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An Effective Bismuth-Catalyzed Benzylation of Arenes and Heteroarenes

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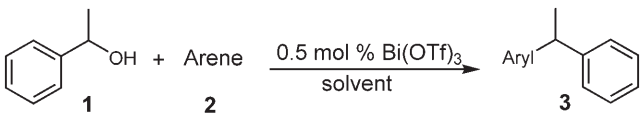
Abstract: A highly efficient $Bi(OTf)_3$-catalyzed benzylation of arenes and heteroarenes has been developed. The mild reaction conditions, high yields, operational simplicity and practicability, broad scope, and remarkably low catalyst loading render this environment friendly process an attractiv approach to diarylmethane derivatives. The extension to an intramolecular variant of this procedure provides a valuable route to substituted fluorenes.

Keywords: arylation; benzylation; bismuth; catalysis; diarylmethanes; Friedel–Crafts alkylation

The functionalization of arenes and heteroarenes is of great synthetic importance in the preparation of pharmaceuticals, agrochemicals, and fine chemicals. Consequently, various procedures for the acylation and alkylation of aromatic compounds have been reported.[1–8] In a classical manner, Friedel–Crafts reactions are based on the reaction of arenes with acyl or alkyl chlorides in combination with stoichiometric amounts of Lewis acid catalysts, such as aluminum(III) chloride. Generally, drastic reaction conditions with regard to temperature and acidity are applied along with the production of large amounts of salt by-products. Additionally, the electrophiles have to be preformed and co-production of hydrogen halides often induces side reactions. Thus, due to the increasing demand for efficient, economic and environmentally friendly processes, the development of direct catalytic carbon-carbon bond forming reactions of arenes in which products are obtained from the reaction of prior unmodified substrates is an exciting task. Recently, interesting examples of such catalytic functionalizations of arenes have been reported.[8–12] Considerable progress has been made in the metal-catalyzed Friedel–Crafts alkylation of arenes to generate products containing a diarylmethane moiety commonly found in biologically active compounds. In addition to reports on lanthanide triflate catalysts,[13–16] Beller and co-workers demonstrated that late transition metal salts such as $RhCl_3$, $IrCl_3$, H_2PdCl_4, H_2PtCl_6 and $HAuCl_4$ effectively catalyze the addition of benzyl acetates and benzyl alcohols to arenes.[17,18] Due to the high catalyst loading (5–10 mol%) and expenses of the late transition metals employed, this group recently disclosed an excellent iron-catalyzed benzylation of arenes.[19] Using 10 mol% of inexpensive $FeCl_3$, the addition of benzyl alcohols and benzyl acetates to various arenes and heteroarenes could be well performed. We herein report the application of yet another highly efficient catalyst, a bismuth salt, for this important carbon-carbon bond formation.

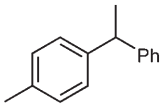
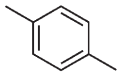
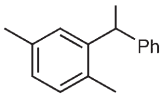
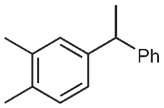
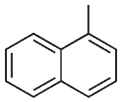
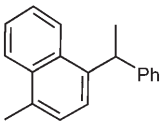
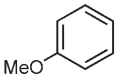
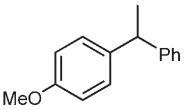
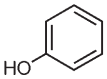
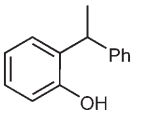
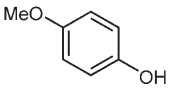
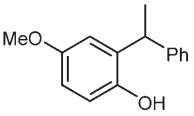
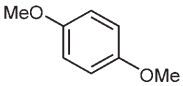
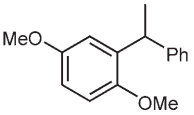
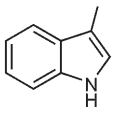
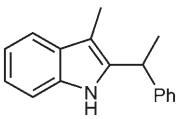
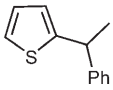
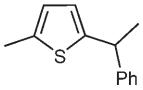
Attracted by the direct addition of benzyl alcohol to arenes, and the fact that certain bismuth salts are compatible with air and moisture, we wondered whether $Bi(OTf)_3$ could be a catalyst for this process. Hence, initial explorations of the $Bi(OTf)_3$-catalyzed reaction of phenylethyl alcohol **1** with arenes **2** (Scheme 1) concentrated on varying the reaction parameters, such as catalyst loading, temperature, concentration, and solvent.

From these experiments the best results with respect to yield and selectivity were obtained when the reaction was performed with 0.5 mol% of bismuth catalyst at elevated temperatures. Further investigations concentrated on the reactivity of various arenes and heteroarenes (Table 1). As anticipated several electron-rich arenes, such as toluene, 1,2- and 1,4-xylene, 1-methylnaphthalene, phenol, and anisole gave the corresponding diarylmethane products **3** in good to excellent isolated yields. Additionally, hetero-



Scheme 1. Reaction of arenes with phenylethyl alcohol catalyzed by 0.5 mol% of $Bi(OTf)_3$.

Table 1. Reaction of 1-phenylethanol with several arenes.[a]

Entry	Arene **2**	Major Product **3**	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	Selectivity[c]
1			-	100	4	72	5:1:3[d]
2			-	100	3	71	10:1[d]
3			-	100	1	79	9:1.3:1[d]
4			$MeNO_2$	100	1	89	99:1
5			CH_2Cl_2	55	1	95	4:1
6			CH_2Cl_2	55	1	71	4:1
7			CH_2Cl_2	55	8	58	10:1
8			CH_2Cl_2	55	4	82	5:1
9			$MeNO_2$	100	8	44	99:1
10			CH_2Cl_2	55	1	65	3:1
11			CH_2Cl_2	55	1	89	14.7:2.6:1

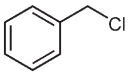
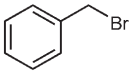
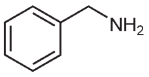
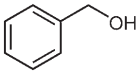
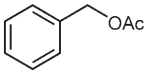
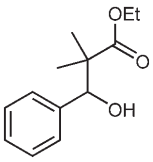
[a] Reactions were carried out with 1-phenylethyl alcohol (1.0 mmol), arene (3.0 mmol), solvent (3 mL), and 0.5 mol % $Bi(OTf)_3$. Reactions were stopped after complete conversion of 1-phenylethyl alcohol.
[b] Isolated yields after silica gel chromatography.
[c] Regioselectivity was determined by ^1H NMR or ^{13}C NMR spectroscopy and comparison with literature data.
[d] But-1-ene-1,3-diyldibenzene.

arenes such as thiophene or 2-methylthiophene reacted well, and even the products of nitrogen-containing arenes, such as 3-methylindole were obtained. This is important to note since, so far, only few examples of metal-catalyzed benzylations of nitrogen-containing heterocycles have been reported.[20]

Following the successful bismuth-catalyzed benzylation of arenes and heteroarenes by employing 1-phenylethyl alcohol we decided to test the scope of the benzylation reagent. The reaction of enantiomerically pure *(S)*-1-phenylethanol with *para*-xylene led to the racemic product, which indicates the formation of a carbocation as intermediate.

Benzyl chloride and benzyl bromide, as well as benzylamine did not show any reactivity in the $Bi(OTf)_3$-catalyzed alkylation of anisole. However, benzyl alco-

Table 2. Reaction of anisole with different benzylating reagents.[a]

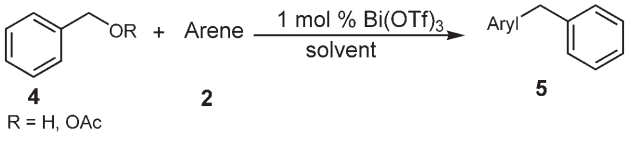
Entry	Benzylating reagent	Yield [%][b]
1		–
2		–
3		–
4		91
5		92
6		59

[a] Reactions were carried out with anisole (3.0 mmol), benzylating reagent (1.0 mmol) and 0.5–5 mol% $Bi(OTf)_3$.
[b] Isolated yields after silica gel chromatography.

hol, benzyl acetate and 3-hydroxy-3-phenylpropanoate gave the desired products in good isolated yields (Table 2).

Hence, we tested the benzylation of several arenes and heteroarenes by employing benzyl alcohol and benzyl acetate **4** as the electrophile (Scheme 2). Again, we observed complete conversion of the benzylating reagents after short reaction times and under mild reaction conditions.

Isolated yields of the products **5** after chromatography were a slightly lower for the benzyl alcohol as compared to the benzyl acetate which, at first, glance can be explained by the better acetate leaving group (Table 3). However, when compared to the benzyl acetate the reaction of 1-phenylethyl alcohol (Table 1) gave similar results, although in the latter case stoichiometric amounts of water are produced which were expected to deactivate the catalyst. Hence, in contrast to many metal triflates, $Bi(OTf)_3$ is a mild and water-tolerable catalyst and even performing the reaction in aqueous media might be feasible.



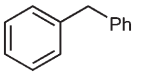
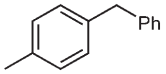
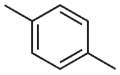
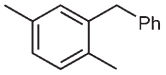
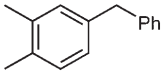
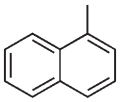
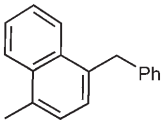
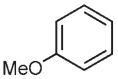
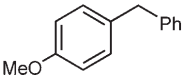
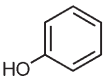
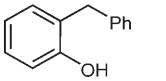
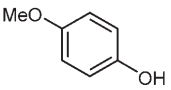
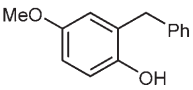
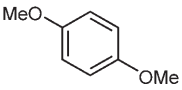
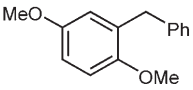
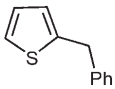
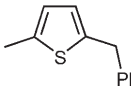
Scheme 2. $Bi(OTf)_3$-catalyzed reaction of arenes with benzyl alcohol and benzyl acetate.

Having established an efficient bismuth-catalyzed intermolecular benzylation of arenes we decided to extend this procedure to an intramolecular version as it would lead to fluorenes, which have shown to be valuable scaffolds for blue light emitting polymers. However, so far only few synthetic approaches to fluorenes have been reported, and intramolecular arylations have only been achieved using harsh reaction conditions, such as refluxing in sulfuric acid.[21–22] To prevent the given limitations we applied $Bi(OTf)_3$ as catalyst for the intramolecular arylation. Using 1 mol% of $Bi(OTf)_3$, the biphenyl derivatives **6** and **7** were reacted to afford the substituted fluorenes **8** and **9** and subsequent isolation provided the products in excellent yields (Scheme 3). Given the low catalyst loading and mild reaction conditions, as well as generally good functional group tolerance, the bismuth-catalyzed intramolecular arylation is a good alternative route to substituted fluorene derivatives.

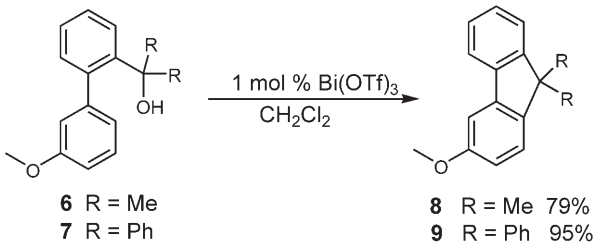
To show that this method is not restricted to the arylation of benzyl alcohol and derivatives, we wondered if it would be possible to use other nucleophiles instead of arenes. Hence, we analyzed the alkylation reaction of 1-phenylethanol **1** with acetylacetone **10** as the nucleophile (Scheme 4). The desired product **11** could be isolated after 8 h in moderate yield. In the case of diethyl malonate as a nucleophile no alkylated product could be observed. While previous alkylations could only be performed with benzyl bromide as electrophile in the presence of cobalt salts or stoichiometric amounts of a Lewis acid such as BF_3, this is the first example of a Lewis-acid catalyzed alkylation of acetylacetone with 1-phenylethanol.

In summary, we have developed an efficient $Bi(OTf)_3$-catalyzed Friedel–Crafts-type benzylation of several arenes and heteroarenes. Compared to previous alkylations with benzyl alcohol and derivatives this method requires remarkably small amounts of highly reactive, inexpensive and non-toxic $Bi(OTf)_3$ catalyst. The mild reaction conditions, short reaction times, operational simplicity and practicability render this transformation an attractive approach to diarylmethane derivatives, which could be isolated in good to excellent yields. Additionally, an extension of this procedure to an intramolecular variant provided a valuable route to substituted fluorenes. Explorations of this bismuth-catalyzed benzylation using other nucleophiles, such as acetylacetone provided the alkylated products and showed the principal feasibility of this method. Further investigations are directed toward the use of further nucleophiles and the extension to a possible asymmetric variant of this transformation.

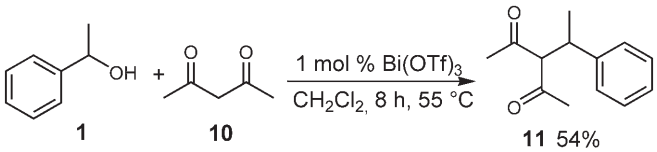
Table 3. Reaction of benzyl alcohol (R = H) and benzyl acetate (R = OAc) with arenes.[a]

Entry	Arene	Major Product	R	Solvent	t [h]	Yield [%][b]	Selectivity[c]
1			H	-	2	59	-
			Ac	-	5	79	-
2			H	-	2	69	1.4:1
			Ac	-	5	90	1.3:1
3			H	-	2	76	-
			Ac	-	5	92	-
4			H	-	2	73	1.9:1
			Ac	-	5	95	1.9:1
5			H	$MeNO_2$	2	66	-
			Ac	$MeNO_2$	5	68	-
6			H	$MeNO_2$	2	91	1.4:1
			Ac	$MeNO_2$	5	92	1.4:1
7			H	$MeNO_2$	2	66	2.7:1:1.7
			Ac	$MeNO_2$	5	58	3:1:1.7
8			H	$MeNO_2$	2	67	1.4:1
			Ac	$MeNO_2$	5	63	1.2:1
9			H	$MeNO_2$	2	57	-
			Ac	$MeNO_2$	5	67	-
10			H	$MeNO_2$	3	35	1.3:1
			Ac	$MeNO_2$	5	58	2:1
11			H	$MeNO_2$	3	58	1:1
			Ac	$MeNO_2$	5	61	1:1

[a] Reactions were carried out with benzyl alcohol or benzyl acetate (1.0 mmol), arene (3.0 mmol), solvent (3 mL), and 1 mol% $Bi(OTf)_3$. Reactions were stopped after complete conversion of benzyl alcohol or benzyl acetate.
[b] Isolated yields after silica gel chromatography or distillation.
[c] Regioselectivity was determined by ^1H NMR or ^{13}C NMR and comparison with the literature data.



Scheme 3. Intramolecular $Bi(OTf)_3$-catalyzed arylation.



Scheme 4. $Bi(OTf)_3$-catalyzed alkylation of acetylacetone.

Experimental Section

General Remarks

Unless otherwise noted, all commercially available compounds were used as supplied without further purification. Solvents for chromatography were technical grade and distilled prior to use. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel-aluminum plates with F-254 indicator, visualized by irradiation with UV light. Column chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 250 spectrometer in $CDCl_3$. Data are reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated [bs (broad singlet), s (singlet), d (doublet), t (triplet), m (multiplet)]; coupling constants (*J*) are in Hertz (Hz). Mass spectra (ESI-MS) were conducted on a VG-Platform II

(Fisons Instruments). IR spectra were recorded on a Jasco FT/IR-420 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). All data of known compounds are in agreement with literature data, while the new compounds were fully characterized.

General Synthetic Procedure

$Bi(OTf)_3 \cdot 4\ H_2O$ (0.005 mmol), benzylating reagent (3 mmol) and arene (1 mmol) were added to a 10 mL flask and solvent (3 mL of nitromethane or dichloromethane) was added if appropriate. The reaction mixture was heated until complete conversion of the benzylating reagent was observed. The reaction mixture was allowed to cool to room temperature, solvents were removed under vacuum, and the crude product was purified by silica gel column chromatography or distillation.

1-Methyl-4-(1-phenylethyl)naphthalene (Table 1, Entry 4): ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.98$–7.90 (m, 2H), 7.41–7.29 (m, 2H), 7.22 (s, 2H), 7.20–7.02 (m, 6H), 4.81 (q, 1H, $J = 7.14$ Hz), 2.59 (s, 3H), 1.66 (d, 3H, $J = 7.14$ Hz); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 147.0$, 139.8, 133.1, 132.9, 131.8, 128.5, 127.7, 126.3, 126.0, 125.6, 125.2, 124.9, 124.6, 124.1, 40.5, 22.7, 19.6; IR (neat): $\nu = 3060$, 3025, 2966, 2931, 2871, 1947, 1871, 1806, 1600, 1514, 1492, 1450, 1423, 1390, 1372, 1335, 1257, 1163, 1075, 1029, 1011, 978, 908, 833, 786, 756, 726, 700, 561 cm^{-1}; ESI-MS : $m/z = 247.0$ (MH^+); anal. calcd. for $C_{19}H_{18}$: C 92.64, H 7.36; found: C 92.39, H 7.43.

3-Methyl-2-(1-phenylethyl)-1*H*-indole (Table 1, Entry 9): ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.46$ (bs, 1H), 7.45–7.41 (m, 1H), 7.27–7.11 (m, 6H), 7.05–7.00 (m, 2H), 4.39 (q, 1H, $J = 7.3$ Hz), 2.21 (s, 1H), 1.61 (d, 1H, $J = 7.3$ Hz); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 143.9$, 138.0, 135.2, 129.5, 128.7, 127.4, 126.6, 121.2, 119.2, 118.3, 110.5, 106.8, 36.3, 20.2, 8.7; IR (neat): $\nu = 3424$, 3052, 3025, 2969, 2915, 2872, 1876, 1600, 1493, 1462, 1332, 1293, 1239, 1027, 1008, 742, 701 cm^{-1}; ESI-MS: $m/z = 235.7$ (MH^+); anal. calcd. for $C_{17}H_{17}N$: C 86.77, H 7.28, N 5.95; found: C 86.88, H 7.31,N 6.03.

2-Methyl-5-(1-phenylethyl)thiophene (Table 1, Entry 11): ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.23$–7.05 (m, 5H), 6.48–6.43 (m, 2H), 4.15 (q, 1H, $J = 7.1$ Hz), 2.29 (s, 3H), 1.56 (d, 3H, $J = 7.1$ Hz); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 148.5$, 146.3, 138.1, 128.6, 127.4, 126.6, 124.6, 123.3, 41.0, 23.3, 15.4; IR (neat): $\nu = 3060$, 3025, 2967, 2918, 2872, 1600, 1492, 1451, 1373, 1230, 1048, 800, 699 cm^{-1}; MS (ESI): $m/z = 202.6$ (MH^+); anal. calcd. for $C_{13}H_{14}S$: C 77.18, H 6.97; found: C 77.16, H 6.98

3-Methoxy-9,9-diphenyl-9*H*-fluorene (9): ^{1}H NMR ($CDCl_3$): $\delta = 7.65$ (d, 1H, $J = 7.5$ Hz), 7.18–7.02 (m, 15H), 6.75 (dd, 1H, $J = 2.3$ Hz, 8.5 Hz), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 159.6$, 152.0, 146.2, 143.5, 141.5, 140.1, 128.2, 128.1, 127.8, 127.4, 126.9, 126.6, 126.3, 120.1, 114.1, 105.1, 64.9, 55.5; IR (KBr): $\nu = 3056$, 3006, 2962, 2932, 1620, 1580, 1489, 1444, 1344, 1291, 1214, 1168, 1037, 859, 806, 752, 743, 726, 699, 632, 590 cm^{-1}; mp 197–200 °C; ESI-MS: $m/z = 349$ (MH^+); anal. calcd. for $C_{26}H_{20}O$: C 89.62, H 5.79; found: C 89.48, H 6.00.

Acknowledgements

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