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Selective sp^3 C–H Bond Activation Based on a Carbocation Relay: Friedel–Crafts Reaction with Alkanes as the Alkylating Component

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A highly efficient and selective intramolecular Friedel–Crafts reaction of 3-methylbutyl or 4-methylpentyl-substituted aromatics has been developed using a carbocation relay strategy through selective sp^3 C–H bond activation, providing a facile and cost-effective approach for the construction of benzocyclic compounds. A variety of 1,1-dimethylindane and naphthalene derivatives have been prepared from very simple starting materials in good yields with high selectivity. The present strategy has provided a new example of a Friedel–Crafts reaction with alkanes as the alkylating component and constitutes a convenient approach to selective C–H bond activation and functionalization of alkane derivatives.

Introduction

Carbocations are electron-deficient species that are extremely important intermediates in organic reactions.[1] For example, it is well-known that carbocations are the key intermediate in Friedel–Crafts (F–C) alkylations; alkyl halides, alkenes, and alcohols usually serve as the alkylating reagents to form the carbocations under the catalysis of various acids.[2] Although research into carbocations has been developing for over 100 years, the field is still continuing to be of major significance in both academia and industry.[3] Recently, research on C–H bond activation has attracted increasing interest.[4] However, most of the reported work in this area has focused on C–H bond activation of aromatics,[4] and only very few studies have centered on activation of the alkane C–H bond.[5] On the other hand, the isoparaffin-olefin alkylation catalyzed by various super acids is a very important process for producing high-octane alkylates in the petrochemical industry;[6] in this process an intermediate *i*-C_8^+ cation abstracts a hydride from isobutane to give excellent yields of products and the formed *tert*-butyl cation keeps the catalytic cycle going.[6a] In the present work, we would like to report a new example of a Friedel–Crafts reaction with alkane as the alkylating component that operates through sp^3 C–H bond activation and involves a carbocation relay strategy.

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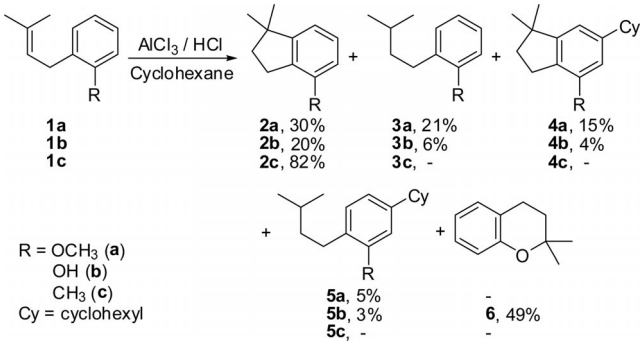
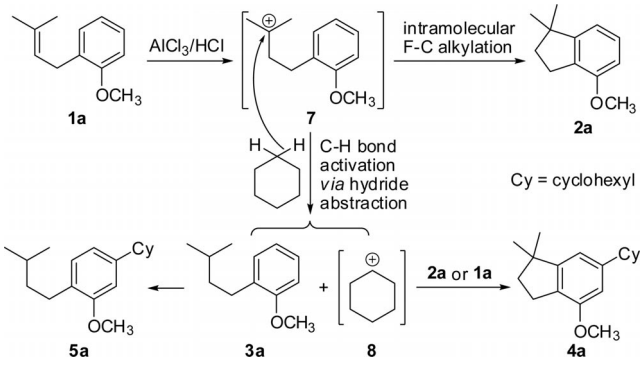
Results and Discussion

As a synthetic route to the key intermediate, 4-methoxy-1,1-dimethylindane (**2a**), which is used in the synthesis of analogous anti-HIV molecules,[7] an intramolecular F–C cyclization of 1-methoxy-2-(3-methyl-2-butenyl)benzene (**1a**) in the presence of a Lewis acid was designed. The F–C reaction of **1a** was carried out under the catalysis of $AlCl_3$/HCl in cyclohexane at room temperature (Scheme 1). As expected, the normal intramolecular F–C product **2a** was isolated in 30% yield. It is interesting to note that the reductive product 1-methoxy-2-(3-methylbutyl)benzene (**3a**), and cyclohexyl-substituted products 6-cyclohexyl-4-methoxy-1,1-dimethylindane (**4a**) and 4-cyclohexyl-2-methoxy-1-(3-methylbutyl)benzene (**5a**) were simultaneously obtained in yields of 21, 15, and 5%, respectively. The formation of these by-products clearly indicates that the cyclohexyl cation **8** must be involved in the course of reaction. However, because neither cyclohexene nor cyclohexyl halide (or alcohol) is present in the reaction system, it can be deduced that the formation of the cyclohexyl cation **8** originates from the reaction solvent cyclohexane, either by direct C–H activation with $AlCl_3$/HCl or by hydride abstraction with an alternative cation. The pathway for direct C–H bond activation of cyclohexane by $AlCl_3$/HCl was easily excluded on the basis of experimental facts that no reaction occurred for **2a** or **3a** in cyclohexane in the absence of olefins such as cyclohexene or **1a**. Therefore, the formation of cyclohexyl cation **8** must be due to hydride abstraction by cation **7** from a cyclohexane molecule. As depicted in Scheme 2, the olefin **1a** can be easily protonated in the presence of $AlCl_3$/HCl to form carbocation **7**, which might either immediately undergo an intramolecular F–C alkylation to afford the expected cyclization product **2a**, or proceed to hydride abstraction from solvent cyclohexane to afford the reductive product **3a** and the cyclohexyl cation **8**.

Further intermolecular F–C alkylation of **8** with **3a** and **2a**/**1a** yields **5a** and **4a**, respectively (Scheme 2). On the basis of the experimental results mentioned above, it can be concluded that, in the present reaction system, a carbocation relay has occurred that involves intermolecular hydride abstraction from an sp^3 C–H bond by a cation, providing an interesting and potentially useful strategy for C–H bond activation.



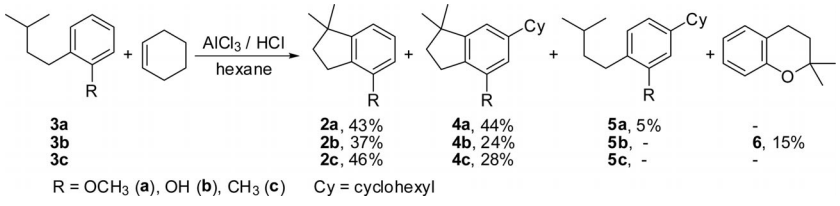
Scheme 1. F–C reaction of the 1-substituted 2-(3-methyl-2-butenyl)benzenes **1a**–**c**.



Scheme 2. Proposed reaction pathway for the formation of unexpected products **3a**, **4a**, and **5a** in the F–C reaction of **1a**.

To investigate the generality of the above reaction system, the F–C reactions of substrates 2-(3-methyl-2-butenyl)-phenol (**1b**) and 1-methyl-2-(3-methyl-2-butenyl)benzene (**1c**) were also carried out under the same experimental conditions. As shown in Scheme 1, the reaction of **1c** affords the intramolecular F–C product 1,1,4-trimethylindane (**2c**) selectively in 82% isolated yield and no other products were observed. On the other hand, the reaction of **1b** furnished the O-cyclized 2,2-dimethylchromane (**6**) as the major product (49%), the normal cyclized F–C product 4-hydroxy-1,1-dimethylindane (**2b**) in 20% yield, and the reductive product 2-(3-methylbutyl)phenol (**3b**) in 6% yield. Moreover, two cyclohexyl-substituted products, 6-cyclohexyl-4-hydroxy-1,1-dimethylindane (**4b**) and 5-cyclohexyl-2-(3-methylbutyl)phenol (**5b**) were also isolated, albeit with low yields (4 and 3%, respectively). In the ^1H NMR spectrum of **5b**, the presence of two doublets and one singlet at the aromatic field implies that either the C4 or C5 position of the phenyl ring was substituted by the cyclohexyl group. To identify the exact position of the cyclohexyl group on the phenyl ring in product **5b**, HMBC spectra were further determined. The proton of the phenyl ring at δ = 7.02 ppm (doublet) could be correlated to C-1′ at δ = 27.42 ppm in the ^{13}C NMR spectrum, which confirms that the cyclohexyl group in **5b** is situated at the C5-position of the phenyl ring. The HMBC spectra of **4b** clearly show that cyclohexyl substitution occurs at the *meta*-position relative to the hydroxyl group. The formation of products **3b**–**5b** in the reaction of **1b** again supports the involvement of cyclohexyl cation **8** in the reaction system, and this result suggests the possibility of using alkanes as the alkylating reagent in the Friedel–Crafts alkylation through a cation relay strategy.

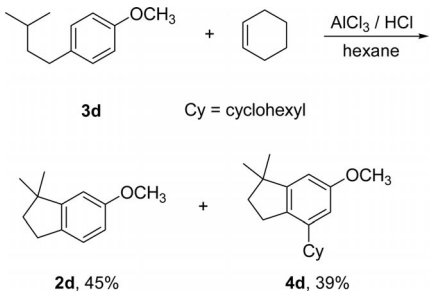
The observed phenomena of hydride abstraction by the cation (Schemes 1 and 2) prompted us to carry out an intramolecular F–C reaction of alkane substrate, 1-methoxy-2-(3-methylbutyl)benzene (**3a**), by activation of a sp^3 C–H bond through a cation relay. The formation of cation **8** was realized by reaction of readily available cyclohexene with $AlCl_3$/HCl in hexane at room temperature. The cation **8**, generated in situ, was expected to abstract a hydride from the alkyl aromatic substrate **3a** to form the more stable tertiary carbocation **7** and generate the reductive product cyclohexane. As shown in Scheme 3, under these experimental conditions, two intramolecular cyclization products, 4-methoxy-1,1-dimethylindane (**2a**) and 6-cyclohexyl-4-methoxy-1,1-dimethylindane (**4a**), were obtained in 43 and 44% isolated yields, respectively. In contrast, the intermolecular 'normal' alkylation product **5a** was only afforded in 5% yield. Incidentally, purification of the products by flash silica gel chromatography could be problematic because TLC analysis of compounds **3a**/**5a** reveals almost the same R_f values, and products **2a**/**4a** also exhibit very similar polarities. After initial attempts to separate the products by HPLC failed, the demethylation reactions were carried out with BBr_3 in CH_2Cl_2 in good yields. Fortunately, the two demethylated derivatives could be separated from the mixtures.



Scheme 3. F–C reaction of 1-substituted 2-(3-methylbutyl)benzenes **3a**–**c** by activation of an sp^3 C–H bond through a cation relay.

Under the reaction conditions described above, the F–C reaction of analogous alkyl aromatics **3b**–**c** was further investigated (Scheme 3). The cyclization of **3b** gave the product 4-hydroxy-1,1-dimethylindane (**2b**), 6-cyclohexyl-4-hydroxy-1,1-dimethylindane (**4b**), and 2,2-dimethylchroman (**6**) in the yields of 37, 24, and 15%, respectively. Similarly, the F–C reaction of **3c** afforded the cyclic product **2c** and 6-cyclohexyl-1,1,4-trimethylindane (**4c**) in yields of 46 and 28%, respectively.

In addition, the effect of a methoxy group on the phenyl ring on the product distribution was also examined by taking 1-methoxy-4-(3-methylbutyl)benzene (**3d**) as the substrate (Scheme 4). Under identical experimental conditions to those described above, the reaction of **3d** in the presence of cyclohexene afforded two cyclized products, 6-methoxy-1,1-dimethylindane (**2d**) and 4-cyclohexyl-6-methoxy-1,1-dimethylindane (**4d**), as an inseparable mixture in 45 and 39% yields (determined by ^{1}H NMR spectroscopic analysis), respectively.

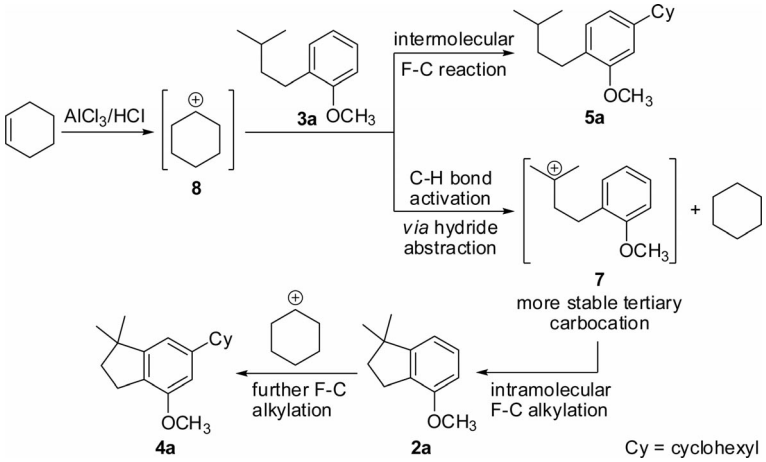


Scheme 4. F–C reaction of 1-methoxy-4-(3-methylbutyl)benzene (**3d**) by activation of an sp^3 C–H bond through a cation relay.

On the basis of the experimental results described above, the reaction pathway of **3a** is outlined in Scheme 5. It is clear that the formation of cyclized products **2a** and **4a** can be attributed to the C–H bond activation of **3a** by the cyclohexyl cation **8** under the catalysis of $AlCl_3$/HCl. In fact, none of the products were observed for the reaction of **3a** in cyclohexane without cyclohexene under otherwise identical reaction conditions. This experiment further supports the involvement of cyclohexene and its related carbocation **8**. The relatively unstable secondary cyclohexyl cation **8** is inclined to be transformed into a more stable tertiary carbocation **7** and regenerate cyclohexane. The resultant carbocation **7** subsequently undergoes intramolecular F–C alkylation to afford cyclization product **2a** and then further intermolecular F–C reaction of **2a** with cyclohexyl cation **8**.

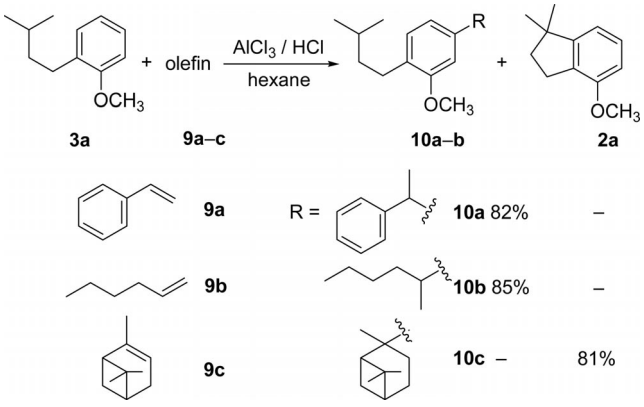
The total yields of the intramolecular F–C reaction of **3a**–**d** using the cation relay strategy can be as high as 61–87%, indicating the advantageous features of the present strategy. These examples have provided solid support for the mechanism of hydride abstraction proposed in Scheme 5, which demonstrates that not only haloalkanes, alkenes, and alkanols, but also alkanes can be utilized as efficient alkylating partners in the F–C reactions.

As shown in Schemes 3 and 4, although the F–C reaction of alkane substrates **3a**–**d** catalyzed by $AlCl_3$/HCl, in the presence of cyclohexene, were able to give the cyclization products **2a**–**d** and **4a**–**d** with total yields of 61–87% on the basis of a cation relay strategy, the intermolecular F–C reaction of alkane substrates **3** or the further F–C reaction of primary intramolecular F–C cyclization product **2** with cyclohexyl cation **8** is still a problematic issue in terms of the chemoselectivity of the reaction. Therefore, in situ generation of a primordial carbocation with matched stability and reactivity is particularly important for a good balance between the carbocation relay with the alkane substrate and intermolecular electrophilic reactivity towards aromatics. Accordingly, we further optimized the olefin additives used to generate the primordial carbocation to improve the chemoselectivity of the reaction. As shown in Scheme 6, the addition of either styrene (**9a**) or 1-hexene (**9b**) to the reaction of **3a** afforded only intermolecular F–C adducts **10a** and **10b** (82 and 85%, respectively) without formation of



Scheme 5. Proposed reaction pathway for the F–C reaction of an alkane substrate **3a** by activation of its sp^3 C–H bond through a cation relay of **8**.

any of the expected intramolecular F–C cyclization product **2a** by a carbocation relay. It was pleasing to find that (+)-α-pinene (**9c**) was able to work well as the primordial carbocation precursor in the reaction, affording the intramolecular F–C cyclization product **2a** as the sole product, albeit in 37% isolated yield with 50% recovery of **3a**. The yield of **2a** was substantially improved to 81% with complete conversion of **3a** by treating the reaction mixture at room temperature for 17 h then at reflux temperature for 5 h. This result clearly indicates that the primordial carbocation from α-pinene (**9c**) can effectively activate the tertiary C–H bond of **3a** to realize the carbocation relay and consequently furnish the intramolecular F–C reaction. The formation of intermolecular F–C product **10c** was completely inhibited, probably due to the steric hindrance and relatively low reactivity of the carbocation formed by α-pinene (**9c**) towards phenyl rings.

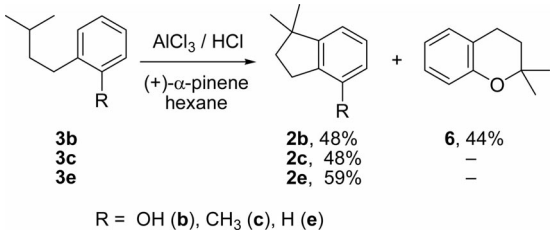


Scheme 6. The influence of olefin additives on the chemoselectivity of the reaction.

In the present catalytic system, the acid plays a key role in both the catalytic activity and selectivity. A variety of acids, including $AlCl_3$/HCl, $AlCl_3$, $HCl_{(g)}$, CH_3SO_3H, TsOH, conc. H_2SO_4, CF_3CO_2H, CF_3SO_3H, and $Sc(OTf)_3$ were examined for the reaction of **3a** in the presence of α-pinene (**9c**) as the primordial carbocation precursor. It was found that, besides $AlCl_3$/HCl, only CF_3SO_3H was effective, affording the expected intramolecular F–C product (**2a**) in 60% yield.

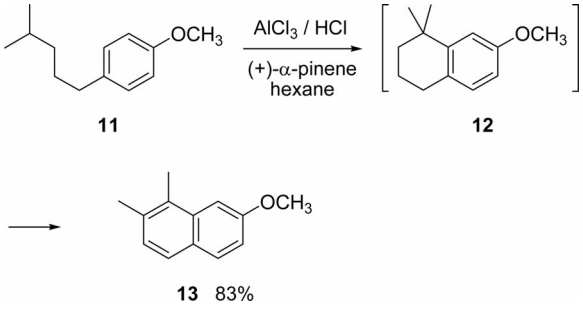
The influence of the amount of acid used and of the workup conditions on the yields of product **2a** were also investigated (Table 1). It was found that **2a** was obtained in satisfactory yields (60–81%) when stoichiometric amounts of $AlCl_3$/HCl or CF_3SO_3H were applied (Table 1, entries 1 and 4). Notably, the yields of **2a** greatly diminished (<32%) when the acid loading was decreased to 0.5 equiv. and below (Table 1, entries 2, 5, and 6). The workup protocol was also crucial for the isolated yield of **2a**; treating the reaction mixture with $NaHCO_3$ (aq.) at 0 °C was found to be better than treatment with H_2O at room temperature (Table 1, entries 4 and 3).

Under the optimized reaction conditions [$AlCl_3$/HCl as the catalyst and (+)-α-pinene as the olefin additives for the generation of primordial carbocation], the intramolecular F–C reaction of various alkyl-substituted benzenes **3b**, **3c**, and **3e** were carried out to investigate the substituent effect, affording the corresponding 1,1-dimethylindane derivatives **2b**, **2c**, and **2e** in moderate yields without the formation of intermolecular products (Scheme 7). The relatively low yields of **2c** and **2e** were due to the volatile properties of their starting materials **3c** and **3e**.



Scheme 7. F–C reaction of 1-substituted 2-(3-methylbutyl)benzenes **3b**, **3c**, and **3e** under the optimized conditions.

Finally, 1-methoxy-4-(4-methylpentyl)benzene (**11**), having a six-carbon side chain, was examined as a substrate for the F–C reaction to prepare the 1,2,3,4-tetrahydronaphthalene derivative under the optimized reaction conditions



Scheme 8. F–C reaction of 1-methoxy-4-(4-methylpentyl)benzene (**11**) under the optimized conditions.

Table 1. The influence of reaction conditions and workup on the yields of F–C reactions of the substrate **3a** with (+)-α-pinene (2 equiv.) catalyzed by $AlCl_3$ or CF_3SO_3H.

Entry	Acid	Acid loading [equiv.]	Workup	Isolated yield of **2a** [%]
1	$AlCl_3$/HCl	1–3	20% HCl	79–81
2	$AlCl_3$/HCl	0.5	20% HCl	32
3	CF_3SO_3H	1	H_2O/r.t.	32
4	CF_3SO_3H	1	$NaHCO_3$ (aq.)/0	60
5	CF_3SO_3H	0.2	$NaHCO_3$ (aq.)/0	27
6	$CF_3SO_3H/AlCl_3$	0.1–0.05/0.1	–	ND

(Scheme 8). Surprisingly, only the naphthalene derivative **13** was isolated in 83% yield, and no expected product **12** was obtained at all. It is assumed that compound **12** was probably generated as the primary product and then converted into the final, stable product **13** after undergoing a methyl shift and aromatization. When the reaction was carried out under an argon atmosphere, a compound with molecular ionic peak at *m*/*z* = 190 $[M]^+$ corresponding to the intermediate **12** was indeed observed by GC–MS analysis. This experimental evidence confirmed the assumption discussed above.

In summary, a highly efficient and selective intramolecular Friedel–Crafts reaction of 3-methylbutyl-substituted aromatics has been developed by using a carbocation relay strategy through selective sp^3 C–H bond activation, providing a facile and cost-effective approach to the construction of benzocyclic compounds. The present strategy has provided a new example of a Friedel–Crafts reaction with alkanes as the alkylating component and represents a convenient approach to selective C–H bond activation and functionalization of alkane derivatives. Further studies on the extension and application of these reactions are underway.

Experimental Section

General Methods: Melting points were measured with an SGW X-4 apparatus. Reactions were monitored by analytical thin-layer chromatography (TLC) on 0.2 mm silica-gel plates, and visualization of the developed chromatogram was enabled by UV absorbance or by using an ethanolic phosphomolybdic acid dip. Flash chromatography was performed using silica gel (300–400 mesh) with the indicated solvent system. ^{1}H NMR spectra were recorded with a Varian Mercury 300, Varian 400 or Spect 500 spectrometer, HMBC and ^{13}C NMR spectra were recorded with a Drx 400 or Spect 500 spectrometer; the solvent used was $CDCl_3$ unless indicated. All chemical shifts are reported in ppm on the δ scale relative to an internal standard of TMS (^{1}H) or the signals of the solvent (^{13}C). Mass spectra were recorded with an Agilent 5973N MSD (EI) instrument. High-resolution mass spectra (HR-MS) were recorded with a Waters Micromass GCT spectrometer.

Typical Procedure for Friedel–Crafts Reaction of 3-Methylbutenyl-Substituted Aromatics: Cyclization was carried out in a three-necked 250-mL flask equipped with an HCl(g) inlet tube and an air condenser fitted with a $CaCl_2$ drying tube. A cyclohexane solution of **1a** (0.15 mL, 140 mg, 0.79 mmol) was added dropwise to a stirred suspension of powdered aluminum chloride (120 mg, 0.9 mmol) in cyclohexane (25 mL) at r.t. in an atmosphere of HCl(g). The reaction mixture was stirred for 3 h and then quenched by slow addition of 1 N hydrochloric acid. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried with anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (petroleum ether) to provide **3a** as a colorless oil (29 mg, 21%), **5a** as a clear oil (11 mg, 5%), **2a** as a clear oil (40 mg, 30%), and **4a** as a white powder (31 mg, 15%).

1-Methoxy-2-(3-methylbutyl)benzene (3a):[8] ^{1}H NMR (400 MHz): δ = 0.92–0.95 (m, 6 H, CH_3), 1.43–1.47 (m, 2 H, 2′-H), 1.56–1.61 (m, 1 H, 3′-H), 2.59–2.63 (m, 2 H, 1′-H), 3.81 (s, 3 H, CH_3O), 6.82–6.89 (m, 2 H, 4-H, 6-H), 7.12–7.22 (m, 2 H, 3-H, 5-H) ppm.

4-Cyclohexyl-2-methoxy-1-(3-methylbutyl)benzene (5a): ^{1}H NMR (300 MHz): δ = 0.93–0.97 (m, 6 H, CH_3 of isopentyl), 1.24–1.48 (m, 7 H, 2′-H of isopentyl, 5 H of cyclohexyl), 1.54–1.61 (m, 1 H, 3′-H of isopentyl), 1.82–1.90 (m, 5 H of cyclohexyl), 2.37–2.52 (m, 1 H, 1′-H of cyclohexyl), 2.55–2.63 (m, 2 H, 1′-H of isopentyl), 3.81 (s, 3 H, CH_3O), 6.69 (d, *J* = 7.5 Hz, 1 H, 3-H), 6.71–6.74 (m, 1 H, 5-H), 7.04 (d, *J* = 7.2 Hz, 1 H, 6-H) ppm. MS (EI): *m*/*z* (%) = 260 (44.06) $[M]^+$, 203 (100), 91 (21.51), 121 (28.76), 204 (16.88), 41 (12.17), 115 (11.25), 117 (10.02). HR-MS: calcd. for $C_{18}H_{28}O$ 260.2140; found 260.2141.

4-Methoxy-1,1-dimethylindane (2a):[9] ^{1}H NMR (400 MHz): δ = 1.25 (s, 6 H, 1-CH_3), 1.92 (t, *J* = 7.2 Hz, 2 H, 2-H), 2.84 (t, *J* = 7.2 Hz, 2 H, 3-H), 3.82 (s, 3 H, CH_3O), 6.67 (d, *J* = 8.0 Hz, 1 H, 5-H), 6.77 (d, *J* = 7.6 Hz, 1 H, 7-H), 7.15–7.19 (m, 1 H, 6-H) ppm.

6-Cyclohexyl-4-methoxy-1,1-dimethylindane (4a): M.p. 65–67 °C. ^{1}H NMR (300 MHz): δ = 1.25 (s, 6 H, 1-CH_3), 1.32–1.51 (m, 5 H of cyclohexyl), 1.73–1.93 (m, 7 H, 2-H, 5 H of cyclohexyl), 2.46–2.54 (m, 1 H, 1′-H of cyclohexyl), 2.79 (t, *J* = 7.2 Hz, 2 H, 3-H), 3.83 (s, 3 H, CH_3O), 6.54 (s, 1 H, 5-H), 6.63 (s, 1 H, 7-H) ppm. MS (EI): *m*/*z* (%) = 258 (42.74) $[M]^+$, 243 (100), 161 (21.51), 121 (19.50), 244 (19.43), 55 (11.64), 128 (9.65), 259 (9.19), 129 (7.90). HR-MS: calcd. for $C_{18}H_{26}O$ 258.1984; found 258.1980.

2-(3-Methylbutyl)phenol (3b):[10] Colorless oil. ^{1}H NMR (300 MHz): δ = 0.94–0.96 (m, 6 H, 1-CH_3), 1.47–1.53 (m, 2 H, 2′-H), 1.60–1.63 (m, 1 H, 3′-H), 2.59–2.63 (m, 2 H, 1′-H), 5.55 (br., 1 H, OH), 6.75–6.77 (m, 1 H, 6-H), 6.84–6.86 (m, 1 H, 4-H), 7.03–7.12 (m, 2 H, 3-H, 5-H) ppm.

5-Cyclohexyl-2-(3-methylbutyl)phenol (5b): Colorless oil. ^{1}H NMR (500 MHz): δ = 0.90–0.98 (m, 6 H, CH_3), 1.24–1.38 (m, 5 H of cyclohexyl), 1.45–1.51 (m, 2 H, 2′-H), 1.54–1.61 (m, 1 H, 3′-H), 1.71–1.85 (m, 5 H of cyclohexyl), 2.37–2.41 (m, 1 H, 1′-H of cyclohexyl), 2.54–2.58 (m, 2 H, 1′-H), 3.69 (br., 1 H, OH), 6.60 (s, 1 H, 6-H), 6.70–6.73 (m, 1 H, 4-H), 7.02 (d, *J* = 7.6 Hz, 1 H, 3-H) ppm. ^{13}C NMR (125 MHz): δ = 153.15, 147.36, 129.70, 126.00, 119.24, 113.72, 77.28, 77.02, 76.77, 44.07, 39.03, 34.44, 27.97, 27.42, 26.90, 26.18, 22.55 ppm. MS (EI): *m*/*z* (%) = 246 (45.11) $[M]^+$, 189 (100), 107 (22.1), 190 (16.48), 133 (10.34), 247 (8.83), 176 (7.21), 108 (6.61). HR-MS: calcd. for $C_{17}H_{26}O$ 246.1984; found 246.1979.

4-Hydroxy-1,1-dimethylindane (2b): White prismatic crystals; m.p. 88–89 °C (ref.[11] 88–88.5 °C). ^{1}H NMR (400 MHz): δ = 1.24 (s, 6 H, 1-CH_3), 1.96 (t, *J* = 6.9 Hz, 2 H, 2-H), 2.82 (t, *J* = 6.9 Hz, 2 H, 3-H), 4.55 (br., 1 H, OH), 6.63 (d, *J* = 7.5 Hz, 1 H, 5-H), 6.75 (d, *J* = 7.5 Hz, 1 H, 7-H), 7.09 (t, *J* = 7.8 Hz, 1 H, 6-H) ppm.

6-Cyclohexyl-4-hydroxy-1,1-dimethylindane (4b): White power; m.p. 74–76 °C. ^{1}H NMR (400 MHz): δ = 1.24 (s, 6 H, 1-CH_3), 1.35–1.57 (m, 5 H of cyclohexyl), 1.71–1.88 (m, 5 H of cyclohexyl), 1.94 (t, *J* = 6.9 Hz, 2 H, 2-H), 2.46–2.54 (m, 1′-H of cyclohexyl), 2.76 (t, *J* = 6.9 Hz, 2 H, 3-H), 4.48 (br., 1 H, OH), 6.50 (s, 1 H, 5-H), 6.60 (s, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz): δ = 154.92, 151.33, 149.02, 125.09, 111.30, 77.34, 77.02, 76.71, 44.66, 44.49, 41.45, 34.67, 28.61, 26.96, 26.20, 25.64 ppm. MS (EI): *m*/*z* (%) = 244 (35.42) $[M]^+$, 229 (100), 147 (30.55), 230 (19.99), 55 (15.67), 159 (15.00), 145 (14.62), 83 (12.58). HR-MS: calcd. for $C_{17}H_{24}O$ 244.1827; found 244.1826.

2,2-Dimethylchroman (6):[12] Colorless oil. ^{1}H NMR (400 MHz): δ = 1.33 (s, 6 H, 2-CH_3), 1.79 (t, *J* = 7.6 Hz, 2 H, 3-H), 2.77 (t, *J* = 7.6 Hz, 2 H, 4-H), 6.76–6.83 (m, 2 H, 6-H, 8-H), 7.04–7.09 (m, 2 H, 5-H, 7-H) ppm.

1,1,4-Trimethylindane (2c):[13] Colorless oil. ^{1}H NMR (400 MHz): δ = 1.24 (s, 6 H, 1-CH_3), 1.98–1.93 (m, 2 H, 2-H), 2.24 (s, 3 H, 4-CH_3), 2.80 (t, J = 7.42 Hz, 2 H, 3-H), 6.94–6.97 (m, 2 H, 7-H, 5-H), 7.06–7.11 (m, 1 H, 6-H) ppm.

Typical Procedure for Friedel–Crafts Reaction of 3-Methylbutyl-Substituted Aromatics: Cyclization was carried out in a three-necked 250-mL flask equipped with an HCl(g) inlet tube and an air condenser fitted with a $CaCl_2$ drying tube. A hexane solution of **3a** (0.17 mL, 150 mg, 0.84 mmol) and cyclohexene (0.16 g, 0.2 mL, 2.0 mmol) were added dropwise to a stirred suspension of powdered aluminum chloride (120 mg, 0.9 mmol) in hexane (25 mL) at r.t. in an atmosphere of HCl(g). The reaction mixture was stirred for 19 h and then quenched by slow addition of 1 N hydrochloric acid. The organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried with anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (petroleum ether) to provide **5a** as a colorless oil (10 mg, 5%), **2a** as a colorless oil (65 mg, 43%), and **4a** as a white powder (95 mg, 44%).

6-Cyclohexyl-1,1,4-trimethylindane (4c): Colorless oil. ^{1}H NMR (400 MHz): δ = 1.24 (s, 6 H, 1-CH_3), 1.30–1.49 (m, 5 H of cyclohexyl), 1.81–1.93 (m, 7 H, 2-H, 5H of cyclohexyl), 2.23 (s, 3 H, 4-CH_3), 2.54–2.56 (m, 1 H, 1′-H of cyclohexyl), 2.76 (t, J = 7.2 Hz, 2 H, 3-H), 6.83 (s, 2 H, 5-H, 7-H) ppm. MS (EI): m/z (%) = 242 (53.59) $[M]^+$, 241 (100), 243 (72.06), 43 (69.35), 55 (67.79), 41 (66.24), 244 (19.96), 44 (9.52). HR-MS: calcd. for $C_{18}H_{26}$ 242.2035; found 242.2030.

6-Methoxy-1,1-dimethylindane (2d):[14] Colorless oil. ^{1}H NMR (400 MHz): δ = 1.26 (s, 6 H, 1-CH_3), 1.91–1.94 (m, 2 H, 2-H), 2.79–2.84 (m, 2 H, 3-H), 3.80 (s, 3 H, CH_3O), 6.68–6.71 (m, 2 H, 5-H, 7-H), 7.08–7.11 (m, 1 H, 4-H) ppm.

4-Cyclohexyl-6-methoxy-1,1-dimethylindane (4d): Colorless oil. ^{1}H NMR (400 MHz): δ = 1.24 (s, 6 H, 1-CH_3), 1.32–1.49 (m, 5 H of cyclohexyl), 1.74–1.92 (m, 7 H, 2-H, 5H of cyclohexyl), 2.23 (s, 3 H, 4-CH_3), 2.51–2.55 (m, 1 H, 1′-H of cyclohexyl), 2.79 (t, J = 7.2 Hz, 2 H, 3-H), 3.83 (s, 3 H, CH_3O), 6.53 (s, 1 H, 7-H), 6.60 (s, 1 H, 5-H) ppm. MS (EI): m/z (%) = 258 (52.46) $[M]^+$, 243 (100), 174 (30.24), 175 (29.98), 159 (23.32), 244 (19.16), 161 (16.74), 128 (13.74). HR-MS: calcd. for $C_{18}H_{26}O$ 258.1984; found 258.1988.

1-(3-Methylbutyl)-2-methoxy-4-(1-phenylethyl)benzene (10a): Colorless oil. ^{1}H NMR (300 MHz): δ = 0.93 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 1.43–1.56 (m, 2 H, 2′-H), 1.59–1.64 (m, 4 H, 3′-H, CH_3 of phenylethyl), 2.53–2.64 (m, 2 H, 1′-H), 3.81 (s, 3 H, CH_3O), 4.03–4.11 (m, 1 H, 1′-H of phenylethyl), 6.67 (d, J = 8.4 Hz, 1 H, 5-H), 6.91 (d, J = 8.1 Hz, 1 H, 6-H), 6.97 (s, 1 H, 3-H), 7.15–7.30 (m, 5 H, phenyl of phenylethyl) ppm. MS (EI): m/z (%) = 282 (44.53) $[M]^+$, 267 (100), 268 (21.78), 225 (19.80), 165 (16.89), 105 (14.55), 211 (13.29), 283 (10.08). HR-MS: calcd. for $C_{20}H_{26}O$ 282.1984; found 282.1988.

4-(2-Hexyl)-1-(3-methylbutyl)-2-methoxybenzene (10b): Colorless oil. ^{1}H NMR (300 MHz): δ = 0.92 (s, 3 H, CH_3 of hexyl), 0.95 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 1.17–1.28 (m, 7 H, 2 × CH_2 of hexyl, CH_3 of hexyl), 1.44–1.68 (m, 5 H, 2′-H, 3′-H, CH_2 of hexyl), 2.58–2.65 (m, 2 H, 1′-H), 2.85–2.94 (m, 1 H, 1′-H of hexyl), 3.79 (s, 3 H, CH_3O), 6.63 (d, J = 7.8 Hz, 1 H, 5-H), 6.89–6.91 (m, 2 H, 3-H, 6-H) ppm. MS (EI): m/z (%) = 262 (38.09) $[M]^+$, 205 (100), 219 (42.55), 149 (36.05), 191 (29.14), 233 (28.47), 91 (18.43), 135 (15.82). HR-MS: calcd. for $C_{18}H_{30}O$ 262.2297; found 262.2301.

1,1-Dimethylindane (2e):[15] Colorless oil. ^{1}H NMR (400 MHz): δ = 1.26 (s, 6 H, CH_3), 1.90–1.96 (m, 2 H, 2-H), 2.84–2.92 (m, 2 H, 3-H), 7.18–7.23 (m, 2 H, 4-H, 7-H), 7.25–7.30 (m, 2 H, 5-H, 6-H) ppm.

7-Methoxy-1,2-dimethylnaphthalene (13):[16] Pale-yellow oil. ^{1}H NMR (400 MHz): δ = 2.49 (s, 3 H, CH_3), 2.56 (s, 3 H, CH_3), 3.96 (s, 3 H, OCH_3), 7.10 (dd, J = 8.6, 2.7 Hz, 1 H, 3-H), 7.18 (d, J = 8.2 Hz, 1 H, 6-H), 7.28 (d, J = 2.4 Hz, 1 H, 8-H), 7.56 (d, J = 8.8 Hz, 1 H, 4-H), 7.71 (d, J = 9.0 Hz, 1 H, 5-H) ppm.

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