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Benzylation of arenes through $FeCl_3$-catalyzed Friedel–Crafts reaction via C–O activation of benzyl ether

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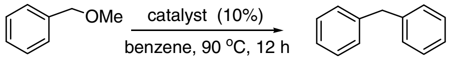
ABSTRACT

Various benzyl ethers were converted to benzyl arenes via a $FeCl_3$-catalyzed Friedel–Crafts alkylation reaction under mild condition in good yields. This method also offered a simple and practical approach to synthesize di- or tri-aryl methanes and aryl heteroaryl methanes through the activation of C–O bonds.

Friedel–Crafts alkylation is one of the most powerful methods in organic synthesis, which has been broadly applied to the construction of C–C bonds for a long history. Originally, Friedel–Crafts reactions took place between alkyl halides and electron rich arenes in the presence of different Lewis Acids.[1] In the past several decades, Friedel–Crafts reactions have been widely investigated and various reagents were introduced to those transformations, such as alkenes and acyl chlorides.[2] Other developments realized the alkylation of arenes with alcohols[3] and esters[4] as the alkylating reagents. Generally, large amount of Lewis acids or Brönsted acids was required to facilitate those Friedel–Crafts reactions.[5] Herein, we reported a new methodology to carry out the benzylation of electron rich arenes and substituted thiophenes through benzylic sp^3 C–O activation of benzyl methyl ether.

Recently, much attention has been paid to the utilization of iron complexes in catalytic organic transformations due to their readily availability, inexpensiveness, and environmentally friendliness.[6] Many efforts have been made to construct C–C and C–X bonds (X = N, O, etc.) by coupling reactions catalyzed by iron complexes.[7] Among those developments, a noteworthy progress was the iron-catalyzed Friedel–Crafts alkylation of arenes with low catalyst loading under relatively mild conditions.[8] In those reactions, benzylic alcohol and its acetate have been utilized to conduct the benzylation of arenes.[9] Different from esters and alcohols, ethers are among the most stable organic compounds, which were broadly used as the solvent. Under relatively harsh conditions, ethers could react with different reagents.[10] Due to their commercial availability, much attention has been drawn to the activation of etheric C–O bonds through transition-metal catalyzed coupling reactions to construct C–C bonds.[11] However, most studies in this field were focused on the aryl/alkenyl C–OMe.[12] Various transition-metal catalysts, such as palladium and nickel complexes, have been exploited effectively and efficiently in this field.[13] In contrary, the activation of sp^3 C–O in saturated ether is much more challenging,

Table 1
Benzylation of benzene with benzyl methyl ether (**1a**) under different conditions[a]



1a **2a**

Entry	Catalyst	Conversion[b] (%)	Yield[c] (%)
1	–	0	0
2	CuCl	<5	0
3	$CuCl_2$	<5	0
4	$CuBr_2$	<5	0
5	$Cu(OAc)_2$	<5	0
6	$ZnCl_2$	0	0
7	$AlCl_3$	<5	<5
8	$MgCl_2$	<5	0
9	$Fe(OAc)_2$	<5	0
10	$FeCl_2$	<5	<5
11	$Fe(NO_2)_3 \cdot 9H_2O$	<5	0
12	$Fe(acac)_3$	<5	0
13[d]	$FeCl_3$	>99	83
15	$InCl_3$	<5	<5
16	$AuCl_3$	12	12
17	AuCl	<5	<5
18	$CoCl_2$	<5	0
19	HOTf	<5	0
20	HCl	<5	0

[a] Reaction condition: benzyl methyl ether (**1a**) (0.5 mmol), benzene (1 mL), and catalyst (10 mol %) were mixed and heated to 90 for 12 h.
[b] Conversion was determined by GC with *n*-dodecane as an internal standard.
[c] Yield was determined by GC with *n*-dodecane as an internal standard if without further note.
[d] Isolated yield.

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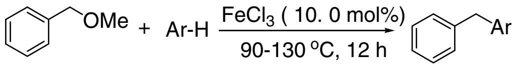
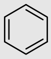
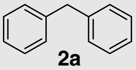
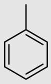
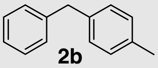
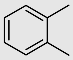
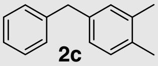
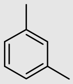
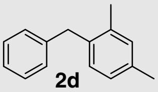
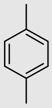
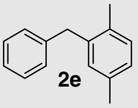
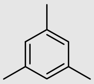
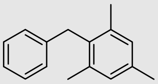
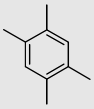
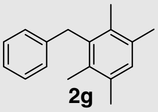
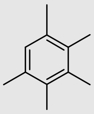
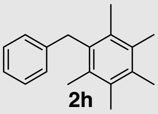
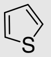
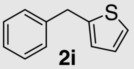
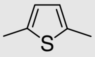
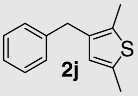
which is arising from not only the high bond energy, but also the selectivity issue between two different C–O bonds in unsymmetrical ethers. Since benzylic sp^3 C–O bond is relatively active, we focused on the reaction of benzyl methyl ether. Actually, direct application of benzyl ether through sp^3 C–O activation is rarely reported. In our recent studies, the methylation of benzylic sp^3 C–O bonds via Ni-catalyzation was demonstrated.[14] This report showed the good reactivities of benzyl methyl ethers in Friedel–Crafts alkylation via $FeCl_3$ catalyzation.

Table 2
Benzylation of different arenes with benzyl methyl ether[a]



1a 2

Entry	Arenes	Main product	T (°C)	Yield[b] (%) (regioselectivity)
1		 2a	90	83
2		 2b	90	90 (58:42)
3		 2c	90	86 (65:35)
4		 2d	90	88 (79:21)
5		 2e	90	90
6		 2f	130	75
7		 2g	130	86
8[c]		 2h	130	72
9		 2i	100	75 (94:6)
10		 2j	100	80

[a] Reaction condition: arene (1 mL), benzyl methyl ether (0.5 mmol), no solvent, $FeCl_3$ (10.0 mol %) at the proper temperature for 12 h.

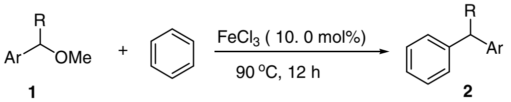
[b] Isolated yields and the ratio of the isomers were determined by ^{1}H NMR.

[c] The reaction was carried out with pentamethylbenzene (0.5 mmol), benzyl methyl ether (**1a**, 0.5 mmol), and $FeCl_3$ (10.0 mol %) under solvent-free condition at 130 °C for 12 h.

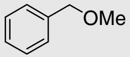
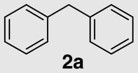
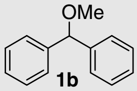
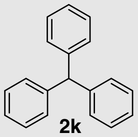
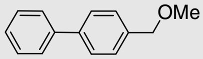
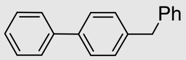
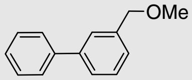
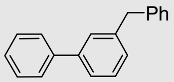
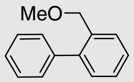
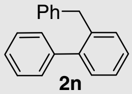
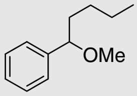
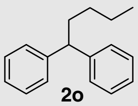
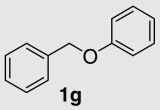
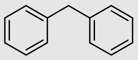
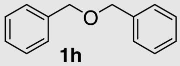
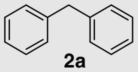
Our attempt was started by investigating the traditional Friedel–Crafts reaction with benzene as the reaction partner. Under different conditions, we observed only a very small amount of diphenyl methane by GC as the desired product with some common Lewis acids as the catalysts (Table 1). Afterward, we started searching for the possibility to activate the sp^3 C–O bond with iron salts. To our delight, the Friedel–Crafts reaction performed well in the presence of commercially available iron(III) chloride ($FeCl_3$) (entry 13). This reaction took place under mild condition (90 °C) and was compatible with both air and moisture. The desired product was obtained with a complete conversion and an excellent isolated yield. When the temperature was lowered to 60 °C, the transformation also took place very smoothly but with longer time. However, some other iron salts, such as $FeCl_2$ and $Fe(acac)_3$ were not suitable for this transformation.

Other than benzene, different arenes were systematically investigated under the standard condition (Table 2). We observed that: (1) various methyl-substituted benzenes showed high reactivities, including those with two or more methyl groups equipped on the

Table 3
Benzylation of benzene with different benzyl methyl ethers[a]



1 2

Entry	1	Product 2	Yield[b] (%)
1	 1a	 2a	83
2	 1b	 2k	90
3	 1c	 2l	33
4	 1d	 2m	35
5	 1e	 2n	67
6	 1f	 2o	48
7	 1g	 2a	27
8	 1h	 2a	68

[a] Reaction condition: benzyl ether 1 (0.5 mmol), benzene (1 mL), $FeCl_3$ (10.0 mol %) at 90 for 12 h.

[b] Isolated yields.

phenyl ring (entries 2–8). The selectivity of this benzylation was controlled by both electronic effect and steric effect. For example, with toluene as the substrate, benzylation occurred at *para* and *ortho* position with a 58:42 ratio in high efficiency (entry 2). With polysubstituted substrates, such as mesitylene, 1,2,4,5-tetramethyl benzene, and pentamethylbenzene, the benzylation took place at higher temperature and lower yields were obtained, which may arise from the severe steric hindrance of methyl groups (entries 6–8). It is of importance to note that the benzylation could run under solvent-free condition with 1:1 ratio of pentamethylbenzene and benzyl methyl ether, which illustrated that the transformation could be realized in high atomic economy (entry 8). (2) Thiophene and 2,5-dimethylthiophene were also submitted to this transformation and the corresponding products formed in good efficiency and high selectivity (entries 9 and 10).

We further tested different benzyl ethers in this transformation (Table 3). The results indicated that: (1) both benzyl methyl ether and diphenylmethyl methyl ether were suitable for this transformation (entries 1 and 2); (2) *para*- and *meta*-phenyl substituted benzyl ether showed poor reactivity (entries 3 and 4), while *ortho*-substituted substrate performed much better in this transformation (entry 5). The reason for the different reactivities of those substrates is still obscure; (3) compared with diphenylmethyl methyl ether, secondary benzyl methyl ether showed relatively poor reactivity, since the substrate also went through elimination pathway to form styrene derivative as the byproduct (entry 6); (4) benzyl phenyl ether was submitted to this transformation and the desired product **2a** was isolated in a relatively low yield (entry 7), but highly regioselectivity was observed that only benzylic sp^3 C–O bond was cleaved and phenyl sp^2 C–O bond was kept untouched; (5) dibenzyl ether also showed good reactivity and desired biphenyl methane was obtained in good yield, and both benzyl groups could be transformed into the final products (entry 8).

In summary, we first developed a cleavage of benzylic sp^3 C–O bonds in benzyl ethers, fulfilling the Friedel–Crafts benzylation of arenes via $FeCl_3$-catalyzation. Various benzyl ethers and arenes were systematically studied. This study offered a simple and practical method to synthesize di- or tri-aryl methane and arylheteroaryl methane under mild condition. Further studies to use this method to construct the useful structural units and functional groups in target molecules are underway.

Acknowledgments

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