatic nucleophiles: Arenes bearing an activating *ortho*/*para* directing group (Tables 3 and 4), arenes bearing a deactivating *ortho*/*para* directing group (Table 5), and arenes bearing a deactivating *meta* directing group (Table 6).[17] Two conditions were screened for each substrate combination: The use of a) the nucleophile as the solvent and b) 4 equivalents of nucleophile relative to the benzylic hydroxamate in dichloromethane or 1,2-dichloroethane. As expected, benzylations with electron-rich arenes all proceeded smoothly to give the monobenzylated products in excellent yield and with regioselectivities typical for a Friedel–Crafts process (Table 3, entries 1–5). Remarkably, *para*-anisaldehyde, containing an unprotected aldehyde, gave the desired product as a single regioisomer in acceptable yield (Table 3, entry 6), despite the use of excess $BF_3{\cdot}OEt_2$. Trifluoromethoxybenzene and an activated pyridine derivative were also compatible as reagents (Table 3, entries 7 and 8). We also studied the scope and limitation of the benzylating agent. Electron-rich and halogenated electrophiles reacted at room temperature with toluene to provide the corresponding products in quantitative yields (Table 4, entries 1–4). These electrophiles were also compatible with the reaction using 4 equivalents of arene. Of note, even highly deactivated benzyl hydroxamates containing $CF_3$, CN, $CO_2Me$, and $NO_2$ groups were viable

***Table 2:*** Comparison of different leaving groups.[a]

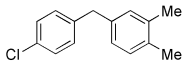
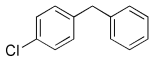
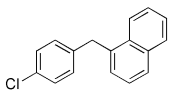
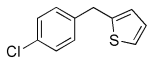
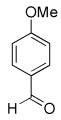
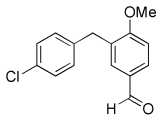
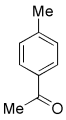
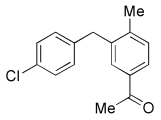
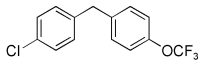
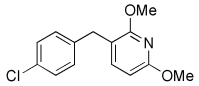
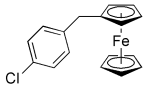



1, 4–7 2 3

| Entry | R | *T* [°C] | Conversion [%] (ratio)[b] |
|---|---|---|---|
| 1 |  (**1**) | 25 | 100 (55:43:2) |
| 2 | OH (**4**) | 25 | 5% (n.d.) |
| 3 | OAc (**5**) | 25 | <5% (n.d.) |
| 4 | $OCH_3$ (**6**) | 25 | n.r. (–) |
| 5 | Cl (**7**) | 25 | n.r. (–) |

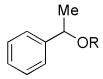
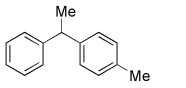
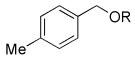
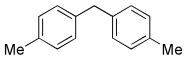
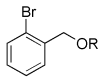
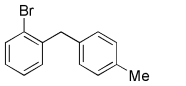
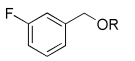
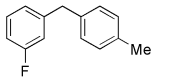
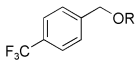
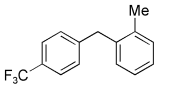
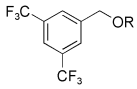
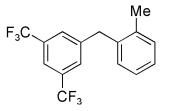
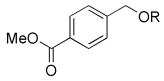
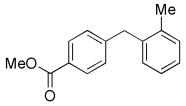
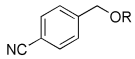
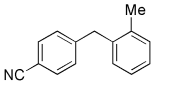
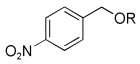
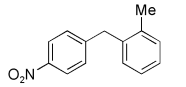
[a] Conditions: benzylic substrate (0.4 mmol), $BF_3{\cdot}OEt_2$ (1.6 mmol), toluene (**2**; 4 mL), RT, 24 h. [b] Conversion and ratio of regioisomers determined by GC/MS with *n*-dodecane as internal standard.

***Table 3:*** Benzylation of activated, *ortho*/*para*-directing nucleophiles with *para*-chlorobenzyl hydroxamate **1**.[a]

| Entry | Arene | Major product | *T* [°C] | Yield [%][b] (ratio)[c] |
|---|---|---|---|---|
| 1a[d] |  |  | 25 | 99 (65:35) |
| 1b | | | 35 | 90 (53:47) |
| 2a[d] |  |  | 25 | 99 (–) |
| 2b | | | 40 | 77 (–) |
| 3 |  |  | 40 | 87 (70:30) |
| 4 |  |  | 40 | 89 (65:35) |
| 5 |  |  | 50 | 52 (99:1) |
| 6 |  |  | 45 | 50 (99:1) |
| 7 |  |  | 40 | 63 (93:7) |
| 8 |  |  | 45 | 83 (97:3) |
| 9 |  |  | 35 | 89 (–) |

[a] Reaction conditions: benzylic hydroxamate (0.4 mmol), $BF_3{\cdot}OEt_2$ (1.6 mmol), arene (1.6 mmol), $CH_2Cl_2$ (4 mL), 24 h. [b] Yields of isolated products. [c] Ratio of regioisomers determined by GC/MS. [d] Arene (4 mL), no solvent. [e] 1,2-Dichloroethane (4 mL) was used as solvent. R = [N(CH$_3$)(Ac)].

***Table 4:*** Benzylation of toluene (**2**) with various benzyl hydroxamates.[a]

| Entry | Benzylating agent | Major product | *T* [°C] | Yield [%][b] (ratio)[c] |
|---|---|---|---|---|
| 1a[d] |  |  | 25 | 99 (93:7) |
| 1b | | | 25 | 90 (93:7) |
| 2a[d] |  |  | 25 | 99 (70:30) |
| 2b | | | 25 | 89 (77:23) |
| 3a[d] |  |  | 25 | 99 (64:32:4) |
| 3b | | | 50 | 75 (64:33:3) |
| 4a[d] |  |  | 25 | 99 (50:43:7) |
| 4b | | | 50 | 74 (50:43:7) |
| 5a[d] |  |  | 70 | 99 (60:35:5) |
| 5b[e] | | | 85 | 70 (60:34:6) |
| 6[d] |  |  | 85 | 90 (50:41:9) |
| 7a[d] |  |  | 45 | 99 (49:38:13) |
| 7b[e] | | | 65 | 73 (50:37:12) |
| 8a[d] |  |  | 65 | 99 (53:37:10) |
| 8b[e] | | | 85 | 65 (53:38:9) |
| 9[d] |  |  | 80 | 93 (55:40:5) |

[a] Reaction conditions: benzylic hydroxamate (0.4 mmol), $BF_3{\cdot}OEt_2$ (1.6 mmol), toluene (**2**; 1.6 mmol), $CH_2Cl_2$ (4 mL), 24 h. [b] Yields of isolated products. [c] Ratio of regioisomers determined by GC/MS. [d] Toluene (**2**; 4 mL), no solvent. [e] 1,2-dichloroethane (4 mL) was used as solvent. R = [N(CH$_3$)(Ac)].

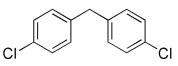
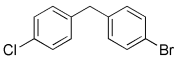
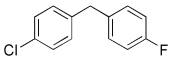
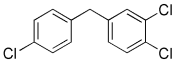
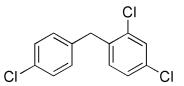
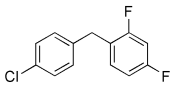
substrates, although higher temperatures were required (Table 4, entries 5–9).

Aryl halides, which are considered as prototypical deactivated arenes in classical Friedel–Crafts reactions,[17,18] are also excellent substrates (Table 5). The use of the arene as solvent is not necessary, and good yields can be obtained with 4 equivalents of arene at 40 °C (Table 5, entries 1–3). The dihalogenated nucleophiles 1,3-dichlorobenzene and 1,3-difluorobenzene (entries 5 and 6) delivered the corresponding products with excellent regioselectivity and yield.

Benzylation of the electron-deficient arenes methyl benzoate and trifluoromethylbenzene can also be achieved with these reagents. With somewhat activated electrophiles, acceptable yields are obtained at 45–50 °C (Table 6, entries 1–4). The coupling of two electron-deficient substrates is also possible at higher temperatures, including the *meta*-selective trifluoromethylarylation of *para*-trifluoromethyl- and *para*-nitro hydroxamates. This is, to the best of our knowledge, one of the few reported examples of the formation of these products by a Friedel–Crafts-type process.[19]

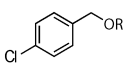
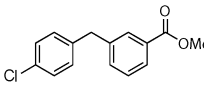
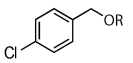
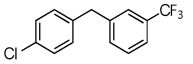
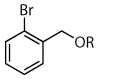
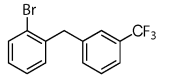
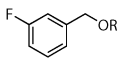
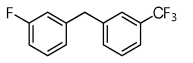
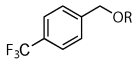
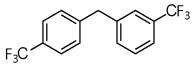
The advantage of the hydroxamate leaving group is that it is chemically stable to a range of reagents and conditions, but can be selectively activated by $BF_3{\cdot}OEt_2$. To demonstrate this,

***Table 5:*** Benzylation of deactivated, *ortho*/*para*-directing nucleophiles with *para*-chlorobenzyl hydroxamate **1**.[a]

| Entry | Arene | Major product | *T* [°C] | Yield [%][b] (ratio)[c] |
|---|---|---|---|---|
| 1a[d] |  |  | 25 | 99 (77:23) |
| 1b | | | 40 | 76 (70:30) |
| 2a[d] |  |  | 25 | 99 (78:22) |
| 2b | | | 40 | 75 (70:30) |
| 3a[d] |  |  | 25 | 99 (88:12) |
| 3b | | | 40 | 77 (87:13) |
| 4 |  |  | 45 | 53 (79:21) |
| 5 |  |  | 45 | 63 (98:2) |
| 6 |  |  | 45 | 62 (99:1) |

[a] Reaction conditions: *para*-chlorobenzyl hydroxamate **1** (0.4 mmol), $BF_3{\cdot}OEt_2$ (1.6 mmol), arene (1.6 mmol), $CH_2Cl_2$ (4 mL), 24 h. [b] Yields of isolated products. [c] Ratio of regioisomers determined by GC/MS. [d] Arene (4 mL), no solvent.

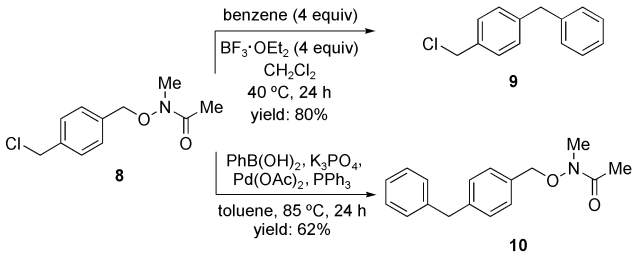
***Table 6:*** Benzylations of deactivated, *meta*-directing methyl benzoate and trifluoromethylbenzene with various benzyl hydroxamates.[a]

| Entry | Benzylating agent | Major product | *T* [°C] | Yield [%][b] (ratio)[c] |
|---|---|---|---|---|
| 1 |  |  | 45 | 53 (91:9) |
| 2[d] |  |  | 45 | 53 (99:1) |
| 3[e] |  |  | 50 | 65 (99:1) |
| 4[e] |  |  | 50 | 73 (98:2) |
| 5[e] |  |  | 85 | 90 (97:3) |
| 6[e] |  |  | 65 | 73 (97:3) |
| 7[e] |  |  | 95 | 55 (95:5) |

[a] Reaction conditions: benzylic hydroxamate (0.4 mmol), $BF_3{\cdot}OEt_2$ (1.6 mmol), arene (1.6 mmol), $CH_2Cl_2$ (4 mL), 24 h. [b] Yields of isolated products. [c] Ratio of regioisomers determined by GC/MS. [d] Arene (8 mL), no solvent, 24 h. [e] Arene (4 mL), no solvent, 24 h. R = [N(CH$_3$)(Ac)].

we examined the functionalization of *para*-chloromethylbenzyl hydroxamate **8** (Scheme 2). A Friedel–Crafts reaction of this electrophile with benzene and $BF_3{\cdot}OEt_2$ gave only product from displacement of the hydroxamate. In contrast,




***Scheme 2.*** Chemoselective functionalization by Friedel–Crafts or Suzuki–Miyaura reactions.

the benzylic halide can be selectively arylated by a Suzuki–Miyaura cross-coupling with phenyl boronic acid.[20] In the latter case, the benzylic halide is exclusively functionalized while the hydroxamate remains unchanged.

To confirm our hypothesis that the selective activation of the hydroxamate by $BF_3{\cdot}OEt_2$ and reversible formation of the benzylic cation is responsible for the success of this reaction we performed a cross-over experiment in which two different benzylic hydroxamates were exposed to trifluomethylbenzene at 45 °C for 30 min (see Supporting Information for details). Quenching the reaction prior to completion revealed the formation of benzyl hydroxamates arising from cross-over of the starting materials, clearly indicating that disassociation to the hydroxamic acid and the benzyl cation is reversible.

Hydroxamate leaving groups offer a new entry to operationally simple and selective Friedel–Crafts benzylations. The unique propensity of these otherwise inert substrates towards activation by $BF_3{\cdot}OEt_2$, most likely in a reversible manner that avoids build-up of highly reactive carbocations, offers a convenient approach to aromatic functionalization. We anticipate that variation in the structure of the hydroxamate, which offers two sites for elaboration, or the Lewis acid will allow further improvements in reactivity, yield, and regioselectivity. The low reaction temperatures, simple workup, and clean reactions make this process an attractive and complementary approach to other emerging methods for aromatic CH functionalization.

Received: July 30, 2011
Published online: September 22, 2011

**Keywords:** arenes · benzylation · boron · CH activation · Friedel–Crafts reaction

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