

Friedel–Crafts Reaction

Iron-Catalyzed Friedel–Crafts Benzylolation with Benzyl TMS Ethers at Room Temperature

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Abstract: Friedel–Crafts benzylations between unactivated arenes and benzyl alcohol derivatives are clean and straightforward processes to construct biologically useful di- and tri-arylmethanes. We have established an efficient iron-catalyzed Friedel–Crafts benzylolation method at room temperature that uses benzyl TMS ethers as substrates, which are poorly reactive under common nucleophilic substitution conditions. The reaction seems to progress through iron-cat-

alyzed self-condensation of the benzyl TMS ether to the corresponding dibenzylic ether. The use of excess arene relative to benzyl TMS ether produced mono-benzylated arene (di- and tri-arylmethane products), whereas the use of excess benzyl TMS ether versus arene provided bis-benzylated arene (polyarylated products) in high yields and regioselectivities. In previous methods, the latter double Friedel–Crafts benzylations hardly proceed.

Introduction

Friedel–Crafts benzylations^[1–8] between unactivated arenes and benzyl alcohol derivatives are clean and straightforward processes to construct di- and tri-arylmethanes,^[9,10] which are useful substructures that are present in various biologically active compounds. Reactivity is strongly dominated by the Lewis or Brønsted acidities of the reagents and the dissociative capacity of the activated benzyl alcohol functionality on the substrate because the nucleophilicities of the arenes are very low (especially, halogenated arenes are less reactive). Therefore, the application of heat and/or the use of a significant excess of arene is required in many cases, although many reactions that use free benzyl alcohols,^[2] acetates,^[3] alkyl halides,^[4] methyl ethers,^[5] benzyl ethers,^[6] and hydroxamates^[7] as the substrates have already been reported in the literature. On the other hand, silyl ethers are traditionally utilized for protection of the alcohol functionality and are tolerated under the nucleophilic conditions due to the low dissociative capacity of the siloxy functionality as a leaving group.^[11] Very recently, we discovered that silyl ethers are suitable substrates for iron-catalyzed azidation reactions,^[12,13] and other research groups have also reported the reactions between silyl ethers and reactive carbon nucleophiles, such as allylsilanes^[14] and enol acetates.^[15] Although Friedel–Crafts reactions with silyl ethers have been

reported in the literature, only electron-rich arenes could be adopted and a large excess of arene (as the solvent) was required.^[8] We now report an efficient Friedel–Crafts benzylolation between silyl ethers and a wide variety of arenes (including halogenated arenes) at room temperature in the presence of FeCl₃. Although various catalysts were utilized in similar reactions,^[1–8] and cheap and versatile reagent FeCl₃ has been adopted in a Friedel–Crafts benzylolation of free alcohols^[3b] and methyl ethers,^[5] high temperatures and long reaction times were required. The present reaction can provide di- and tri-arylmethanes by use of excess arene (3 equiv) relative to silyl ether (1 equiv). Furthermore, the use of excess silyl ether (4 equiv) relative to arene (1 equiv) gave the corresponding bis-benzylated arenes,^[16] which are quite difficult to synthesize by previous methods.^[17]

Results and Discussion

The Lewis acid efficiency was evaluated in the Friedel–Crafts benzylolation of 1-phenylethyl TMS ether (**1a**) and *ortho*-xylene (3 equiv), a comparatively weak nucleophile, in (CH₂Cl)₂ at room temperature (Table 1). Consequently, FeCl₃, FeBr₃, and AuCl₃ (5–10 mol%) were found to be the most efficient catalysts to produce the desired product **2** in near quantitative yield in a short time (Table 1, entries 1–3 and 6). The Friedel–Crafts benzylolation did not proceed when other Lewis acids ([Fe(acac)₃], FeCl₂·4H₂O, InCl₃, BF₃·Et₂O, CuCl₂, AgOAc; Table 1, entries 4, 5, and 8–11) or Brønsted acid TFA (Table 1, entry 12) were used. In these cases, desilylated byproduct 1-phenylethanol (**3**) and self-condensation product bis(1-phenylethyl)ether (**4**) were obtained instead of **2**. Solvents (CH₂Cl)₂ and CH₂Cl₂ were found to be suitable, whereas the reactions in CHCl₃, THF, or toluene did not proceed (the effect of the solvent and other Lewis acids are described in the Supporting Information) Fur-

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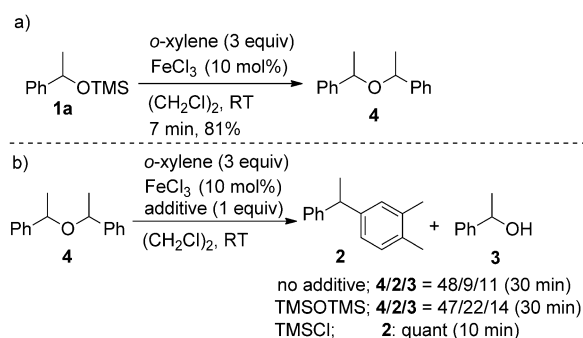
Table 1. Reaction of *o*-xylene with 1-phenylethyl TMS ether (**1**).

		Reaction		Products			
		$\text{Ph-CH(OH)Me} + \text{Ph-CH}_2\text{Me} \xrightarrow[\text{RT}]{\text{catalyst (10 mol\%)}}$		2	3	4	
R	Catalyst	t [h]	Yield [%] ^[a]	1	2	3	4
1	TMS 1a	FeCl ₃	1	0	92 ^[b]	0	0
2 ^[c]	TMS 1a	FeCl ₃	2	0	97	0	0
3	TMS 1a	FeBr ₃	1	0	90 ^[b]	0	0
4	TMS 1a	[Fe(acac) ₃] ^[d]	3	87	0	0	0
5	TMS 1a	FeCl ₃ ·4H ₂ O	3	94	0	0	0
6	TMS 1a	AuCl ₃	3	0	96	0	0
7	TMS 1a	AlCl ₃	3	0	42	0	58
8	TMS 1a	InCl ₃	3	0	0	48	26
9	TMS 1a	BF ₃ ·Et ₂ O	3	0	0	73	0
10	TMS 1a	CuCl ₂	3	99	0	0	0
11	TMS 1a	AgOAc	3	95	0	0	0
12	TMS 1a	TFA ^[e]	3	76	0	14	0
13	TES 1b	FeCl ₃	1.5	0	91 ^[b]	0	0
14	TBS 1c	FeCl ₃	2.5	0	93 ^[b]	0	0
15	H 3	FeCl ₃	6	0	68 ^[b]	0	0

[a] Yields were determined by ¹H NMR spectroscopy with 1,4-dioxane as an internal standard, unless otherwise noted. [b] Isolated yield. [c] FeCl₃ (5 mol%) was used. [d] acac = acetylacetonate. [e] TFA = trifluoroacetic acid.

thermore, triethyl silyl (TES) and *tert*-butyldimethyl silyl (TBS) ethers **1b** and **1c** could also undergo the iron-catalyzed Friedel–Crafts reaction in (CH₂Cl)₂ to give **2** in excellent yield (Table 1, entries 13 and 14), whereas the reaction of the free-alcohol **3** resulted in lower yield (68%) and elongation of the reaction time (Table 1, entry 15).

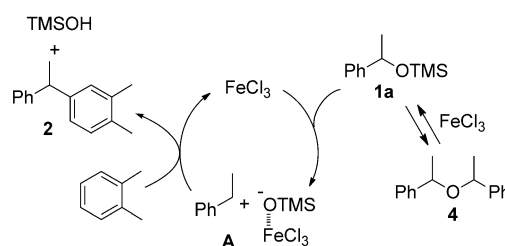
In the present Friedel–Crafts benzylation with TMS ethers, the dibenzylic ether that results from self-condensation of the substrate is obtained as a reaction intermediate. When the reaction of **1a** was interrupted after 7 min, ether **4** was isolated in 81% yield (Scheme 1a).^[18] Furthermore, after isolation, **4** was reacted with *ortho*-xylene in the presence of FeCl₃ and TMSCl^[19] to quantitatively give the desired Friedel–Crafts product **2** after only 10 min at room temperature.^[20] Use of TMSOTMS^[21] as an additive slightly improved the reaction efficiency relative to the reaction without any additives (Scheme 1b). The FeCl₃-catalyzed Friedel–Crafts benzylation of **3** required a longer reaction time (6 h) to obtain a moderate



Scheme 1.

yield (68%) of **2** (Table 1, entry 15). Based on these experimental results, the dibenzylic ether generated might be transformed into the TMS ether, which works as the main electrophile in the present Friedel–Crafts reaction. The TMS ether **1a** and dibenzylic ether **4**^[22] are in equilibrium under FeCl₃-catalyzed conditions, and the original or regenerated **1a** is rapidly converted to the corresponding benzyl cation intermediate (**A**), which is trapped by the arene to afford the desired product (Scheme 2).^[23]

Encouraged by the precise process observed for the FeCl₃-



Scheme 2. Proposed mechanism.

catalyzed reaction of **1a**, we next examined the scope of various benzylic TMS ethers in the reaction with 1,3-dimethoxybenzene, selected for its high nucleophilicity and utility as a synthetic precursor to other useful skeletons (Table 2). Secondary benzyl TMS ethers 1-(4-methoxyphenyl)ethyl TMS ether and methoxy-, chloro-, or fluoro-substituted benzhydrol TMS ethers efficiently underwent the FeCl₃-catalyzed Friedel–Crafts reaction to construct the corresponding di- or tri-arylmethane structures with efficient yields within 1 h (Table 2, entries 1–5). A sterically hindered, tertiary benzyl TMS ether was also amenable to the present reaction and the use of TMSCl as an additive was found to effectively promote the reaction progress (Table 2, entry 6). The progression of the Friedel–Crafts benzylation of primary benzyl TMS ethers was difficult, except in the case of the electron-rich substrate with an electron-donating methoxy substituent on the aromatic ring of the benzyl TMS ether (Table 2, entry 7 versus 8). Furthermore, the high reactivity of TMS ethers enabled chemoselective Friedel–Crafts benzylation at the siloxy functionality (to supply the diaryl alkylchloride) without competing Friedel–Crafts alkylation of an alkyl chloride within the same molecule (Table 2, entry 9). The addition of TMSCl also accelerated the reaction progress, as noted previously (Table 2, entry 6). Additionally, TMS ethers derived from allyl alcohols could be adapted to give the corresponding di- or tri-aryl-substituted products in excellent yields (Table 2, entries 10 and 11).

An investigation into the scope of the reaction of **1a** with various arenes revealed that monosubstituted arenes, toluene, anisole, and TBS-protected phenol, underwent the present Friedel–Crafts reaction in a *para*-selective manner (Table 3, entries 1–3) and the reactions with mesitylene and 1,2-dimethoxybenzene as substrates were also successful (Table 3, entries 4 and 5). Halogenated arenes are useful synthetic precursors for the synthesis of biaryls, boronated esters, and aromatic amines

Table 2. Friedel–Crafts reaction between various benzyl TMS ethers and 1,3-dimethoxybenzene.

TMS ether	Product	Yield [%]	t [min]
1 ^[a]		92	60
2 ^[a]		95	15
3 ^[a]		83	60
4		94	5
5		93	15
6		80 (97) ^[b]	30 (90) ^[b]
7		trace	24 h
8		81	5
9		37 (77) ^[b]	24 h (24 h) ^[b]
10 ^[c]		83	150
11		91	15

[a] FeCl₃ (10 mol%) was used. [b] TMSCl (1 equiv) was used as an additive. [c] FeBr₃ (5 mol%) was used.

by transition-metal-catalyzed cross-coupling reactions, therefore the reactions of nucleophilic halogenated arenes were next challenged. Although the arene that bore only a halogen substituent did not react with **1 a** under the present FeCl₃-catalyzed Friedel–Crafts benzylation conditions, the halogenated anisole derivatives were efficient nucleophiles (Table 3, entries 6–13). The reaction of *ortho*-iodoanisole with **1 a** did not proceed at room temperature, the application of heat (70 °C) or addition of TMSCl at room temperature led to high yields of the desired Friedel–Crafts product with perfect regioselectivity (Table 3, entries 6 and 7). *Ortho*-bromoanisole was also reactive in the presence of TMSCl (Table 3, entry 8). *Meta*-haloanisoles were more reactive and the reactions efficiently proceeded at room temperature to give the desired products with high regioselectivities (Table 3, entries 9–12). The reaction of *para*-iodoanisole required the addition of TMSCl and a reaction tem-

Table 3. Scope of the arene nucleophile.

Arene	Product	Yield [%]	t [h]
1 ^[a]		84 (<i>o/p</i> =10:90)	24
2 ^[a]		95 (<i>o/p</i> =18:82)	3
3		65 (<i>o/p</i> =31:69)	0.5
4		99	6
5		74	1.5
6 ^[b]		75	5
7 ^[c]		quant	10.5
8 ^[c]		69	0.75
9		90	3
10		84	1
11 ^[c]		85 ^[d]	2
12		70 ^[d]	1
13 ^[b,c]		56	24

[a] Arene (30 equiv) was used. [b] Heated at 70 °C. [c] TMSCl (1 equiv) was used as an additive. [d] A slight amount of the regioisomer was obtained as a byproduct (see the Supporting Information).

perature of 70 °C to provide the corresponding product (Table 3, entry 13).

It is worth noting that the use of an excess of benzyl TMS ether (4 equiv) relative to arene (1 equiv) effectively supplied the corresponding bis-benzylated arenes,^[16] which were hardly obtained by previous methods (Table 4).^[17] Various methoxy-, chloro-, or fluoro-substituted benzhydrol derivatives could efficiently undergo the FeCl₃-catalyzed Friedel–Crafts bis-benylation with 1,3-dimethoxybenzene to give the corresponding polyaryl products in good to quantitative yields (Table 4, entries 1–4). The reactions of anisole also gave the bis-benzylated products; the third benzylation was probably inhibited due to steric repulsion (Table 4, entries 5 and 6). Furthermore, the bis-benzylation of *meta*-iodoanisole gave the desired iodinated Friedel–Crafts products, which are well suited for further synthetic modification (Table 4, entries 7–9).

Conclusion

We have established an efficient and mild Friedel–Crafts benzylation reaction that uses benzyl TMS ethers, which are generally stable under the nucleophilic substitution conditions. The present reactions are catalyzed by the safe and cheap iron catalyst FeCl₃ and can proceed at room temperature to give versatile polyaryl products with di- and tri-arylmethane skeletons.

Table 4. Double Friedel–Crafts benzylation.

Arene	R	Product	Yield [%]	t [h]
1	H		quant	20
2	OMe		78	48
3	Cl		65	6
4	F		quant	0.25
5	H		quant	6.5
6	F		quant	24
7	H		76	24
8 ^[a]	Cl		36 ^[b]	24
9	F		70	18

[a] TMSCl (1 equiv) was used as an additive. [b] 37% of the monosubstituted product was obtained as an intermediate (see the Supporting Information).

TMSCl, generated during the reaction process, efficiently facilitated the reaction. Synthetically useful halogenated arenes could be used as nucleophiles, and the present reaction can be applied to a benzylic TMS ether that also bears an alkyl chloride, which is commonly reactive under Lewis acid catalyzed Friedel–Crafts alkylation conditions, without the occurrence of competing alkylation.

Experimental Section

Typical procedure for Friedel–Crafts monobenylation (Tables 1–3)

Arene (0.6 mmol, 3 equiv) and FeCl₃ (0.01 mmol, 5 mol%) were added to a solution of a benzyl silyl ether (0.2 mmol, 1 equiv) in (CH₂Cl)₂ (0.2 M). The mixture was stirred at room temperature under argon. After an adequate reaction time, the mixture was quenched with water and extracted with CH₂Cl₂. The combined organic layers were dried with Na₂SO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/EtOAc (30:1) as an eluent.

Typical procedure for Friedel–Crafts bis-benylation (Table 4)

Arene (0.2 mmol, 1 equiv) and FeCl₃ (0.02 mmol, 10 mol%) were added to a solution of a benzyl silyl ether (0.8 mmol, 4 equiv) in (CH₂Cl)₂ (0.2 M). The mixture was stirred at room temperature

under argon. After an adequate reaction time, the mixture was quenched with water and extracted with CH₂Cl₂. The combined organic layers were dried with Na₂SO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/EtOAc (20:1) as an eluent.

Characterization

Compound 2: ¹H and ¹³C NMR spectra of the product were identical to those reported in reference [3a]. ¹H NMR (400 MHz, CDCl₃): δ = 7.29–7.21 (m, 4H), 7.18–7.16 (m, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.03–6.95 (m, 2H), 4.08 (q, *J* = 7.2 Hz, 1H), 2.21 (s, 6H), 1.61 ppm (d, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 146.7, 143.9, 136.4, 134.1, 129.6, 129.0, 128.3, 127.5, 125.9, 124.9, 44.4, 21.9, 19.8, 19.3 ppm.

Compound 4 (diastereomeric mixture): ¹H and ¹³C NMR spectra of the product were identical to those reported in reference [24]. ¹H NMR (400 MHz, CDCl₃): δ = 7.37–7.34 (m, 4H), 7.30–7.27 (m, 14H), 7.24–7.20 (m, 2H), 4.53 (q, *J* = 6.4 Hz, 2H), 4.25 (q, *J* = 6.4 Hz, 2H), 1.46 (d, *J* = 6.4 Hz, 6H), 1.38 ppm (d, *J* = 6.4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ = 144.2, 144.1, 128.4, 128.2, 127.4, 127.1, 126.3, 126.2, 74.6, 74.4, 24.7, 23.0 ppm.

1,3-Dimethoxy-4-[1-(4-methoxyphenyl)ethyl]benzene (Table 2, entry 1): ¹H and ¹³C NMR spectra of the product were identical to those reported in references [2e] and [25]. ¹H NMR (400 MHz, CDCl₃): δ = 7.14 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 9.2 Hz, 1H), 6.82–6.79 (m, 2H), 6.43–6.41 (m, 2H), 4.42 (q, *J* = 7.2 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 1.52 ppm (d, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 159.0, 157.7, 157.5, 138.8, 128.5, 127.8, 113.4, 103.9, 98.6, 55.4, 55.3, 55.2, 36.1, 21.2 ppm.

4-Bis(4-methoxyphenyl)methyl-1,3-dimethoxybenzene (Table 2, entry 2): Colorless oil; ¹H NMR (400 MHz, CDCl₃): δ = 7.00–6.96 (m, 4H), 6.81–6.77 (m, 4H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 6.38 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.72 (s, 1H), 3.77 (s, 3H), 3.76 (s, 6H), 3.69 ppm (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 159.3, 157.9, 157.7, 136.7, 130.5, 130.1, 125.8, 113.4, 103.7, 98.6, 55.6, 55.2, 55.1, 47.4 ppm; IR (ATR): $\tilde{\nu}$ = 2998, 2932, 2834, 1607, 1503, 1460, 1291, 1240, 1206, 1174, 1113, 1031, 820, 731, 567 cm⁻¹; HRMS (ESI): *m/z*: calcd for C₂₃H₂₅O₄: 365.1747 [*M*+H]⁺; found: 365.1751.

1-Benzydryl-2,4-dimethoxybenzene (Table 2, entry 3): ¹H and ¹³C NMR spectra of the product were identical to those reported in reference [2k]. ¹H NMR (400 MHz, CDCl₃): δ = 7.27–7.23 (m, 4H), 7.19–7.15 (m, 2H), 7.09–7.07 (m, 4H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.38 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.83 (s, 1H), 3.77 (s, 3H), 3.68 ppm (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 159.4, 158.0, 144.2, 130.7, 129.4, 128.0, 125.9, 125.2, 103.7, 98.6, 55.5, 55.3, 49.1 ppm.

4-Bis(4-chlorophenyl)methyl-1,3-dimethoxybenzene (Table 2, entry 4): Colorless oil; ¹H NMR (400 MHz, CDCl₃): δ = 7.24–7.20 (m, 4H), 6.99–6.96 (m, 4H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 2.8 Hz, 1H), 6.39 (dd, *J* = 8.4, 2.8 Hz, 1H), 5.73 (s, 1H), 3.78 (s, 3H), 3.68 ppm (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 159.7, 157.8, 142.2, 131.9, 130.6, 130.4, 128.3, 124.1, 103.8, 98.7, 55.5, 55.3, 48.0 ppm; IR (ATR): $\tilde{\nu}$ = 3001, 2958, 2934, 2836, 1610, 1585, 1488, 1260, 1207, 1088, 1013, 907, 807, 731, 574, 520 cm⁻¹; HRMS (ESI): *m/z*: calcd for C₂₁H₁₈O₂Cl₂: 372.0678 [*M*]⁺; found: 372.0680.

4-Bis(4-fluorophenyl)methyl-1,3-dimethoxybenzene (Table 2, entry 5): ¹H and ¹³C NMR spectra of the product were identical to those reported in reference [26]. ¹H NMR (400 MHz, CDCl₃): δ = 7.04–7.01 (m, 4H), 6.98–6.93 (m, 4H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.41 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.78 (s, 1H), 3.80 (s, 3H), 3.70 ppm (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 162.5, 160.0,

159.6, 157.8, 139.7, 139.6, 130.6, 130.5, 130.4, 124.8, 115.0, 114.8, 103.7, 98.6, 55.5, 55.3, 47.7 ppm.

1,3-Dimethoxy-4-(1-methyl-1-phenylethyl)benzene (Table 2, entry 6): ^1H and ^{13}C NMR spectra of the product were identical to those reported in reference [2j]. ^1H NMR (400 MHz, CDCl_3): δ = 7.34 (d, J = 8.4 Hz, 1H), 7.23–7.15 (m, 4H), 7.11–7.07 (m, 1H), 6.49 (dd, J = 8.4, 2.4 Hz, 1H), 6.38 (d, J = 2.4 Hz, 1H), 3.80 (s, 3H), 3.33 (s, 3H), 1.64 ppm (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ = 159.4, 151.7, 131.2, 127.5, 127.0, 125.6, 125.5, 124.7, 103.5, 100.6, 55.2, 55.1, 41.4, 29.8, 29.7 ppm.

1,3-Dimethoxy-4-(4-methoxybenzyl)benzene (Table 2, entry 8): ^1H and ^{13}C NMR spectra of the product were identical to those reported in reference [27]. ^1H NMR (500 MHz, CDCl_3): δ = 7.11 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 2H), 6.45 (d, J = 2.0 Hz, 1H), 6.40 (dd, J = 8.0, 2.0 Hz, 1H), 3.83 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.76 ppm (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ = 159.0, 157.8, 157.4, 133.2, 130.1, 129.5, 129.2, 122.3, 113.4, 113.1, 103.6, 103.5, 98.2, 55.1, 54.9, 34.0 ppm.

4-(3-Chloro-1-phenylpropyl)-1,3-dimethoxybenzene (Table 2, entry 9): Colorless oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.26–7.23 (m, 4H), 7.19–7.15 (m, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.46–6.42 (m, 2H), 4.50 (t, J = 7.6 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.50–3.39 (m, 2H), 2.50–2.41 ppm (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ = 159.4, 158.1, 143.8, 128.3, 128.1, 128.0, 126.1, 124.5, 104.2, 98.8, 55.4, 55.3, 43.4, 40.6, 37.7 ppm; IR (ATR): $\tilde{\nu}$ = 3026, 2999, 2935, 2835, 1610, 1503, 1452, 1289, 1206, 1156, 1033, 935, 698 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{17}\text{H}_{20}\text{O}_2\text{Cl}$: 291.1146 $[\text{M}+\text{H}]^+$; found: 291.1136.

1,3-Dimethoxy-4-[(E)-1-phenylbut-1-en-3-yl]benzene (Table 2, entry 10): ^1H and ^{13}C NMR spectra of the product were identical to those reported in reference [2j]. ^1H NMR (400 MHz, CDCl_3): δ = 7.35 (d, J = 7.6 Hz, 2H), 7.29–7.24 (m, 2H), 7.20–7.15 (m, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.47–6.39 (m, 4H), 4.02–3.96 (m, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 1.38 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 159.1, 157.7, 138.0, 135.3, 128.4, 127.9, 127.8, 126.8, 126.6, 126.1, 104.1, 98.7, 55.4, 55.3, 34.7, 20.1 ppm.

1,3-Dimethoxy-4-[(E)-1,3-diphenylallyl]benzene (Table 2, entry 11): ^1H and ^{13}C NMR spectra of the product were identical to those reported in reference [2k]. ^1H NMR (400 MHz, CDCl_3): δ = 7.35 (d, J = 7.6 Hz, 2H), 7.29–7.16 (m, 8H), 7.06 (d, J = 7.6 Hz, 1H), 6.66 (dd, J = 16.0, 7.2 Hz, 1H), 6.47–6.44 (m, 2H), 6.26 (d, J = 16.0 Hz, 1H), 5.22 (d, J = 7.2 Hz, 1H), 3.78 (s, 3H), 3.74 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 159.5, 157.9, 143.7, 137.6, 132.8, 130.8, 129.8, 128.6, 128.4, 128.1, 127.0, 126.2, 126.0, 124.5, 104.1, 98.9, 55.5, 55.3, 46.4 ppm.

1-Methyl-4-(1-phenylethyl)benzene (Table 3, entry 1): ^1H and ^{13}C NMR spectra of the product were identical to those reported in reference [2f]. Mixture of regioisomers: ^1H NMR (400 MHz, CDCl_3): δ = 7.29–7.25 (m, 2H), 7.23–7.20 (m, 2H), 7.18–7.14 (m, 1H), 7.12–7.07 (m, 4H), 4.31 (q, J = 7.2 Hz, 0.09H), 4.11 (q, J = 7.2 Hz, 0.91H), 2.30 (s, 2.73H), 2.23 (s, 0.27H), 1.62 (d, J = 7.2 Hz, 2.73H), 1.60 ppm (d, J = 7.2 Hz, 0.27H); ^{13}C NMR (100 MHz, CDCl_3): δ = 146.6, 143.4, 135.5, 129.0, 128.3, 127.5, 127.4, 125.9, 44.3, 21.9, 21.0 ppm.

1-Methoxy-4-(1-phenylethyl)benzene (Table 3, entry 2): ^1H and ^{13}C NMR spectra of the product were identical to those reported in reference [28]. ^1H NMR (400 MHz, CDCl_3): δ = 7.29–7.23 (m, 2H), 7.21–7.12 (m, 5H), 6.82 (d, J = 8.8 Hz, 2H), 4.10 (q, J = 7.6 Hz, 1H), 3.77 (s, 3H), 1.61 ppm (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 157.8, 146.7, 138.5, 128.5, 128.3, 127.5, 125.9, 113.7, 55.2, 43.9, 22.0 ppm.

1-Tert-butylidimethylsiloxy-4-(1-phenylethyl)benzene (Table 3, entry 3): Colorless oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.29–7.25 (m, 2H), 7.21–7.14 (m, 3H), 7.06 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz,

2H), 4.08 (q, J = 7.2 Hz, 1H), 1.60 (d, J = 7.2 Hz, 3H), 0.97 (s, 9H), 0.17 ppm (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ = 153.7, 146.9, 138.9, 128.4, 128.3, 127.6, 125.9, 119.7, 44.0, 25.7, 22.1, 18.2, –4.4 ppm; IR (ATR): $\tilde{\nu}$ = 3028, 2957, 2929, 2857, 1607, 1508, 1463, 1252, 1172, 1013, 913, 835, 778, 697 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{20}\text{H}_{29}\text{OSi}$: 313.1982 $[\text{M}+\text{H}]^+$; found: 313.2011.

1-Mesityl-1-phenylethane (Table 3, entry 4): ^1H and ^{13}C NMR spectra of the product were identical to those reported in reference [29]. ^1H NMR (400 MHz, CDCl_3): δ = 7.27–7.23 (m, 2H), 7.18–7.13 (m, 3H), 6.82 (s, 2H), 4.63 (q, J = 7.6 Hz, 1H), 2.26 (s, 3H), 2.11 (s, 6H), 1.65 ppm (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 145.4, 140.0, 136.5, 135.4, 129.9, 128.1, 126.8, 125.2, 37.8, 21.0, 20.7, 16.8 ppm.

1,2-Dimethoxy-4-(1-phenylethyl)benzene (Table 3, entry 5): ^1H and ^{13}C NMR spectra of the product were identical to those reported in reference [30]. ^1H NMR (400 MHz, CDCl_3): δ = 7.30–7.26 (m, 2H), 7.22–7.16 (m, 3H), 6.79–6.78 (m, 2H), 6.72 (d, J = 1.6 Hz, 1H), 4.10 (q, J = 7.2 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 1.62 ppm (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 148.8, 147.3, 146.6, 139.0, 128.3, 127.5, 126.0, 119.3, 111.2, 111.0, 55.9, 55.8, 44.3, 22.1 ppm.

2-Iodo-1-methoxy-4-(1-phenylethyl)benzene (Table 3, entries 6 and 7): ^1H and ^{13}C NMR spectra of the product were identical to those reported in reference [31]. ^1H NMR (400 MHz, CDCl_3): δ = 7.63–7.62 (m, 1H), 7.30–7.26 (m, 2H), 7.19–7.16 (m, 3H), 7.12 (dd, J = 8.4, 2.4 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 4.05 (q, J = 7.6 Hz, 1H), 3.82 (s, 3H), 1.59 ppm (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 156.4, 146.0, 140.7, 138.4, 128.6, 128.4, 127.4, 126.1, 110.8, 86.0, 56.3, 43.5, 21.9 ppm.

2-Bromo-1-methoxy-4-(1-phenylethyl)benzene (Table 3, entry 8): Colorless oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.40 (d, J = 2.4 Hz, 1H), 7.31–7.26 (m, 2H), 7.20–7.17 (m, 3H), 7.10 (dd, J = 8.8, 2.4 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 4.07 (q, J = 7.2 Hz, 1H), 3.86 (s, 3H), 1.60 ppm (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 154.1, 146.0, 140.1, 132.4, 128.4, 127.5, 127.4, 126.2, 111.8, 111.5, 56.2, 43.7, 21.9 ppm; IR (ATR): $\tilde{\nu}$ = 3026, 2965, 2931, 2837, 1603, 1494, 1452, 1285, 1259, 1054, 814, 700 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{15}\text{H}_{15}\text{OBr}$: 290.0301 $[\text{M}]^+$; found: 290.0307.

3-Iodo-1-methoxy-4-(1-phenylethyl)benzene (Table 3, entry 9): Pale-yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.38 (d, J = 2.8 Hz, 1H), 7.30–7.25 (m, 2H), 7.22–7.17 (m, 3H), 7.03 (d, J = 8.8 Hz, 1H), 6.85 (dd, J = 8.8, 2.8 Hz, 1H), 4.43 (q, J = 6.8 Hz, 1H), 3.76 (s, 3H), 1.56 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 158.0, 145.4, 140.7, 128.3, 128.2, 127.8, 126.0, 124.4, 114.7, 101.3, 55.5, 47.5, 21.8 ppm; IR (ATR): $\tilde{\nu}$ = 3024, 2963, 2929, 2833, 1595, 1484, 1283, 1228, 1016, 843, 772, 697, 554 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{15}\text{H}_{15}\text{OI}$: 338.0162 $[\text{M}]^+$; found: 338.0162.

3-Bromo-1-methoxy-4-(1-phenylethyl)benzene (Table 3, entry 10): Colorless oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.30–7.26 (m, 2H), 7.22–7.16 (m, 3H), 7.10–7.08 (m, 2H), 6.81 (dd, J = 8.4, 2.4 Hz, 1H), 4.56 (q, J = 7.6 Hz, 1H), 3.77 (s, 3H), 1.58 ppm (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 158.2, 145.4, 137.4, 129.0, 128.3, 127.7, 126.0, 124.7, 117.9, 113.8, 55.5, 42.7, 21.5 ppm; IR (ATR): $\tilde{\nu}$ = 3060, 3025, 2965, 2931, 2835, 1603, 1488, 1284, 1229, 1028, 857, 774, 697, 556 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{15}\text{H}_{14}\text{OBr}$: 289.0233 $[\text{M}-\text{H}]^-$; found: 289.0236.

3-Chloro-1-methoxy-4-(1-phenylethyl)benzene (Table 3, entry 11): Colorless oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.29–7.25 (m, 2H), 7.22–7.15 (m, 3H), 7.11 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 8.8, 2.8 Hz, 1H), 4.57 (q, J = 7.2 Hz, 1H), 3.77 (s, 3H), 1.58 ppm (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 158.3, 145.4, 135.8, 134.2, 129.0, 128.3, 127.6, 126.0, 114.7, 113.1,

55.5, 40.2, 21.3 ppm; IR (ATR): $\tilde{\nu}$ = 3026, 2966, 2932, 2835, 1605, 1491, 1285, 1232, 1041, 880, 698 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{15}\text{H}_{15}\text{OCl}$: 246.0806 $[M]^+$; found: 246.0840.

3-Fluoro-1-methoxy-4-(1-phenylethyl)benzene (Table 3, entry 12): Colorless oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.30–7.22 (m, 4H), 7.20–7.16 (m, 1H), 7.09 (t, J = 8.8 Hz, 1H), 6.63 (dd, J = 8.0, 2.4 Hz, 1H), 6.57 (dd, J = 12.0, 2.4 Hz, 1H), 4.39 (q, J = 7.2 Hz, 1H), 3.76 (s, 3H), 1.60 ppm (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 145.5, 128.8, 128.7, 128.3, 127.4, 126.1, 109.7, 109.6, 101.7, 101.5, 55.5, 37.1, 20.9 ppm; IR (ATR): $\tilde{\nu}$ = 3027, 2966, 2930, 2853, 1625, 1506, 1304, 1155, 1107, 1027, 949, 698 cm^{-1} ; HRMS (ESI) m/z : calcd for $\text{C}_{15}\text{H}_{15}\text{OF}$: 230.1101 $[M]^+$; found: 230.1077.

4-Iodo-1-methoxy-2-(1-phenylethyl)benzene (Table 3, entry 13): Colorless oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.46 (dd, J = 8.8, 2.4 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.29–7.25 (m, 2H), 7.22–7.17 (m, 3H), 6.60 (d, J = 8.8 Hz, 1H), 4.48 (q, J = 7.2 Hz, 1H), 3.73 (s, 3H), 1.54 ppm (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 156.8, 145.5, 137.6, 136.3, 135.9, 128.2, 127.6, 125.9, 113.0, 83.2, 55.5, 37.3, 20.8 ppm; IR (ATR): $\tilde{\nu}$ = 3025, 2962, 2928, 2852, 1584, 1484, 1283, 1243, 1133, 1029, 805, 699 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{15}\text{H}_{16}\text{OI}$: 339.0240 $[M+H]^+$; found: 339.0224.

4,6-Dibenzhydryl-1,3-dimethoxybenzene (Table 4, entry 1): ^1H and ^{13}C NMR spectra of the product were identical to those reported in reference [2k]. ^1H NMR (400 MHz, CDCl_3): δ = 7.26–7.10 (m, 12H), 6.96–6.94 (m, 8H), 6.46 (s, 1H), 6.40 (s, 1H), 5.76 (s, 2H), 3.65 ppm (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ = 156.3, 144.1, 132.7, 129.1, 127.9, 125.7, 123.9, 95.4, 55.8, 49.0 ppm.

4,6-Bis(4,4'-dimethoxybenzhydryl)-1,3-dimethoxybenzene (Table 4, entry 2): Colorless solid; m.p. 157–159 °C; ^1H NMR (400 MHz, CDCl_3): δ = 6.84 (d, J = 8.4 Hz, 8H), 6.69 (d, J = 8.8 Hz, 8H), 6.43 (s, 1H), 6.31 (s, 1H), 5.62 (s, 2H), 3.75 (s, 12H), 3.71 ppm (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ = 157.5, 156.1, 136.6, 132.4, 129.9, 124.5, 113.2, 95.5, 55.8, 55.1, 47.4 ppm; IR (ATR): $\tilde{\nu}$ = 2998, 2932, 2834, 1608, 1506, 1241, 1173, 1095, 1031, 807, 729, 541 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{38}\text{H}_{38}\text{NaO}_6$: 613.2561 $[M+Na]^+$; found: 613.2558.

4,6-Bis(4,4'-dichlorobenzhydryl)-1,3-dimethoxybenzene (Table 4, entry 3): Colorless solid; m.p. 240–242 °C; ^1H NMR (400 MHz, CDCl_3): δ = 7.17–7.13 (m, 8H), 6.81 (d, J = 8.4 Hz, 8H), 6.43 (s, 1H), 6.08 (s, 1H), 5.63 (s, 2H), 3.72 ppm (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ = 156.5, 142.0, 132.0, 131.9, 130.3, 128.2, 123.0, 95.2, 55.7, 48.1 ppm; IR (ATR): $\tilde{\nu}$ = 2925, 2852, 1612, 1506, 1400, 1300, 1203, 1091, 1015, 806, 518 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{34}\text{H}_{26}\text{O}_2\text{Cl}_4$: 606.068 $[M]^+$; found: 606.0686.

4,6-Bis(4,4'-difluorobenzhydryl)-1,3-dimethoxybenzene (Table 4, entry 4): Colorless solid; m.p. 193–196 °C; ^1H NMR (400 MHz, CDCl_3): δ = 6.89–6.82 (m, 16H), 6.44 (s, 1H), 6.10 (s, 1H), 5.67 (s, 2H), 3.72 ppm (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ = 162.4, 160.0, 156.4, 139.5, 139.4, 132.0, 130.4, 130.3, 123.5, 114.9, 114.7, 95.1, 55.7, 47.7 ppm; IR (ATR): $\tilde{\nu}$ = 3070, 2924, 2854, 1600, 1503, 1301, 1223, 1203, 1155, 1030, 823, 724, 532 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{34}\text{H}_{25}\text{O}_2\text{F}_4$: 541.1796 $[M-H]^-$; found: 541.1794.

2,4-Dibenzhydryl-1-methoxybenzene (Table 4, entry 5): ^1H and ^{13}C NMR spectra reported in product were identical to those in reference [32]. ^1H NMR (400 MHz, CDCl_3): δ = 7.24–7.12 (m, 12H), 7.01–7.00 (m, 8H), 6.90 (dd, J = 8.4, 2.4 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 2.4 Hz, 1H), 5.87 (s, 1H), 5.37 (s, 1H), 3.68 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 155.5, 144.4, 143.7, 135.4, 132.3, 131.8, 129.3, 129.2, 128.1, 128.0, 126.0, 125.9, 110.4, 55.9, 55.6, 49.4 ppm.

2,4-Bis(4,4'-difluorobenzhydryl)-1-methoxybenzene (Table 4, entry 6): Colorless solid; m.p. 163–166 °C; ^1H NMR (500 MHz,

CDCl_3): δ = 6.95–6.87 (m, 17H), 6.78 (d, J = 8.5 Hz, 1H), 6.47 (d, J = 1.5 Hz, 1H), 5.80 (s, 1H), 5.34 (s, 1H), 3.68 ppm (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ = 162.3, 162.2, 160.4, 160.3, 155.5, 155.4, 139.8, 139.7, 139.6, 139.1, 139.0, 135.3, 132.2, 131.2, 130.5, 130.4, 128.2, 115.1, 115.0, 114.9, 114.8, 110.4, 55.5, 54.3, 48.1 ppm; IR (ATR): $\tilde{\nu}$ = 3041, 2943, 2838, 1601, 1501, 1221, 1157, 1109, 1097, 1031, 1016, 821, 565 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{33}\text{H}_{24}\text{OF}_4$: 512.1758 $[M]^+$; found: 512.1757.

4,6-Dibenzhydryl-3-iodo-1-methoxybenzene (Table 4, entry 7): Colorless solid; m.p. 133–136 °C; ^1H NMR (400 MHz, CDCl_3): δ = 7.37–7.30 (m, 1H), 7.24–7.09 (m, 12H), 6.90–6.89 (m, 8H), 6.43 (s, 1H), 5.72 (s, 1H), 5.66 (s, 1H), 3.67 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 155.7, 143.0, 138.1, 132.9, 132.7, 129.3, 129.0, 128.2, 128.0, 127.2, 126.2, 126.0, 121.5, 99.4, 59.8, 55.9, 49.4 ppm; IR (ATR): $\tilde{\nu}$ = 3059, 3024, 2934, 2836, 1598, 1482, 1449, 1255, 1126, 1029, 907, 731, 696 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{33}\text{H}_{27}\text{NaOI}$: 589.0999 $[M+Na]^+$; found: 589.1017.

4,6-Bis(4,4'-dichlorobenzhydryl)-3-iodo-1-methoxybenzene (Table 4, entry 8): Colorless solid; m.p. 183–187 °C; ^1H NMR (400 MHz, CDCl_3): δ = 7.29 (s, 1H), 7.19–7.14 (m, 8H), 6.78 (dd, J = 8.8, 2.8 Hz, 8H), 6.12 (s, 1H), 5.61 (s, 1H), 5.56 (s, 1H), 3.69 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 155.8, 140.9, 140.8, 137.3, 132.5, 132.3, 132.2, 131.9, 130.5, 130.2, 128.5, 128.4, 121.8, 99.8, 58.5, 55.9, 48.5 ppm; IR (ATR): $\tilde{\nu}$ = 3024, 2935, 2838, 1486, 1254, 1089, 1014, 906, 804, 731, 520 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{33}\text{H}_{22}\text{OCl}_4\text{I}$: 700.9475 $[M-H]^-$; found: 700.9494.

4,6-Bis(4,4'-difluorobenzhydryl)-3-iodo-1-methoxybenzene (Table 4, entry 9): Colorless solid; m.p. 138–140 °C; ^1H NMR (500 MHz, CDCl_3): δ = 7.29 (s, 1H), 6.90–6.80 (m, 16H), 6.14 (s, 1H), 5.65 (s, 1H), 5.59 (s, 1H), 3.69 ppm (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ = 162.4, 162.3, 160.4, 160.3, 155.7, 138.5, 138.4, 138.3, 138.2, 137.9, 132.5, 132.3, 130.7, 130.6, 130.3, 130.2, 121.6, 115.2, 115.1, 115.0, 114.9, 99.6, 58.2, 55.8, 48.1 ppm; IR (ATR): $\tilde{\nu}$ = 3042, 2937, 2840, 1601, 1505, 1483, 1225, 1158, 1126, 838, 579 cm^{-1} ; HRMS (ESI): m/z : calcd for $\text{C}_{33}\text{H}_{23}\text{OF}_4\text{I}$: 638.0724 $[M]^+$; found: 638.0726.

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- [20] The use of a catalytic amount of TMSCl (30 mol%) gave 74% yield of **2** after 0.5 h.
- [21] TMSOTMS was obtained during the FeCl₃-catalyzed azidation that used TMS ethers, reported in our recent paper. See reference [12].
- [22] The Friedel–Crafts benzylation with benzylic alcohols as substrates produced dibenzyl ethers by a self-condensation reaction, which was accompanied by the generation of water (see references [2b,f]). The resulting dibenzyl ethers relatively easily underwent hydrolysis to the starting benzylic alcohols under the reaction conditions. Hence, the efficiency of the Friedel–Crafts benzylation was rather reduced.
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