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The synthetic potential of graphite-catalyzed alkylation

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Abstract—Unmodified graphite is introduced as a mild catalyst for alkylation of aromatic compounds and primary alcohols, applicable when utilization of strong Lewis acids is not feasible. The electrophilic intermediate has a significant carbocationic character and can be formed on a partially rate-limiting step.

1. Introduction

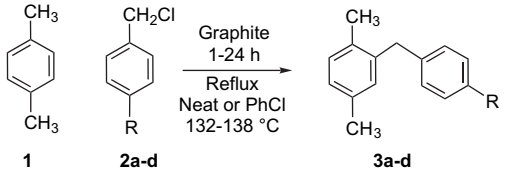
Carbonaceous materials have received a great deal of attention as possible catalysts[1–13] and construction blocks for the design of new materials in the field of nanotechnology.[14] A number of reactions can be catalyzed by norit or charcoal, such as racemization of 1,1′-binaphthyl[6] and nucleophilic substitution.[7] Compared to other types of carbonaceous catalysts, graphite has a relatively low surface area, which makes it inactive for many reactions in the absence of co-catalysts.[6] However, unmodified graphite is able to catalyze several reactions, such as benzoylation of aromatic compounds,[2] cleavage of ethers,[3] and oxidation.[4,5]

As opposed to other types of carbon and graphite-supported catalysts, the mechanism of catalytic activity of unmodified graphite remains largely unexplored. One reaction that has been studied is the graphite-catalyzed reduction of nitrobenzene by hydrazine.[10] However, there is no data in the literature on the mechanism of graphite-catalyzed alkylation, acylation, and many other important organic reactions. The recently described procedure[1] for the graphite-catalyzed alkylation of aromatic hydrocarbons employed the compound to be alkylated as a solvent, which precludes applicability of the reaction to high boiling, solid, rare, or toxic substrates.

In the present study, we have shown that graphite can be employed for reactions, where the use of traditional Lewis acids is not feasible due to the instability of reactants (e.g., carbocation rearrangement, Fries rearrangement). In our suggested method, labile groups such as primary halide, aromatic esters, and ethers remain intact. Exploring the reaction for various reactants and under various conditions, we have identified the limits of applicability of graphite as a catalyst for alkylation. Along with developing a simple and convenient procedure for alkylation of functionalized aromatic compounds, we shed light on the possible reaction mechanism.

2. Results and discussion

We found that the amount of the catalyst for benzylation of *p*-xylene **1** with benzyl chloride **2a** could be significantly decreased while providing practical yields of the reaction product **3a** (Scheme 1). While using 0.25 g of graphite per 1 mmol of **2a** produced **3a** at a yield of 96% (Table 1, entry 1), 0.05 g of the catalyst still afforded an 89% yield (Table 1, entry 3).



Scheme 1. Benzylation of *p*-xylene.

Further decrease in the amount of graphite to 0.0125 g per 1 mmol of **2a** led to a slight decrease in the yield (82%), apparently due to the saturation of the catalytic surface (Table 1, entry 4). However, the yield of the benzylation product was still in the practically acceptable range.

Reduction of the reaction time from 24 to 6 h did not lead to a significant decrease in the yield of **3a**, which still exceeded 80% (Table 1, entry 5). Therefore, we have optimized the procedure of the graphite-catalyzed benzylation of *p*-xylene.

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Table 1. Graphite-catalyzed alkylation of *p*-xylene

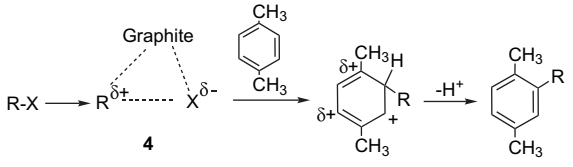
Entry	Alkylating agent	Ratio (alkylating agent/xylene)	Graphite (gram per 1 mmol of alkylating agent)	Additional conditions	*t* (h)	Yield (%)
1	**2a**	Neat	0.25	—	24	96
2	**2a**	Neat	0.125	—	24	91
3	**2a**	Neat	0.05	—	24	89
4	**2a**	Neat	0.0125	—	24	82
5	**2a**	Neat	0.25	—	6	87
6	**2a**	Neat	0.25	—	3	83
7	**2a**	Neat	0.25	—	1	67
8	**2a**	1:4	0.25	PhCl solvent, 1.25 mL per 1 mmol of **2a**	24	92
9	**2a**	1:8	0.25	PhCl solvent, 1.25 mL per 1 mmol of **2a**	3	29
10	**2a**	1:4	0.25	PhCl solvent, 0.625 mL per 1 mmol of **2a**	3	1
11	**2a**	Neat	0.25	PhCOOH, 1 mmol per 1 mmol of **2a**	3	23
12	**2a**	Neat	0.25	CH_3COOH, 1 mmol per 1 mmol of **2a**	3	0
13[15]	**2a**	Neat	0.125	—	1.5	88
14[15]	BnBr	Neat	0.125	—	1.5	100
15	**2b**	1:1	0.05	PhCl solvent, 2.5 mL per 1 mmol of **2b**	24	83
16	**2b**	Neat	0.05	—	24	100
17	**2c**	1:1	0.1	PhCl solvent, 2.5 mL per 1 mmol of **2c**	24	38
18	**2c**	Neat	0.1	—	24	47
19	**2d**	Neat	0.05	—	24	100
20	*n*-O_2NBnCl	Neat	0.05	—	24	0
21	*n*-MeO_2CBnCl	Neat	0.05	—	24	0
22[15]	2-Bromobutane	Neat	0.125	—	1.5	78
23	2-Bromobutane	Neat	0.125	48% Aqueous HBr added	1.5	97
24	2-Bromobutane	Neat	0	48% Aqueous HBr added	1.5	0
25	2-Bromobutane	Neat	0.125	Graphite was pre-treated with dry HBr gas	1.5	78
26	2-Bromobutane	Neat	0.125	Scaled up (×10) reaction of **22**	1.5	64
27	2-Bromopentane	Neat	0.143	**16**/**17**=3:1	1.5	87
28	3-Bromopentane	Neat	0.143	**16**/**17**=3:1	1.5	86
29	2-Butyl tosylate	Neat	0.125	—	1.5	0
30	2-Chlorobutane	Neat	0.125	—	1.5	0

Formation of **3a** proceeded efficiently when benzyl chloride and *p*-xylene (bp 138 °C) reacted in 1:4 molar ratio in an inert solvent chlorobenzene (bp 132 °C, Table 1, entry 8). In general, better yields of the product of alkylation were achieved when the reaction was run under neat conditions than in chlorobenzene as a solvent. Significantly higher concentration of the substrate under neat conditions increased the reaction rate and suppressed undesired alkylation of the reaction product. Nevertheless, performing the reaction in chlorobenzene rather than in the bulk of a reactant, usually led to the reaction product in a practical yield, which expanded the applicability of the method to high boiling and solid substrates as exemplified later in the text.

Alkylation by benzyl chlorides, containing a moderately electron-donating *p*-substituent (compounds **2b**,**d**, Scheme 1) led to higher conversions and provided significantly better yields than the unsubstituted benzyl chloride (Table 1, entries 16 and 19). In *p*-substituted benzyl chlorides, the *p*-position is occupied by the substituent, which makes the reaction product less susceptible to the subsequent alkylations. Thus, alkylation of *p*-xylene with 4-methylbenzyl chloride **2b** in chlorobenzene afforded the product **3b** in an excellent yield (83%) even for a lower ratio (1:1) between the reagent and the compound to be alkylated (Table 1, entry 15). The reaction produced a quantitative yield of **3b** when it was performed in the bulk of *p*-xylene (Table 1, entry 16). Alkylation of *p*-xylene by 4-(chloromethyl)phenyl acetate **2d** quantitatively afforded the phenyl ester **3d**, which cannot be synthesized by the traditional Friedel–Crafts alkylation due to the competing Fries rearrangement (Table 1, entry 19).

However, benzylation of *p*-xylene by 4-methoxybenzyl chloride **2c** (1:1 molar ratio) produced the product **3c** with a moderate yield of 38% (Table 1, entry 17). When *p*-xylene was used as a solvent, the yield of the ester **3c** increased to 47% due to the higher concentration of the compound to be alkylated (Table 1, entry 18).

As opposed to the benzylating agents **2a–d** with relatively electron-rich aromatic nuclei, 4-carboxybenzyl chloride, 4-carbomethoxybenzyl chloride, and 4-nitrobenzyl chloride were inactive under the reaction conditions (Table 1, entries 20 and 21). This pattern of reactivity suggests that the step involving the formation of an alkylating carbocation-like species (**4**, Scheme 2) is one of the partially rate-determining steps of the whole reaction sequence. Additional stabilization of the transition state (electron donating substituents in the benzylating agent), leading to this intermediate, accelerates the reaction, whereas insufficient stabilization (electron-withdrawing substituents) blocks alkylation. In other words, low acidity of graphite makes it significantly more difficult to generate an incipient carbocation from benzyl halides with an electron-withdrawing substituent.



Scheme 2. Possible mechanism for graphite-catalyzed alkylation.

The intermediacy of a well-stabilized, selective, and moderately active carbocation complex is consistent with our prior observation that benzylation of toluene with benzyl chloride does not produce the reaction product of *meta*-substitution.[1] This observation is consistent with the seminal work of Olah,[15] who reported that the electron-donating effect of the *p*-substituent increases both the positional and substrate selectivities of $TiCl_4$ catalyzed alkylation by the series of *p*-substituted benzyl chlorides. Olah's explanation of this tendency rests on the assumption that the early transition states of benzylation generated by stronger electrophiles change through the continuum of states to the late transition states as the electron-donating effect of the substituent increases. Later, the detailed kinetic studies of both competitive and non-competitive benzylations of benzene and toluene suggested that the rate-determining step is the formation of the electrophile,[16] which is consistent with our results.

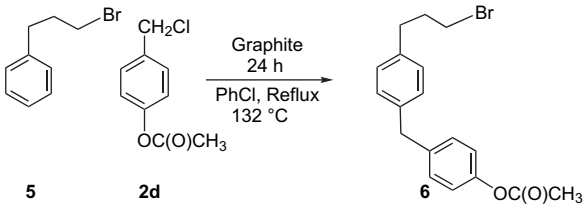
Because of the lack of reactivity of *tert*-butyl bromide toward *p*-xylene,[1] we studied alkylation of *o*-xylene by *tert*-butyl halides. As expected, the reaction yields increased from 53% for *tert*-butyl chloride to 98% for *tert*-butyl bromide[1] and iodide. This trend is similar to the known higher reactivity of benzyl bromide versus benzyl chloride toward *p*-xylene[17a] (Table 1, entries 13 and 14), but is significantly different from the reactivity trend of 2-halobutanes, discussed next.

Alkylation by secondary alkyl bromides evidently proceeds through an intermediate carbocation-like species as well. Recently, we found that 2-bromobutane efficiently alkylates *p*-xylene.[17a] However, bromopropanoic acid was inactive because the development of the positive charge on carbon in the corresponding transition state was disfavored by the neighboring carboxy group. To obtain additional evidence of a highly ionized reactive intermediate, we performed alkylation of *p*-xylene by *R*-2-bromobutane.[18] The reaction yielded an optically inactive product due to racemization of the carbocation-like electrophile.

Keeping in mind that primary alkyl bromides, as opposed to tertiary alkyl halides and benzyl halides, are inert in the graphite-catalyzed alkylation, we explored the marginal group of secondary butyl halides as alkylating agents. We observed an unusual pattern of reactivity in the row of 2-halobutanes: 2-bromobutane was the most active,[17a] and no reaction was observed with 2-chlorobutane (Table 1, entry 30). However, 2-iodobutane showed no activity either,[17a] which contradicts the expectation, based solely on the different dissociation energies of the C–Hal bonds. Even 2-butyl tosylate with an excellent leaving group was found inactive (Table 1, entry 29), which makes secondary bromides special and intriguing alkylating agents in the graphite-catalyzed reactions.

We believe that intercalation of the incipient anion formed during the charge separation in the electrophilic agent between the basal planes of graphite contributes to the stabilization of the electrophilic intermediate, which explains the unique ability of 2-bromobutane to act as an alkylating agent. The properties of the bromide-anion (e.g., size, solvation, and polarizability) are probably optimal for inclusion between the graphitic planes. This phenomenon of intercalation, which led to the increased distance between basal planes, has been documented by X-ray diffraction for alkylation of phenol, catalyzed by graphite in the presence of strong Lewis acids.[9]

Despite the lack of activity of primary alkyl halides,[1] the lack of skeletal rearrangements of the alkyl chain (benzylation of 3-bromo-1-phenylpropane **5**, Scheme 3), and the lack of de-alkylation, we observed a skeletal rearrangement of the electrophilic intermediate during alkylation of *p*-xylene with 2-bromopentane and 3-bromopentane (Table 1, entries 27 and 28). Both reactions produced an identical 3:1 mixture of 1-(methylbutyl)benzene **16** and 1-(ethylpropyl)benzene **17**. The observed **16**:**17** ratio is close to the reported composition of their equilibrated mixture in the presence of aluminum chloride.[19] These data indicate that the electrophilic intermediate is located on the potential energy surface quite close to the straight carbocation that rearranges, according to the following equation: $CH_3CH^+CH_2CH_2CH_3 = CH_3CH_2CH^+CH_2CH_3$. However, the lack of de-alkylation indicates that the graphite-catalyzed reaction is irreversible, which is a distinct difference from the Friedel–Crafts process, catalyzed by strong Lewis acids. In an additional experiment, we refluxed a mixture of 2-*sec*-butyl-1,4-dimethylbenzene **15**, graphite, and an excess of phenol in *p*-xylene solvent. No reaction was observed, which confirms that the graphite-catalyzed alkylation is irreversible.



Scheme 3. Benzylation of 3-bromo-1-phenylpropane.

Performing alkylation of *p*-xylene with 2-bromobutane under highly acidic conditions (in the presence of aqueous HBr) significantly increased the extent of conversion from 78 to 97% (Table 1, entries 22 and 23). However, in the absence of water (electrolytic dissociation is precluded) HBr did not accelerate the reaction (Table 1, entry 25). The significance of graphite as a catalyst was confirmed by the lack of alkylation in the presence of aqueous HBr, but without graphite. Scaling up the reaction by a factor of 10 resulted in a slight decrease in conversion from 78 to 64% (Table 1, entries 22 and 26).

The kinetic experiment revealed that concentration of the product of alkylation increased logarithmically. If we assume that most of the unreacted 2-bromobutane is present in the form of free halide, these data suggest the first order kinetics of 2-bromobutane (Fig. 1).

The first-order dependence on halide does not suggest either a first or second rate-limiting reaction step (Scheme 2). Two possible scenarios may take place: (1) the first step is rate-limiting; (2) the second step is rate-limiting, and the first step is fast enough to bring the starting halide and the electrophilic intermediate close to equilibrium. On

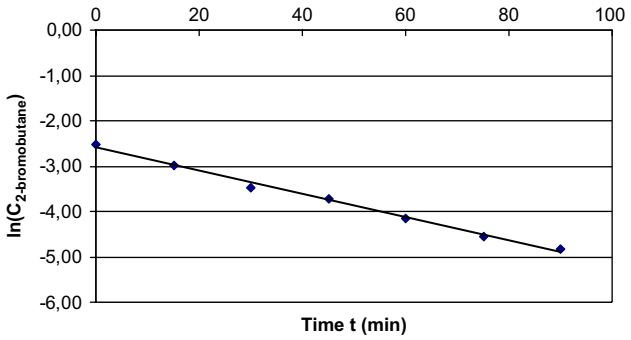
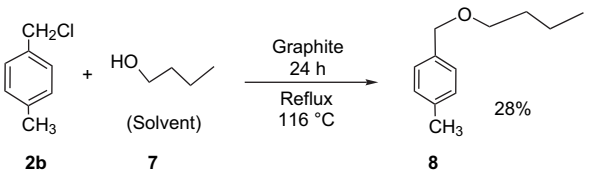


Figure 1. Kinetic data for alkylation of *p*-xylene with 2-bromobutane.

the other hand, the kinetic data allow eliminating the following scenarios: (1) the second step is rate-limiting, the first step is heavily shifted toward the intermediate, and the catalyst is close to saturation (this situation would result in pseudo-zero order on the halide); (2) the first step is rate-limiting, and the formation of the intermediate involves more than one molecule of the halide (this situation would result in a higher reaction order on the halide).

We observed a significant decrease in the extent of conversion in benzylation of *p*-xylene with benzyl chloride when we decreased the concentrations of both the alkylating agent and the substrate. Thus, decreasing the starting concentration of benzyl chloride by half, while using chlorobenzene as a solvent for alkylation of *p*-xylene, reduced the conversion from 92 to 29% (Table 1, entries 8 and 9). The same reaction performed with twice the amount of chlorobenzene solvent, produced just a trace amount of the alkylation product. The influence of the substrate concentration on the reaction outcome indicates that the step of the electrophilic attack (Scheme 2), which involves the compound to be alkylated, is another rate-contributing step in the reaction mechanism similar to the traditional Friedel–Crafts process.

As opposed to the previously discussed graphite-catalyzed benzylation of aromatic compounds, the step of electrophilic species formation seems to be kinetically less important for benzylation of primary alcohols. Replacing the unsubstituted benzyl chloride **2a** with 4-methylbenzyl chloride **2b** in the benzylation of *n*-butanol reaction does not increase the efficiency of the reaction as it does for benzylation of *p*-xylene. The reaction between 4-methylbenzyl chloride **2b** and the bulk of *n*-butanol **7** (Scheme 4) produced ether **8** at 28% conversion, which is very close (29%) to the known graphite-catalyzed benzylation of *n*-butanol with unsubstituted benzyl chloride.[1] The consistent yields indicate that there is no influence of the electron-donating CH_3– group at the *para* position of the benzyl chloride on the reaction outcome.



Scheme 4. Synthesis of 1-(butoxymethyl)-4-methylbenzene.

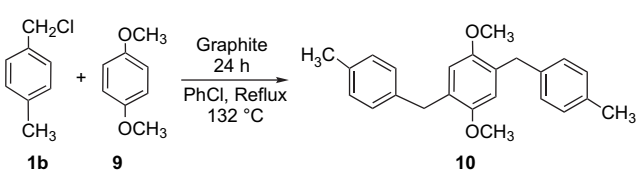
Benzylation of *n*-butanol **7** by unsubstituted benzyl chloride **1a**, carried out at a significantly lower initial concentration of alcohol (chlorobenzene was used as a solvent and the starting materials were mixed in a 1:1 ratio), did not produce any detectable amounts of the product. This suggests the involvement of *n*-butanol in the rate-determining step (probably, an electrophilic attack). It is worth noting that no skeletal rearrangement of *n*-butanol was observed during the reaction, which emphasizes the synthetic value of the graphite-catalyzed alkylation, especially for the substrates, labile under the Williamson conditions.

We found that the graphite catalyst can be recovered from the reaction of alkylation of *p*-xylene by 2-bromobutane. The reaction, catalyzed by the recovered graphite, produced a lower yield (65% vs 78% for the fresh catalyst) of *sec*-butyl-1,4-dimethylbenzene.[20] The catalyst was recovered again and used for the same experiment for the third time. The activity of graphite decreased but it was sufficient to result in 56% yield of the product.

Elucidation of the exact relative contribution of basal planes and their edges to the catalytic activity of graphite toward alkylation is currently underway, and the results will be reported elsewhere. At this moment we know that the catalytic sites on the surface of graphite strongly absorb carboxylic acids, which explains their inhibiting effect on the graphite-catalyzed benzylation of *p*-xylene. Thus, the addition of 10 equiv of benzoic acid reduced the yield of the hydrocarbon **3a** from 83 to 23% (Table 1, entries 6 and 11). The addition of the same amount of acetic acid suppressed the reaction completely (Table 1, entry 12). According to the literature,[21] carboxylic acids strongly bind with functional groups on the surface of graphite, generated by chemisorbed oxygen, which points to their role in catalytic activity.

The synthetic applicability of graphite-catalyzed alkylation is not limited to hydrocarbons. Benzylation of 1,4-dimethoxybenzene **9** with 4-methylbenzyl chloride **2b** (1:1 molar ratio) produced 2,5-di-(4-methylbenzyl)-1,4-dimethoxybenzene **10** (Scheme 5) with a 26% yield based on the alkylating agent. Mixing the reactants in the stoichiometric ratio of 1:2 resulted in nearly the same yield of **10** (28%) on the halide **1b**. However, the yield of the product on the substrate **9** doubled.

The selectivity of graphite-catalyzed alkylation is best illustrated by the benzylation of 3-bromo-1-phenylpropane **5** by 4-(chloromethyl)phenyl acetate **2d**, which produced the bifunctional product **6** (Scheme 3). Neither of the two reactants would be stable under traditional Friedel–Crafts conditions.



Scheme 5. Benzylation of 1,4-dimethoxybenzene.

3. Conclusion

Graphite-catalyzed alkylation of aromatic compounds and primary alcohols proved to be a versatile experimental protocol for organic synthesis, applicable when utilization of strong Lewis acids is not feasible. The reaction mechanism presents an interesting case of controlled charge separation in the step of the formation of the electrophile, which can be fine tuned by varying the structure of the alkylating agent and its leaving group. The extent of charge separation necessary for an electrophilic reaction develops under relatively mild conditions, which makes the reaction a selective approach for the alkylation of aromatic compounds and primary alcohols.

4. Experimental

4.1. General

All necessary materials were purchased from *Aldrich Co*., *Fischer Scientific, GFS Chemicals*, *J. T. Baker Chemical Company*, *Chempure*, *Scientific Adsorbents Incorporated* and were used as such without purification. Graphite powder was purchased from Aldrich (catalogue no. 28,286-3 particles <20 μm). ^{1}H NMR spectra were recorded on a Mercury-200 spectrometer with tetramethylsilane as an internal reference. The reaction progress was monitored by TLC.

4.2. 2-Benzyl-1,4-dimethylbenzene[22] (3a)

(a) A mixture of benzyl chloride (**2a**, 0.460 mL, 4 mmol), *p*-xylene (1, 5.0 mL, solvent), and graphite (1.00 g) was refluxed for 24 h with continuous stirring, cooled to room temperature, and filtered on a fritted funnel with vacuum suction. The solids were washed with hexane (10 mL). The combined filtrates were evaporated in vacuum to yield 2-benzyl-1,4-dimethylbenzene (**3a**, 0.753 g, 96%), identical to the known compound by NMR.[22]
(b) Reaction (a) was conducted with 0.500 g of graphite and provided 0.713 g (91%) of hydrocarbon **3a**.
(c) Reaction (a) was conducted with 0.200 g of graphite and provided 0.698 g (89%) of hydrocarbon **3a**.
(d) Reaction (a) was conducted with 0.050 g of graphite and provided 0.643 g (82%) of hydrocarbon **3a**.
(e) Reaction (a) was conducted by refluxing the reaction mixture for 6 h and provided 0.682 g (87%) of hydrocarbon **3a**.
(f) Reaction (a) was conducted by refluxing the reaction mixture for 3 h and provided 0.651 g (83%) of hydrocarbon **3a**.
(g) Reaction (a) was conducted by refluxing the reaction mixture for 1 h and provided 0.525 g (67%) of hydrocarbon **3a**.
(h) Reaction (a) was conducted using chlorobenzene (5 mL) as a solvent and provided 0.721 g (92%) of hydrocarbon **3a**; *p*-xylene and benzyl chloride were used in a 4:1 ratio.
(i) Reaction (h) was conducted for 3 h with an 8:1 ratio of *p*-xylene and benzyl chloride. The yield of hydrocarbon **3a** was 0.227 g (29%).
(j) Reaction (h) was conducted for 3 h with twice the amount of the solvent (chlorobenzene). The yield of hydrocarbon **3a** was 11 mg (1%).

4.3. 1,4-Dimethyl-2-(4-methylbenzyl)benzene[23] (3b)

(a) A mixture of 4-methylbenzyl chloride (**2b**, 0.26 mL, 2 mmol), *p*-xylene (**1**, 0.25 mL, 2 mmol), chlorobenzene (5.0 mL, solvent), and graphite (0.10 g) was refluxed for 24 h with continuous stirring, cooled to room temperature, and filtered on a fritted funnel with suction. The solids were washed with hexane (10 mL). The combined filtrates were evaporated in vacuum to yield 1,4-dimethyl-2-(4-methylbenzyl)benzene (**3b**, 0.35 g, 83%), which was identical to the known compound by NMR.[23]
(b) Reaction (a) was conducted with *p*-xylene (5 mL) as a solvent and provided 0.42 g (100%) of **3b**.

4.4. 1,4-Dimethyl-2-(4-methoxybenzyl)benzene (3c)

(a) A mixture of 4-methoxybenzyl chloride (**2c**, 0.272 mL, 2 mmol), *p*-xylene (**1**, 0.25 mL, 2 mmol), chlorobenzene (5.0 mL, solvent), and graphite (0.20 g) was refluxed for 24 h with stirring, cooled to room temperature, and filtered on a fritted funnel with suction. The solids were washed with hexane (10 mL). The combined filtrates were evaporated in vacuum and chromatographed on a silica gel column, eluted by 5% ethyl acetate in hexane to yield 174 mg (38%) of 1,4-dimethyl-2-(4-methoxybenzyl)benzene (**3c**) as a colorless oil, n_D^{20} 1.5680. ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3H), 2.30 (s, 3H), 3.80 (s, 3H), 3.90 (s, 2H), 6.8–7.1 (m, 7H). Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.88; H, 8.18.
(b) Reaction (a) was conducted with *p*-xylene (10 mL) as a solvent and provided 215 mg (47%) of **3c**.

4.5. 4-(2,5-Dimethylbenzyl)phenyl acetate (3d)

A mixture of 4-(chloromethyl)phenyl acetate (**2d**, 0.369 g, 2 mmol), *p*-xylene (**1**, 5 mL), and graphite (0.10 g) was refluxed for 24 h with stirring, cooled to room temperature, and filtered on a fritted funnel with suction. The solids were washed with hexane (10 mL). The combined filtrates were evaporated in vacuum to yield 4-(2,5-dimethylbenzyl)-phenyl acetate (**3d**, 0.508 g, 100%). ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3H), 2.22 (s, 3H), 2.23 (s, 3H), 3.90 (s, 2H), 6.9–7.4 (m, 7H). Mp 33–34 °C. Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.46; H, 7.16.

4.6. 1-(Butoxymethyl)-4-methylbenzene[24] (8)

A mixture of 4-methylbenzyl chloride (**2b**, 0.4 mL, 3 mmol), *n*-butanol (**7**, 5 mL), and graphite (0.1 g) was refluxed for 24 h with stirring, cooled to room temperature, and filtered on a fritted funnel with suction. The solids were washed with hexane (10 mL). The combined filtrates were evaporated in vacuum to yield 1-(butoxymethyl)-4-methylbenzene (**8**, 0.150 g, 28%), identical to the known compound.[24] ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H), 1.40 (m, 2H), 1.60 (m, 2H), 2.30 (s, 3H), 3.45 (t, 2H), 4.45 (s, 2H), 7.10 (d, 2H), 7.20 (d, 2H). ^{13}C NMR ($CDCl_3$) δ 14.28, 19.74, 21.47, 32.22, 70.33, 73.05, 128.04, 129.33, 135.99, 137.37.

4.7. Alkylation of 1,4-dimethoxybenzene with 4-methylbenzyl chloride (2b)

(a) A mixture of 1,4-dimethoxybenezene (**9**, 553 mg, 4 mmol), 4-methylbenzyl chloride (**2b**, 0.53 mL, 4 mmol), chlorobenzene (5 mL), and graphite (0.13 g) was refluxed for 24 h with stirring, cooled to room temperature, and filtered on a fritted funnel with suction. The solids were washed with hexane (10 mL) and ethyl acetate (5 mL). The combined filtrates were evaporated in vacuum and triturated with 5 mL of hexane. The solids were filtered off and crystallized from hexane to produce 180 mg (26%) of 2,5-di-(4-methylbenzyl)-1,4-dimethoxybenzene **10**. ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 6H), 3.65 (s, 6H), 3.90 (s, 4H), 6.60 (s, 2H), 7.4 (m, 8H). Mp 152–153 °C. Anal. Calcd for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56. Found: C, 83.49; H, 7.61.

(b) A mixture of 1,4-dimethoxybenezene (**9**, 553 mg, 4 mmol), 4-methylbenzyl chloride (**2b**, 1.06 mL, 8 mmol), chlorobenzene (5 mL), and graphite (0.13 g) was refluxed for 24 h with stirring, cooled to room temperature, and filtered on a fritted funnel with suction. The solids were washed with hexane (10 mL) and ethyl acetate (5 mL). The combined filtrates were evaporated in vacuum, triturated with 5 mL of hexane, and the solids were filtered off to produce 382 mg (28%) of 2,5-di-(4-methylbenzyl)-1,4-dimethoxybenzene **10**, identical to the compound, prepared in experiment (a).

4.8. Alkylation of 1-bromo-3-phenylpropane with 4-(chloromethyl)phenyl acetate (2d)

A mixture of 1-bromo-3-phenylpropane (**5**, 0.30 mL, 2 mmol), 4-(chloromethyl)phenyl acetate (**2d**, 0.369 g, 2 mmol), chlorobenzene (5 mL), and graphite (0.20 g) was refluxed for 24 h with stirring, cooled to room temperature, and filtered on a fritted funnel with suction. The solids were washed with hexane (10 mL) and ethyl acetate (5 mL). The combined filtrates were evaporated in vacuum and separated on a silica gel HPLC column, eluted by 1.3% of ethanol in hexane to yield 0.42 g (60%) of 4-[4-(3-bromopropyl)benzyl]phenyl acetate **6** as a colorless thick oil. ^{1}H NMR ($CDCl_3$) δ 2.15 (m, 2H), 2.25 (s, 3H), 2.75 (t, 2H, J^3=6 Hz), 3.40 (t, 2H, J^3=6 Hz), 3.95 (s, 2H), 6.9–7.2 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 21.39, 33.43, 33.76, 34.39, 41.12, 121.70, 128.94, 129.29, 130.02, 138.62, 138.83, 139.03, 149.13, 169.93. Anal. Calcd for $C_{18}H_{19}BrO_2$: C, 62.26; H, 5.51. Found: C, 62.47; H, 5.28.

4.9. 4-*tert*-Butyl-1,2-dimethylbenzene[1] (11)

(a) A mixture of *tert*-butyl chloride (**12**, 0.38 mL, 3.5 mmol), *o*-xylene (**13**, 5.0 mL, solvent), and graphite (1.000 g) was refluxed for 24 h with continuous stirring, cooled to room temperature, and filtered through a pad of silica gel on a fritted funnel with vacuum suction. The solids were washed with hexane (3×5 mL). The combined filtrates were evaporated in vacuum to yield 4-*tert*-butyl-1,2-dimethylbenzene (**11**, 0.300 g, 53%), identical to the known compound by NMR.[1]

(b) A mixture of *tert*-butyl iodide (**14**, 0.35 mL, 3.5 mmol), *o*-xylene (**13**, 5.0 mL, solvent), and graphite (1.000 g) was refluxed for 24 h with continuous stirring, cooled to room temperature, and filtered through a pad of silica gel on a fritted funnel with vacuum suction. The solids were washed with hexane (3×5 mL). The combined filtrates were evaporated in vacuum to yield 4-*tert*-butyl-1,2-dimethylbenzene (**11**, 0.555 g, 98%), identical to the known compound by NMR.[1]

4.10. 2-*sec*-Butyl-1,4-dimethylbenzene (15)

(a) A mixture of 2-bromobutane (0.44 mL, 4 mmol), *p*-xylene (**1**, 5.0 mL, solvent), 48% aqueous HBr (0.04 mL), and graphite (0.5 g) was refluxed for 1.5 h with continuous stirring, cooled to room temperature, and filtered through a pad of silica gel on a fritted funnel with vacuum suction. The solids were washed with hexane (3×5 mL). The combined filtrates were evaporated in vacuum to yield 2-*sec*-butyl-1,4-dimethylbenzene (**15**, 0.630 g, 97%), identical to the known compound by NMR.[17b]

(b) A mixture of 2-bromobutane (0.44 mL, 4 mmol), *p*-xylene (**1**, 5.0 mL, solvent), and 48% aqueous HBr (0.04 mL) was refluxed for 1.5 h with continuous stirring, cooled to room temperature, and evaporated in vacuum to yield traces (6 mg) of unidentified material.

(c) A mixture of 2-bromobutane (0.44 mL, 4 mmol), *p*-xylene (**1**, 5.0 mL, solvent), and graphite (0.5 g, pretreated overnight with gaseous HBr, produced in a desiccator, containing 1 mL of 48% aqueous HBr and 100 g of P_2O_5) was refluxed for 1.5 h with continuous stirring, cooled to room temperature, and filtered through a pad of silica gel on a fritted funnel with vacuum suction. The solids were washed with hexane (3×5 mL). The combined filtrates were evaporated in vacuum to yield 2-*sec*-butyl-1,4-dimethylbenzene (**15**, 0.506 g, 78%).

(d) A mixture of 2-bromobutane (4.4 mL, 40 mmol), *p*-xylene (**1**, 50 mL, solvent), and graphite (5.0 g) was refluxed for 1.5 h with continuous stirring, cooled to room temperature, and filtered through a pad of silica gel on a fritted funnel with vacuum suction. The solids were washed with hexane (3×50 mL). The combined filtrates were evaporated in vacuum to yield 2-*sec*-butyl-1,4-dimethylbenzene (**15**, 4.15 g, 64%).

(e) A mixture of 2-bromobutane (0.22 mL, 2 mmol), *p*-xylene (**1**, 2.5 mL, solvent), and graphite (0.25 g) was refluxed for an array of times (15, 30, 45, 60, 75, and 90 min) with continuous stirring, cooled to room temperature, and filtered through a pad of silica gel on a fritted funnel with vacuum suction. The solids were washed with hexane (3×5 mL). The combined filtrates were evaporated in vacuum to yield 2-*sec*-butyl-1,4-dimethylbenzene (**15**). The experimental results are presented in Table 2 and Figure 1.

4.11. 2,5-Dimethyl-1-(1-methylbutyl)benzene (16) and 2,5-dimethyl-1-(1-ethylpropyl)benzene (17)

(a) A mixture of 2-bromopentane (0.44 mL, 3.5 mmol), *p*-xylene (**1**, 5.0 mL, solvent), and graphite (0.5 g) was refluxed for 1.5 h with continuous stirring, cooled to room temperature, and filtered through a pad of silica gel on a fritted funnel with vacuum suction. The solids were washed with hexane (3×5 mL). The combined filtrates

Table 2. Kinetic data for alkylation of *p*-xylene with 2-bromobutane

Time t (min)	Conversion (%)	Unreacted 2-bromobutane (%)	$C_{2\text{-bromobutane}}$ (Mol/L)	Ln ($C_{2\text{-bromobutane}}$)
0	0.0	100.0	0.080	−2.53
15	37.0	63.0	0.050	−2.99
30	60.8	39.2	0.031	−3.46
45	70.1	29.9	0.024	−3.73
60	80.6	19.4	0.016	−4.17
75	86.7	13.3	0.011	−4.54
90	90.1	9.9	0.008	−4.84

were evaporated in vacuum to yield 0.494 g (87%) of a mixture of 1-(methylbutyl)benzene[19] (**16**) and 1-(ethylpropyl)benzene[19] (**17**) in the molar ratio of 3:1 (by NMR). This ratio was determined by the integration of the triplet at 0.8 ppm (side chain methyl groups of **17**) and the doublet at 1.2 ppm (one of the two side chain methyl groups of **16**). ^{1}H NMR ($CDCl_3$) δ 0.80 (t), 0.90 (t), 1.20 (d), 1.2–1.3 (m), 1.5–1.7 (m), 2.25 (s), 2.30 (s), 2.65 (m), 2.95 (m), 6.8–7.1 (m).

(b) A mixture of 3-bromopentane (0.44 mL, 3.5 mmol), *p*-xylene (**1**, 5.0 mL, solvent), and graphite (0.5 g) was refluxed for 1.5 h with continuous stirring, cooled to room temperature, and filtered through a pad of silica gel on a fritted funnel with vacuum suction. The solids were washed with hexane (3×5 mL). The combined filtrates were evaporated in vacuum to yield 0.490 g (86%) of a mixture of 1-(methylbutyl)benzene[19] (**16**) and 1-(ethylpropyl)benzene[19] (**17**) in the molar ratio of 3:1 (by NMR).

4.12. Attempt of de-alkylation of 2-*sec*-butyl-1,4-dimethylbenzene (15) by phenol

A mixture of 2-*sec*-butyl-1,4-dimethylbenzene (**15**, 0.19 g, 1.17 mmol), phenol (0.28 g, 3 mmol), *p*-xylene (**1**, 1.0 mL, solvent), and graphite (0.1 g) was refluxed for 1.5 h with continuous stirring, cooled to room temperature, and filtered through a fritted funnel with vacuum suction. The solids were washed with chloroform (3×5 mL). The combined filtrates were evaporated in vacuum to yield 0.47 g of a mixture of the starting materials (by NMR).

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