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Access to "Friedel–Crafts-Restricted" *tert*-Alkyl Aromatics by Activation/Methylation of Tertiary Benzylic Alcohols

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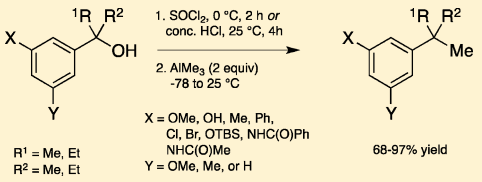
Supporting Information

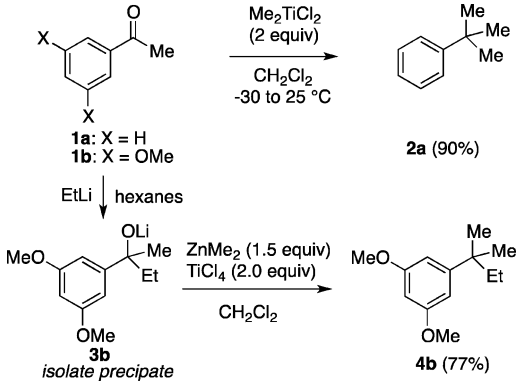
ABSTRACT: Herein we describe a two-step protocol to prepare *m-tert*-alkylbenzenes. The appropriate tertiary benzylic alcohols are activated with $SOCl_2$ or concentrated HCl and then treated with trimethylaluminum, affording the desired products in 68–97% yields (22 examples). This reaction sequence is successful in the presence of a variety of functional groups, including acid-sensitive and Lewis-basic groups. In addition to *t*-Bu groups, 1,1-dimethylpropyl and 1-ethyl-1-methylpropyl groups can also be installed using this method.



INTRODUCTION

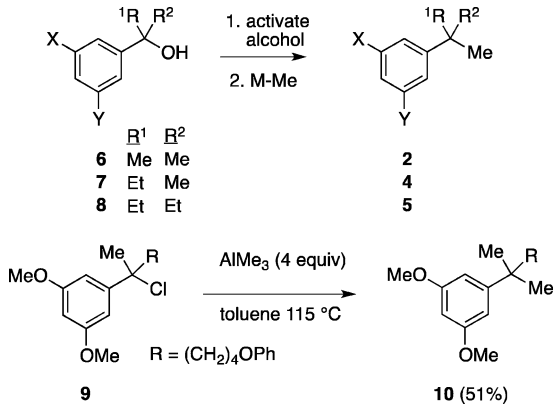
Because of intrinsic substituent directing effects, compounds bearing *tert*-alkyl groups on benzene rings *meta*- to *ortho*-, *para*-directing substituents are challenging to prepare. In the course of our efforts to develop malaria mosquito-selective acetylcholinesterase inhibitors,[1] we required such compounds, which we term "Friedel–Crafts-restricted" *tert*-alkylbenzenes. Traditional strategies to prepare these compounds use "temporary" *o*- or *p*-hydroxy or amino groups to direct Friedel–Crafts[2] or other electrophilic aromatic substitution reactions;[3,4] subsequent removal of the temporary directing group then unveils the desired *meta*-substitution pattern. We sought a more direct route that would benefit from the large number of commercially available *meta*-substituted benzoic acids and acetophenones. One approach that appeared especially promising was Reetz's conversion of aryl ketone **1a** to the corresponding *tert*-alkyl benzene **2a** by treatment with Me_2TiCl_2 (Scheme 1).[5]

Scheme 1. Published Reetz Strategies[5,6] To Convert Aromatic Ketones to *tert*-Alkyl-Substituted Aromatics



Two years earlier, Reetz disclosed a potentially more general strategy:[6] addition of EtLi to **1b**, isolation of the lithium alkoxide **3b**, and final treatment with $ZnMe_2/TiCl_4$ afforded **4b**, which incorporated two different alkyl groups to give a 1,1-dimethylpropyl substituent. These remarkable transformations are worthy of wider application. We envisioned a related strategy starting from tertiary benzylic alcohols: in situ activation of the alcohol followed by treatment with the appropriate methyl organometallic (M-Me) would afford aromatics featuring various *tert*-alkyl groups (Scheme 2).

Scheme 2. Planned Transformation of Tertiary Benzylic Alcohols (6–8) to *tert*-Alkylbenzenes (2, 4, 5) and Precedent from Makriyannis (9)[7]



Although $ZnMe_2$ is known to react with tertiary alkyl and benzylic chlorides,[8] $AlMe_3$ is 20-fold cheaper on a molar basis. Successful use of this reagent (40–51% yield) was demonstrated by Makriyannis in two examples, one of which (**9**)[7] is shown in Scheme 2. Shishido also applied this method to the preparation of CF_3-containing *t*-Bu isosteres from the corresponding tertiary benzylic chlorides.[9] These literature precedents encouraged us to investigate the substrate scope of

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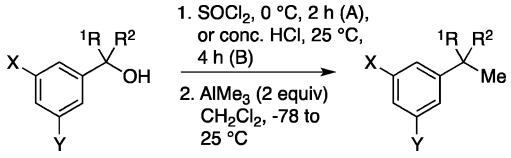
Table 1. Transformation of Tertiary Benzylic Alcohols to *tert*-Alkylbenzenes



entry	compd	X	Y	R^1	R^2	product	activation method	yield (%)
1	**6b**	OMe	OMe	Me	Me	**2b**	A	88
2	**6c**	OMe	H	Me	Me	**2c**	A	93
3	**6d**	OH	H	Me	Me	**2d**	A	83
4	**6e**	Me	Me	Me	Me	**2e**	A	85
5	**6f**	Me	H	Me	Me	**2f**	A	85
6	**6g**	Ph	H	Me	Me	**2g**	A	70
7	**6h**	Cl	H	Me	Me	**2h**	A	93
8	**6i**	Br	H	Me	Me	**2i**	A	81
9	**6j**	OTBS	H	Me	Me	**2j**	A	93
10	**6k**	NHC(O)Ph	H	Me	Me	**2k**	A	97[b]
11	**6l**	NHC(O)Me	H	Me	Me	**2l**	A	89
12	**7b**	OMe	OMe	Et	Me	**4b**	A	68
13	**7c**	OMe	H	Et	Me	**4c**	A	94
14	**7d**	OH	H	Et	Me	**4d**	A	70
15	**7f**	Me	H	Et	Me	**4f**	A	94
16	**7h**	Cl	H	Et	Me	**4h**	A	78[a] (87:13)
17						**4h**	B	95
18	**7i**	Br	H	Et	Me	**4i**	A	72[a] (85:15)
19						**4i**	B	95
20	**8c**	OMe	H	Et	Et	**5c**	A	97
21	**8d**	OH	H	Et	Et	**5d**	A	92
22	**8f**	Me	H	Et	Et	**5f**	A	80
23	**8g**	Ph	H	Et	Et	**5g**	A	71
24	**8h**	Cl	H	Et	Et	**5h**	A	90[a] (56:44)
25						**5h**	B	95[a] (96:4)

[a]Weight recovery of a mixture of the intended methylated and unwanted elimination product (**12h**, **12i**, and **13h**, respectively) following chromatography; the mole ratio (^{1}H NMR) is given in parentheses. [b]Methylation was slow at room temperature; reaction was carried out in 1,2-dichloroethane at 60 °C.

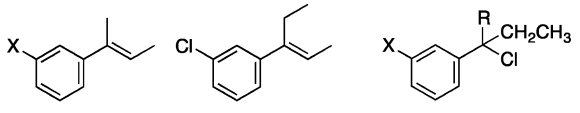
this transformation and determine if much milder conditions could be employed.

RESULTS AND DISCUSSION

Standard synthetic methods were employed to prepare a range of tertiary benzylic alcohols from commercially available acetophenones and carboxylic acids. These compounds (**6b–l**, **7b–d,f,h,i**, and **8c,d,f–h**) varied in the identity of the *meta*-substituents (X and Y) and carbinol alkyl groups (R^1 and R^2, Table 1).

Reactions of dimethylarylcarbinols **6** were explored first. Each tertiary alcohol was activated by treatment with neat $SOCl_2$ (2.5 equiv, 0 °C, activation method A);[10] after 2 h, the residual $SOCl_2$ was removed in vacuo at 0 °C. The residue (whose chemical identity is discussed below) was dissolved in CH_2Cl_2 and cooled to −78 °C, at which point $AlMe_3$ (2 equiv) was added. After being warmed to room temperature overnight, the reaction was cooled to 0 °C and quenched with 1 M HCl. Aqueous workup and chromatographic purification yielded *tert*-butylbenzenes **2b–l** in 68–97% yield (Table 1, entries 1–11). Thus, the reaction sequence tolerates a variety of *meta*-substituents (OMe, OH, Me, Ph, Cl, and Br), including acid-sensitive groups (TBS-protected phenol, **6j**) and amides (**6k**, **6l**). The acid sensitivity of the TBS ether in **2j** was confirmed by its quantitative conversion to **2d** following exposure (1 h) to 1 M HCl in MeOH. Note that moderately strong Lewis base functionalities (OH, OMe, OTBS, NHC(O)R) are compatible with this protocol. With regard to reaction temperature, most reactions of the activated alcohols with $AlMe_3$ were found to proceed at or below room temperature, in contrast to the high-temperature conditions reported for conversion of **9** (Scheme 2, 115 °C).[7] Only in one case was it necessary to perform the reaction at elevated temperature (60 °C, amido-functionalized substrate **6k**). On the basis of our reactions with similar substrates **6b** and **7b**, it seems likely that the conversion of **9** would also proceed well at room temperature.

Reaction of ethylmethylarylcarbinols **7** was nearly as successful as that of dimethylarylcarbinols **6**. As seen in Table 1, entries 12–15, moderate to excellent yields of the desired 1,1-dimethylpropyl derivatives **4** were obtained. Unfortunately, in the case of *m*-Cl and *m*-Br carbinols **7h** and **7i**, the desired products **4h** and **4i** were contaminated with 13–15 mol % of the chromatographically inseparable elimination products (**12h** and **12i**, entries 16 and 18, respectively).



12h: X = Cl
12i: X = Br

13h

14h: X = Cl, R = CH_3
14i: X = Br, R = CH_3
15h: X = Cl, R = CH_2CH_3

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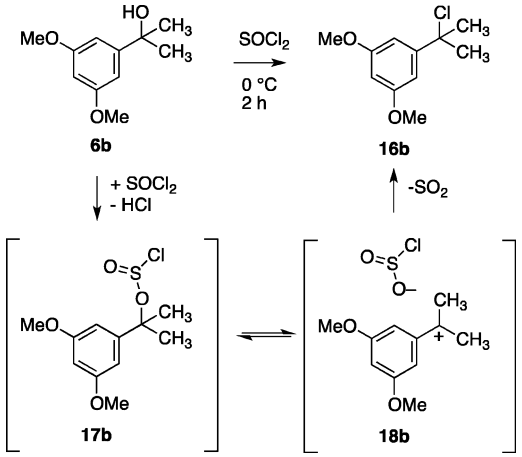
To assess whether this product mixture arose in part from some difficulty in the alcohol activation step, tertiary benzylic chlorides **14h** and **14i** were prepared by treating the corresponding carbinols with concentrated HCl, followed by extractive workup (activation method B). Reaction of **14h** and **14i** with $AlMe_3$ at room temperature afforded the desired products **4h** and **4i** in 95% yield with no trace of the elimination products **12h** and **12i** (Table 1, entries 17 and 19). Finally, reactions of diethylaryl carbinols **8** (Table 1, entries 20–23) gave moderate to excellent yields of 1-ethyl-1-methylpropylbenzenes **5**. Elimination was again seen as a competing side reaction in the *m*-Cl substrate **8h**, giving 44 mol % of **13h** (Table 1, entry 24). Suspecting that some deficiency in the alcohol activation was again responsible, the tertiary benzylic chloride **15h** was prepared. As we had seen for reaction of **14h** and **14i**, reaction of **15h** with $AlMe_3$ gave an excellent yield (93% overall) with only a trace (4%) of the elimination product **13h** (Table 1, entry 25). Our analysis of the chloride intermediate **15h** suggests that the small amount of elimination observed occurred prior to addition of $AlMe_3$.

Given the divergent methylation results seen for **7h**, **7i**, and **8h** using activation method A (treatment with $SOCl_2$) and activation method B (treatment with concd HCl), we investigated the chemical identity of the $SOCl_2$ activation products of two substrates. Treatment of **6b** with $SOCl_2$ at 0 °C for 2 h, followed by rapid concentration in vacuo at 0 °C gave a product that was identical by ^1H and ^{13}C NMR spectroscopy to tertiary benzylic chloride **16b** formed by treatment of **6b** with concentrated HCl. Presumably **6b** quickly reacts with $SOCl_2$ to form the chlorosulfite intermediate **17b**, which then ionizes to a tertiary benzylic carbocation/chlorosulfite ion pair **18b**, ejects SO_2, and recombines to form chloride **16b** (Scheme 3).[11,12]

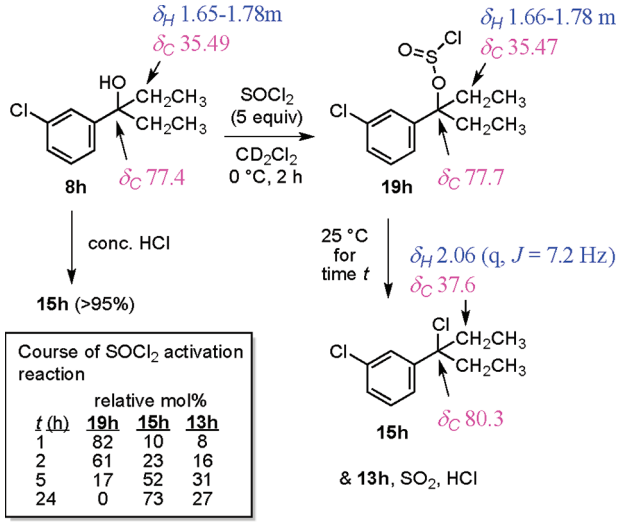
Scheme 3. Rapid Conversion of 6b to 16b on Treatment with $SOCl_2$ at 0 °C and Possible Mechanism



However, treatment of **8h** under the same conditions did not lead to chloride **15h** but rather to an intermediate we tentatively identified as the chlorosulfite **19h**. This compound was nearly identical by ^1H NMR spectroscopy ($CDCl_3$) to starting alcohol **8h**, but was much less polar on TLC, with an R_f very similar to that of tertiary benzylic chloride **15h**. To confirm our conclusion we carried out an NMR study of the reaction of **8h** with $SOCl_2$ (5 equiv) in CD_2Cl_2 (Scheme 4).

After 2 h at 0 °C, the NMR sample tube was allowed to reach room temperature, and ^1H and ^{13}C NMR spectra of the

Scheme 4. Course of the Reaction of 8h with $SOCl_2$; NMR Chemical Shifts Were Measured in CD_2Cl_2



Course of $SOCl_2$ activation reaction

	relative mol%		
t (h)	**19h**	**15h**	**13h**
1	82	10	8
2	61	23	16
5	17	52	31
24	0	73	27

reaction were taken at 1, 2, 5, and 24 h. After 1 h at room temperature, some conversion of **19h** to the chloride **15h** and elimination product **13h** was evident. After 5 h at room temperature, only 17% of the chlorosulfite **19h** remained, giving predominantly chloride **15h** (52%) and elimination product **13h** (31%). At 24 h, all of the chlorosulfite **19h** had been converted to chloride **15h** and elimination product **13h**. Olah has previously noted the tendency of tertiary chlorosulfites to eliminate.[13]

Why would the chlorosulfite **19h** be slower than **17b** in its conversion to the chloride? We note that based on σ_m values, the *m*-Cl substituent (σ_m = 0.37) is more electron-withdrawing than the *m*-OMe substitutent (σ_m = 0.10).[14] If one *m*-Cl substituent is more electron-withdrawing than two *m*-OMe groups, the ionization of the chlorosulfite **19h** would be slower than ionization of **17b**. Thus, it seems likely that the $SOCl_2$ activation of *m*-Cl and *m*-Br ethylmethylaryl carbinols **7h** and **7i** (Br σ_m = 0.37)[14] also progressed only to the chlorosulfite stage after 2 h at 0 °C. The inferior results for these substrates (and **8h**) using the $SOCl_2$ activation method A could be rationalized if tertiary benzylic chlorosulfites are more prone to elimination on treatment with $AlMe_3$ than are the corresponding tertiary benzylic chlorides. As a final control experiment, alcohol **7h** (without any prior activation) was treated with $AlMe_3$ under the standard conditions. As expected, **7h** was recovered and no methylated product **4h** or elimination product **12h** was formed.

To further assess the scope of this methylation protocol we examined two substrate classes expected to be problematic. First, if benzylic carbocation intermediates are formed during both the chlorination and methylation steps, then pyridyldialkylcarbinols might prove challenging substrates, due to the strongly electron-withdrawing nature of the pyridine ring. Hammett σ values for 2-, 3-, and 4-pyridyl rings are reported as 0.71, 0.55, and 0.94, respectively,[15] and we chose to explore reactions of 2-pyridyl tertiary carbinol **20a** and 3-pyridyl tertiary carbinol **20b**. As expected, methylation of these substrates was difficult and required elevated temperatures. Activation of 3-pyridyl substrate **20b** using method A, followed by treatment with $AlMe_3$ at 80 °C in 1,2-dichloroethane, gave the desired methylated product **21b**, but contaminated with 21 mol % of chromatographically inseparable elimination product **22b**.

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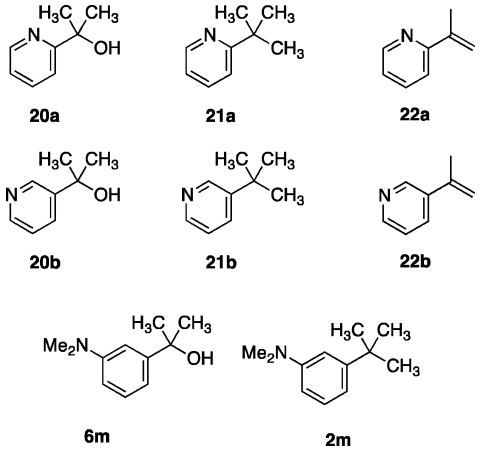
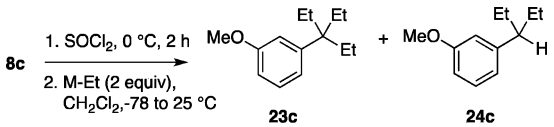


Application of this protocol to **20a** was less successful, giving **21a** and the chromatographically inseparable elimination product **22a** in a 9:91 ratio. Activation of **20a** and **20b** by conversion to the corresponding mesylates[9] was also explored but did not provide improved outcomes. Thus, neither pyridin-2-yl- nor pyridin-3-yldialkylcarbinols (e.g., **20a**, **b**) qualify as good substrates for this reaction. Second, very strong electron-releasing substitutents might be problematic, because they could facilitate self-reaction of the benzylic chloride intermediate. Since hydroxy, alkoxy, silyloxy, and amido substituents were well-tolerated (Table 1, entries 1−3, 9−14, 20, and 21), we explored dimethylamino-substituted aryldimethyl carbinol **6m**. Regardless of the alcohol activation method employed and conditions used for reaction with $AlMe_3$, weight recoveries were very low (<20% of theoretical yield of **2m**). ^1H NMR spectroscopy of the reaction mixture suggested that oligomerization of the activated alcohol had occurred.

The protocol described above allows installation of *tert*-alkyl groups containing at least one methyl group. Installation of a 1,1-diethylpropyl (i.e., triethylcarbinyl) substituent would necessitate use of an ethyl organometallic. To attempt such a transformation, diethylarylcarbinol **8c** was activated with $SOCl_2$ and treated with various ethyl organometallics. Carbinol **8c** was chosen for the high yield observed in its $SOCl_2$-activation/methylation to **5c** (Table 1, entry 17). Use of $AlEt_3$ in the standard protocol did give the intended product **23c** but contaminated with the chromatographically inseparable **24c** (Table 2, entry 1).

Table 2. Attempted Synthesis of 1,1-Diethylpropyl-Substituted Benzene 23c



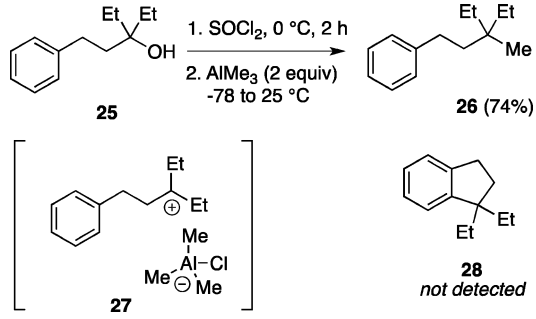
entry	MEt	23c/24c[a]	wt recovery[b] (%)
1	$AlEt_3$	77:23	94
2	$ClAlEt_2$	9:91	72
3	BEt_3	no reaction	NA[c]
4	$ZnEt_2$	46:54	96

[a]Measured by ^1H NMR spectroscopy. [b]Based on the stoichiometry indicated by ^1H NMR spectroscopy. [c]Recovered tertiary benzylic chloride derived from **8c**.

It seemed likely that **24c** arose from β-hydride delivery, as Miller suggested in his studies of the reaction of $AlEt_3$ with aliphatic and benzylic halides.[16] We thus investigated other ethyl organometallics. Interestingly, reaction with $ClAlEt_2$ gave a 9:91 mixture in favor of the hydride addition product **24c** (Table 2, entry 2). Reaction with BEt_3 did not proceed: neither **23c** or **24c** was detected, and the tertiary benzylic chloride derived from **8c** was recovered. Finally, use of $ZnEt_2$ in the protocol gave a nearly 1:1 mixture of **23c** and **24c**. Thus an effective protocol to install the 1,1-diethylpropyl group by ethylation of a diethylaryl carbinol remains elusive.

To conclude our study, we explored reaction of tertiary alcohol **25**, bearing a tethered benzene ring, that was designed to probe the mechanism of the reaction of tertiary chlorides with $AlMe_3$ (Scheme 5).

Scheme 5. Methylation of Tertiary Aliphatic Alcohol 25



In Miller's studies of the reaction of $AlEt_3$ with primary, secondary, tertiary, and benzylic chlorides, it was proposed that the observed product mixtures and relative rates were consistent with the formation of ion-pair intermediates.[16] In this paradigm, the tertiary chloride derived from **25** would react with $AlMe_3$ to form ion-pair intermediate **27**, which could undergo two fates: methyl transfer to **26** or intramolecular Friedel−Crafts alkylation leading to **28**. In the event, **26** was isolated in 74% yield, and Friedel−Crafts product **28** was not detected. Thus, ion pair **27** appears to have a very short lifetime.

CONCLUSION

In closing, based on the work of Reetz,[5,6] Makriyannis,[7] and Shishido,[9] we developed a mild two-step method to place *tert*-alkyl groups on aromatic rings *meta*- to *ortho*, *para*-directing groups. Tertiary benzylic alcohols are activated by treatment with $SOCl_2$ (method A) or concentrated HCl (method B) and in most cases were found to react quickly with $AlMe_3$ at or below room temperature. In addition to *t*-butyl, the 1,1-dimethylpropyl(ethyldimethylcarbinyl) and 1-ethyl-1-methylpropyl(diethylmethylcarbinyl) substitutents were successfully installed. Eleven different aromatic substitution patterns were examined, giving a total of 22 examples in 68−97% yields (Table 1). For substrates bearing moderate electron-withdrawing groups (e.g., *m*-Cl or *m*-Br), activation method B was found to give the best results. However, elimination remained a persistent problem for strongly electron deficient substrates (e.g., pyridin-2-yl and pyridin-3-yl substrates **20a**,**b**). Substrates bearing very strong electron donors (e.g., NMe_2, **6m**) also proved problematic.

EXPERIMENTAL SECTION

General Methods. High-resolution mass spectra (ESI and APCI) were recorded on a time-of-flight LC/MS instrument. Because of their demonstrated lability, characterization of tertiary benzylic chlorides or

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chlorosulfites by HRMS or elemental analysis was not attempted. ^{1}H NMR spectra of known *tert*-alkylbenzenes (i.e., those not listed below) synthesized in this work are provided in the Supporting Information to document purity. Known dimethylarylcarbinols **6b−i,l,m** and **20a,b** were prepared in 89−97% yield by the addition of lithium trimethylmagnesate to the corresponding acetophenones in THF.[17] Known ethylmethylaryl carbinols **7c**, **7d**, **7f**, **7h**, and **7i** were prepared in 87−98% yields by Zn^{2+}-catalyzed addition of EtMgCl to the corresponding acetophenones;[18] ethylmethylaryl carbinol **7b**[19] was prepared in 75% yield by addition of EtMgCl to 3,5-dimethoxyacetophenone. Known diethylarylcarbinols **8c**, **8d**, **8f**, and **8h** and diethylcarbinol **25** were prepared in 86−94% overall yield by conversion of the corresponding benzoic acids to the methyl ester, followed by reaction with EtMgBr (2.5 equiv) in THF.[20] In all cases, analytical data of synthesized known compounds matched that of the literature.

General Procedure for $SOCl_2$ Activation (Method A)/Methylation of Tertiary Benzylic Carbinols. *1-tert-Butyl-3-methoxybenzene (**2c**).*[21] A dry Schlenk flask (50 mL) equipped with a rubber septum and a magnetic stirbar was charged with 2-(3-methoxyphenyl)propan-2-ol (**6c**, 400 mg, 2.41 mmol), placed in an ice bath, and purged with nitrogen. Thionyl chloride (438 mg, 6.02 mmol) was added via syringe, and the reaction was allowed to stir at 0 °C for 2 h; in some cases up to 1 mL of CH_2Cl_2 was added to improve mixing. Volatiles were then removed at 0 °C under reduced pressure. The residue was diluted with dichloromethane (8 mL) and cooled to −78 °C in a dry ice/acetone bath. Trimethylaluminum (2.0 M in hexanes, 2.4 mL, 4.8 mmol) was injected into the flask, allowed to stir for 3 h at −78 °C, and then stirred overnight at room temperature. The reaction was then cooled to 0 °C and cautiously quenched by the addition of HCl (1 M, 10 mL). Following extraction with dichloromethane (3 × 25 mL), the organic layers were combined, washed with brine, dried with anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified on silica gel (5: 1 hexane/ethyl acetate) to yield a colorless oil (368 mg, 93% yield). ^{1}H and ^{13}C NMR spectral data matched those reported in the literature.

*N-(3-tert-Butylphenyl)benzamide (**2k**).* This compound was prepared from *N*-(3-(2-hydroxypropan-2-yl)phenyl)benzamide (**6k**, 17.4 mg, 0.068 mmol) using the procedure described above for **2c**, with a minor modification: following activation via method A, the reaction with $AlMe_3$ was conducted at 60 °C using 1,2-dichloroethane as solvent. Following aqueous workup, the residue was purified on silica gel (5: 1 hexane/ethyl acetate) to yield **2k** as a white solid (16.7 mg, 97% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−7.87 (m, 3H), 7.63 (s, 1H), 7.54−7.45 (m, 4H), 7.32−7.25 (m, 1H), 7.28−7.18 (m, 1H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.73, 152.30, 137.65, 135.11, 131.75, 128.75, 126.99, 121.67, 117.51, 117.37, 34.69, 31.29; HRMS (APCI) 254.1539 calcd for $C_{17}H_{19}NO$ $[M + H]^+$, found 254.1535 (−1.56 ppm).

*1-Methoxy-3-tert-pentylbenzene (**4c**).* This compound was prepared from **7c** (199 mg, 1.10 mmol) using the method A procedure for **2c**, providing 185 mg of **4c** (94% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (t, J = 8.0 Hz, 1H), 6.96 − 6.91 (m, 1H), 6.89 (t, J = 2.0 Hz, 1H), 6.72 (dd, J = 8.0, 2.0 Hz, 1H), 3.81 (s, 3H), 1.63 (q, J = 7.4 Hz, 2H), 1.27 (s, 6H), 0.68 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 151.5, 129.0, 118.71, 118.70, 112.9, 109.9, 55.3, 38.1, 37.0, 28.6, 9.3; HRMS (APCI) 179.1430 calcd for $C_{12}H_{19}O$ $[M + H]^+$, found 179.1429 (−0.79 ppm).

General Procedure for HCl Activation (Method B)/Methylation of Tertiary Benzylic Carbinols. *Chloro-3-tert-pentylbenzene (**4h**).* A flask was charged with 2-(3-chlorophenyl)butan-2-ol (**7h**, 202 mg, 1.09 mmol), to which was added concentrated hydrochloric acid (1.5 mL). The mixture was stirred at room temperature for 3 h prior to being extracted with CH_2Cl_2 (3 × 3 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the corresponding chloride **14h** (containing 2 mol % elimination product **12 h**) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (t, J = 2.0 Hz, 1H), 7.44 (dt, J = 7.7, 1.8 Hz, 1H), 7.26−7.32 (overlapped, 2H), 2.13−2.24 (m, 2H), 1.95 (s, 3H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1, 134.1, 129.4, 127.5, 126.5, 124.3, 73.7, 39.4, 31.2, 9.7. To a solution of the chloride, prepared from the above step, in dichloromethane (7 mL) at −78 °C was added trimethylaluminum in hexanes (2.0 M in hexanes, 1.4 mL, 2.8 mmol), and the reaction mixture was stirred at −78 °C for 3 h, and allowed to warm to room temperature overnight. The reaction was quenched cautiously at 0 °C with HCl (1 M) and extracted with dichloromethane (20 mL × 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to provide methylated product **4h** as a colorless oil (185 mg, 93% for two steps; contains 2 mol % elimination product **12h**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, J = 2.0 Hz, 1H), 7.27−7.22 (overlapped, 2H), 7.16 (dt, J = 7.1, 2.0 Hz, 1H), 1.65 (q, J = 7.4 Hz, 2H), 1.29 (s, 6H), 0.70 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 134.0, 129.2, 126.4, 125.5, 124.2, 38.1, 36.8, 28.3, 9.1; HRMS (EI) calcd for $C_{11}H_{15}Cl$ 182.0862, found 182.0860 (−0.2 mmu, −1.3 ppm).

*Bromo-3-tert-pentylbenzene (**4i**).* This compound (129 mg, oil) was prepared in 95% yield from alcohol **7i** (145 mg, 0.63 mmol) by the method B procedure described above for **4h**. Spectral data for chloride **14i** (containing 2 mol % elimination **12i**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (t, J = 2.0 Hz, 1H), 7.48 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.43 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 2.12−2.23 (m, 2H), 1.94 (s, 3H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 130.4, 129.7, 129.3, 124.8, 122.4, 73.6, 39.4, 31.2, 9.7. Spectral data for **4i**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (t, J = 1.9 Hz, 1H), 7.32 (ddd, J = 7.8, 1.9, 1.0 Hz, 1H), 7.26 (ddd, J = 7.8, 1.9, 1.0 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 1.64 (q, J = 7.5 Hz, 2H), 1.28 (s, 6H), 0.70 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 129.5, 129.3, 128.4, 124.7, 122.4, 38.1, 36.8, 28.3, 9.1. Anal. Calcd for $C_{11}H_{15}Br$: C, 58.17; H, 6.66. Found: C, 58.41; H, 6.87.

*1-Methoxy-3-(3-methylpentan-3-yl)benzene (**5c**).* This compound was prepared from **8c** (260 mg, 1.34 mmol) using the method A procedure for **2c**, providing **5c** (249 mg, 95% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, J = 8.0 Hz, 1H), 6.91 − 6.86 (m, 1H), 6.84 (t, J = 2.2 Hz, 1H), 6.71 (dd, J = 8.0, 2.2 Hz, 1H), 3.81 (s, 3H), 1.72 (dq, J = 14.9, 7.5 Hz, 2H), 1.54 (dq, J = 14.9, 7.5 Hz, 2H), 1.22 (s, 3H), 0.67 (t, J = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 149.7, 128.8, 119.4, 113.6, 109.7, 55.2, 41.5, 35.4, 22.9, 8.9; HRMS (APCI) 193.1587 calcd for $C_{13}H_{21}O$ $[M + H]^+$, found 193.1581 (−3.23 ppm).

*3-(3-Methylpentan-3-yl)phenol (**5d**).* This compound was prepared from **8d** (102 mg, 0.566 mmol) using the method A procedure for **2c**, providing **5d** (93 mg, 92%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (t, J = 8.0 Hz, 1H), 6.86 (ddd, J = 8.0, 1.7, 0.9 Hz, 1H), 6.81 − 6.72 (m, 1H), 6.64 (ddd, J = 8.0, 1.7, 0.9 Hz, 1H), 4.64 (s, 1H), 1.74−1.66 (m, 2H), 1.58 − 1.48 (m, 2H), 1.21 (s, 3H), 0.67 (t, J = 7.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 150.2, 129.1, 119.5, 114.0, 112.2, 41.4, 35.4, 22.8, 8.8; HRMS (APCI) 177.1285 calcd for $C_{12}H_{17}O$ $[M - H]^-$, found 177.1278 (−4.03 ppm).

*1-Methyl-3-(3-methylpentan-3-yl)benzene (**5f**).* This compound was prepared from **8f** (333 mg, 1.87 mmol) using the method A procedure for **2c**, providing **5f** (263 mg, 80%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 − 7.15 (m, 1H), 7.11 − 7.05 (m, 2H), 6.98 (d, J = 7.3 Hz, 1H), 2.35 (s, 3H), 1.73 (dq, J = 14.8, 7.5 Hz, 2H), 1.55 (dq, J = 14.8, 7.5 Hz, 2H), 1.23 (s, 3H), 0.67 (t, J = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 137.3, 127.8, 127.5, 126.0, 123.8, 41.24, 35.3, 23.0, 21.9, 8.9; HRMS (APCI) 370.3468 calcd for $C_{26}H_{44}N$ $[2M + NH_4]^+$, found 370.3496 (7.35 ppm).

*3-(3-Methylpentan-3-yl)-1,1′-biphenyl (**5g**).* This compound was prepared from **8g** (253 mg, 1.05 mmol) using the method A procedure for **2c**, providing **5g** (170 mg, 71%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.69 (m, 2H), 7.59 (t, 1H, J = 1.7 Hz), 7.36−7.52 (m, 5H), 7.34−7.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 142.1, 140.9, 128.8, 128.4, 127.4, 127.2, 125.83, 125.80, 124.3, 41.5, 35.4, 23.1; HRMS (APCI) calcd for $C_{18}H_{22}$ $[M]^+$ 238.1722, found 238.1716 (−2.52 ppm).

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*3-(1-Chloro-3-(3-methylpentan-3-yl)benzene (**5h**).* This compound (28 mg, oil) was prepared in 93% yield from alcohol **8h** (30 mg, 0.15 mmol) via the corresponding chloride using the method B procedure as described for **4h**. Spectral data for chloride **15h** (contains 3 mol % elimination product **13h**) is given below in the section describing NMR analysis of the reaction of **8h** with $SOCl_2$. Spectral data for **5h** (contains 3 mol % elimination product **13h**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, J = 7.8, 2.2 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.15−7.18 (overlapped, 2H), 1.69−1.76 (m, 2H), 1.53−1.60 (m, 2H), 1.24 (s, 3H), 0.68 (t, J = 7.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 134.0, 129.1, 127.0, 125.4, 124.9, 41.5, 35.2, 22.7, 8.7. Anal. Calcd for $C_{12}H_{17}Cl$: C, 73.27; H, 8.71. Found: C, 73.17; H, 8.69.

*2-(3-((tert-Butyldimethylsilyl)oxy)phenyl)propan-2-ol (**6j**).* This compound (710 mg) was prepared as a colorless oil in 89% yield by the addition of lithium trimethylmagnesate[17] to 1-(3-((*tert*-butyldimethylsilyl)oxy)phenyl) ethanone (750 mg, 3 mmol) in THF, using the procedure outlined below for **6k**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (t, J = 8.0 Hz, 1H), 7.07 (ddd, J = 8.0, 1.8, 1.0 Hz, 1H), 6.99 (t, J = 2.1 Hz, 1H), 6.73 (ddd, J = 8.0, 2.5, 1.0 Hz, 1H), 1.57 (s, 6H), 1.00 (s, 9H), 0.22 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 151.2, 129.3, 118.4, 117.4, 116.7, 72.6, 31.9, 25.9, 18.9, −4.2; HRMS (ESI) 249.1675 calcd for $C_{15}H_{25}OSi$ $[M - H_2O + H]^+$ found 249.1655 (−5.52 ppm).

*N-(3-(2-Hydroxypropan-2-yl)phenyl)benzamide (**6k**).* Under nitrogen, a dry 50 mL Schlenk flask equipped with a magnetic stirbar was charged with 15 mL of dry THF and then placed in an ice bath. Methylmagnesium chloride (3 M in ether, 0.84 mL, 2.51 mmol) and methyllithium (3 M in ether, 0.84 mL, 2.51 mmol) were added. After the mixture was stirred at 0 °C for 30 min, a solution of *N*-(3-acetylphenyl)benzamide (200 mg, 0.84 mmol) in 10 mL of dry THF was added. After 1 h, the ice bath was removed, and the reaction was allowed to stir at room temperature overnight. The reaction was cooled to 0 °C, quenched with saturated $NaHCO_3$ solution, and extracted with ethyl acetate (3 × 15 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, and filtered, and the solvent was evaporated under reduced pressure. The residue was purified on silica gel (1:1 hexane/ethyl acetate) to yield **6k** as a white solid (178 mg, 84% yield): ^{1}H NMR (400 MHz, CD_3OD) δ 7.93−7.91 (m, 2H), 7.79 (s, 1H), 7.59−7.48 (m, 4H), 7.31−7.29 (m, 2H), 1.55 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 167.50, 150.36, 138.11, 134.91, 131.42, 128.19, 128.05, 127.18, 120.57, 119.06, 117.45, 71.52, 30.47; HRMS (APCI) calcd for $C_{16}H_{17}NO_2Na$ 279.1184 $[M + Na]^+$, found 279.1179 (−1.9 ppm).

*3-([1,1′-Biphenyl]-3-yl)pentan-3-ol (**8g**).* A modification of Hartmann's procedure[20] was used: methyl 3-phenylbenzoate (499 mg, 2.35 mmol) was dissolved in 5 mL of THF and cooled to −78 °C. EtMgCl (2 M in THF, 3.5 mL, 7.5 mmol) was added and the mixture stirred for 5 h at this temperature, at which point TLC indicated completion. The reaction was quenched by the addition of saturated aq NH_4Cl and warmed to room temperature. Following aqueous workup and column chromatography (5% EtOAc in hexanes), **8g** was obtained as a colorless oil (560 mg, 94%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.72−7.74 (m, 2H), 7.40−7.56 (m, 6H), 2.14 (br s, 1H), 1.93−2.03 (m, 4H), 0.92 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.6, 141.7, 141.0, 128.9, 128.6, 127.5, 127.4, 125.3, 124.7, 124.6, 77.7, 35.2, 8.1; HRMS (APCI) calcd for $C_{17}H_{19}$ $[M - OH]^+$ 223.1481 found 223.1498 (+7.62 ppm).

*3-tert-Butylpyridine (**21b**) and 3-(Prop-1-en-2-yl)pyridine (**22b**).* The method A procedure for **2c** described above was applied to 2-(pyridin-3-yl)propan-2-ol (**20b**, 137 mg, 1 mmol) using 1,2-dichloroethane in place of dichloromethane as solvent and elevating the reaction temperature to 85 °C. This reaction was quenched with 10% $NaHCO_3$ solution, and the resulting mixture was extracted with dichloromethane. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated to afford an inseparable 79:21 mixture of the desired compound **21b** and the undesired elimination product **22b** as a light yellow oil (122 mg, 89% mass recovery).

*Analytical data for 3-tert-butylpyridine (**21b**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, J = 2.6 Hz, 1H), 8.43 (br d, J = 4.8 Hz, 1H), 7.71 (ddd, J = 8.1, 2.6, 1.5 Hz, 1H), 7.25 (dd, J = 5.9, 4.8 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7, 146.2, 133.5, 123.2, 114.4, 31.0.

*Analytical data for 3-(prop-1-en-2-yl)pyridine (**22b**):* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (br.s, 1H), 8.51 (m, 1H), 7.74 (br.d, J = 8.1 Hz, 1H), 7.26 (dd, J = 8.1, 3.0 Hz, 1H), 5.42 (s, 1H), 5.19 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 147.2, 146.8, 140.9, 137.4, 133.6, 123.8, 21.5.

*(3-Ethyl-3-methylpentyl)benzene (**26**).* This compound was prepared from **25** (250 mg, 1.26 mmol) using the method A procedure for **2c**, providing **26** (178 mg, 74%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.37 (m, 2H), 7.23−7.27 (m, 3H), 2.56−2.60 (m, 2H), 1.53−1.57 (m, 2H), 1.38 (q, 4H, J = 7.9 Hz), 0.90−0.94 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 128.4, 125.6, 41.0, 35.3, 31.1, 30.4, 24.1, 8.1. Anal. Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found: C, 88.50; H, 11.66.

Investigation of $SOCl_2$ Activation of Tertiary Benzylic Carbinols. *1-(2-Chloropropan-2-yl)-3,5-dimethoxybenzene (**16b**).*[22] This compound was prepared in 98% yield from alcohol **6b** and concentrated HCl using the same procedure described for the synthesis of chloride **14h** en route to methylated product **4h**. Treatment of **6b** with $SOCl_2$ for 2 h at 0 °C followed by concentration in vacuo gave the identical compound: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, J = 2.2 Hz, 2H), 6.42 (t, J = 2.2 Hz, 1H), 3.84 (s, 6H), 1.99 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 148.7, 104.2, 99.0, 69.5, 55.4, 34.2.

*NMR Study of Reaction of **8h** with $SOCl_2$ in CD_2Cl_2.* Alcohol **8h** (30 mg, 0.15 mmol) was dissolved in 750 μL of CD_2Cl_2, transferred to an NMR tube, and placed in an ice bath. After 5 min, $SOCl_2$ (60 uL, 98 mg, 0.81 mmol) was added, and the tube was agitated to achieve mixing. After 2 h, the tube was removed from the ice bath and allowed to warm to room temperature. ^{1}H and ^{13}C NMR spectra were taken after 1, 2, 5, and 25 h at room temperature. Mole ratios of chlorosulfite **19h**, chloride **15h**, and alkene **13h** were determined by integration (see Scheme 4).

*3-(3-Chlorophenyl)pentan-3-ol (**8h**):* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.32 (t, J = 2.1 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 7.16 (dt, J = 7.8, 1.6 Hz, 1H), 7.12 (ddd, J = 7.4, 2.2, 1.6 Hz, 1H), 1.65−1.78 (m, 4H), 0.65 (t, J = 7.4 Hz, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 148.7, 134.3, 129.6, 126.6, 126.3, 124.3, 77.4, 35.5, 7.9.

*(E)-1-Chloro-3-(pent-2-en-3-yl)benzene (**13h**).* Resonances deduced from examination of a 73:27 mixture of **15h** and **13h**: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.22−7.23 (m, 1H), 7.13−7.15 (m, 3H), 5.66 (q, J = 6.9 Hz, 1H), 2.41 (q, J = 7.6 Hz, 2H), 1.71 (d, J = 6.9 Hz, 3H), 0.88 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 145.6, 141.6, 134.3, 129.9, 126.70, 126.67, 124.8, 123.9, 22.8, 14.2, 13.4.

*1-Chloro-3-(3-chloropentan-3-yl)benzene (**15h**, Contains 3 mol % of Elimination Product **13h**):* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.42 (t, J = 2.0 Hz, 1H), 7.28 (ddd, J = 7.8, 1.9, 1.3 Hz, 1H), 7.21 (dt, J = 7.8, 0.5 Hz, 1H), 7.17 (ddd, J = 7.9, 2.0, 1.3 Hz, 1H), 2.06 (q, J = 7.2 Hz, 4H), 0.78 (t, J = 7.2 Hz, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 145.6, 134.4, 129.7, 127.49, 127.47, 125.3, 80.3, 37.6, 9.3.

*3-(3-Chlorophenyl)pentan-3-yl sulfochloridite (chlorosulfite **19h**):* ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.32 (t, J = 2.1 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 7.16 (dt, J = 7.8, 1.6 Hz, 1H), 7.12 (ddd, J = 7.4, 2.1, 1.6 Hz, 1H), 1.66−1.78 (m, 4H), 0.65 (t, J = 7.4 Hz, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 148.7, 134.3, 129. 9, 126.7, 126.3, 124.3, 77.7, 35.5, 8.0. Note: although the pyramidal geometry at sulfur should render the CH_2 and CH_3 carbons diastereotopic, we could only resolve a single CH_2 resonance and a single CH_3 resonance in the ^{13}C NMR spectrum at 125 MHz.

Attempted Activation/Ethylation of Diethylarylcarbinol 8c. *1-(3-Ethylpentan-3-yl)-3-methoxybenzene (**23c**).* The method A procedure for **2c** described above was applied to diethylarylcarbinol **8c** (255 mg, 1.31 mmol) using triethylaluminum (1.0 M in hexanes, 2.6 mL, 2.6 mmol) in place of trimethylaluminum. This procedure afforded an inseparable 77:23 mixture of the desired compound **23c** and the undesired hydride addition product **21c** as a light yellow oil (245 mg, 94%).

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Analytical data for **23c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, 1H, J = 8 Hz), 6.94 (t, 1H, J = 8 Hz), 6.87 (s, 1H), 6.73 (t, 1H, J = 8 Hz), 4.20 (s, 3H), 1.65 (q, 6H, J = 7.0 Hz), 0.65 (t, 9H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 149.4, 128.6, 119.6, 113.9, 109.5, 55.1, 43.9, 28.8, 8.1; HRMS (APCI) calcd for $C_{14}H_{23}O$ 207.1743 $[M + H]^+$, found 207.1738 (−2.75 ppm).

*1-Methoxy-3-(pentan-3-yl)benzene (**24c**).* The method A procedure for **2c** described above was applied to diethylarylcarbinol **8c** (246 mg, 1.26 mmol), using diethylaluminum chloride (1 M in hexanes, 3.16 mL, 3.16 mmol) in place of trimethylaluminum. This procedure afforded a 9:91 ratio of **23c** and **24c** as a colorless oil (228 mg, 71%). Analytical data for **21c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.212 (t, 1H, J = 7.7 Hz), 6.71−6.76 (m, 3H), 3.80 (s, 3H), 2.27−2.31 (m, 1H), 1.66−1.74 (m, 2H), 1.51−1.58 (m, 2H), 0.78 (t, 3H, J = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 147.7, 129.0, 120.4, 113.8, 110.7, 55.1, 49.8, 29.3, 12.3; HRMS calcd for $C_{12}H_{19}O$ 179.1430 $[M + H]^+$, found 179.1439 (+4.97 ppm).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra (^{1}H and ^{13}C) of all new compounds and ^{1}H NMR spectra of known compounds described in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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