

# Scope and Utility of a New Soluble Copper Catalyst [CuBr–LiSPh–LiBr–THF]: A Comparison with Other Copper Catalysts in Their Ability to Couple One Equivalent of a Grignard Reagent with an Alkyl Sulfonate

Dennis H. Burns,\* Jeffrey D. Miller, Ho-Kit Chan, and Michael O. Delaney†

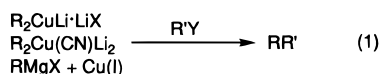
Contribution from the Department of Chemistry, Wichita State University, Wichita, Kansas 67260

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**Abstract:** A mixture of equal amounts of CuBr–SMe<sub>2</sub>, LiBr, and LiSph in THF at 0 °C furnished a new soluble copper catalyst that was highly efficient at coupling primary, secondary, tertiary, aryl, vinyl, and allylic Grignard reagents to primary tosylates and primary Grignard reagents to secondary tosylates and mesylates, all with the use of only 1 equiv of Grignard reagent. The new catalyst was shown to be much more reactive than copper catalysts CuBr and Li<sub>2</sub>CuCl<sub>4</sub> and more efficient in the transference of secondary and tertiary alkyl groups than lower order cuprates (Gilman reagents) and demonstrated more reactivity than the lower order cuprates with its ability to couple primary Grignard reagents to secondary sulfonates. The Grignard reagent/catalyst system was compatible with an ester functionalized tosylate, thus proving to be more chemoselective than a Grignard reagent without the catalyst. The catalyst exhibited good reactivity below room temperature, and with the addition of 6% v/v of HMPA to the catalyst solution, excellent yields of coupled product were obtained within a 25–67 °C temperature range. <sup>1</sup>H NMR demonstrated that the catalyst solution consisted of several species that most likely were composed of copper ligated with thiophenol, THF, and LiBr in aggregated forms.

## Introduction

Substitution reactions resulting in carbon–carbon bond formation mediated by copper reagents have proved useful in organic synthesis. The development of lower order cuprates or Gilman reagents (R<sub>2</sub>CuLi·LiX) and “higher order” cuprates (R<sub>2</sub>CuCNLi<sub>2</sub>)<sup>1</sup> has allowed the coupling of alkyl halides (R'X) and alkyl sulfonates (R'OTs, R'OMs) with several kinds of R groups (eq 1).<sup>2</sup> Thus, cuprates with R groups that are both



saturated, allylic, vinyl, and aryl undergo substitution reactions with the above electrophiles, and while Gilman reagents will only reliably couple with primary alkyl halides and alkyl sulfonates, “higher order” cuprates will couple with secondary halides. One drawback, however, is the need to use several equivalents of cuprate for high conversion of starting material,

generally 2–5 equiv of the Gilman reagent,<sup>3</sup> and 2 (or more) equiv of the “higher order” cuprates.<sup>2b</sup> Not only is there stoichiometric excess of cuprate, but the cuprate reagent itself may contain two of the transferable R groups, and the substitution reaction can therefore waste precious starting material. As an alternative, using a copper catalyst to couple Grignard reagents (RMgX) with alkyl halides and alkyl sulfonates inherently does not waste the R group. Additionally, Grignard reagents are more accessible than lithium reagents, and the copper catalyst may be used in as low as 1–2 mole %.<sup>4a</sup> However, they are intrinsically more basic than cuprates,<sup>4b</sup> and their range of reactivity is more narrow. Good yields of coupled products are generally limited to the use of copper catalysts with primary Grignard and electrophilic reagents.

One of our current projects is the design of metacyclophanes (**1**, **2**) (Scheme 1) that can be used as modular components in molecular devices.<sup>5,6</sup> An important intermediate of these macrocycles is bis-anisole **5**, which can be used in the preparation of both types of metacyclophane structure. Our need for an efficient one-step synthesis of **5** (from 2-bromoanisole) motivated us to search for an efficient copper coupling reagent, since the reaction of 2-lithiated anisole with bis-functionalized electrophiles proved problematic. Furthermore, the ultimate preparation of the cyclophanes in our synthetic scheme required additional substitution reactions (e.g., with the use of compound **3** or **4**), and therefore, a Grignard/copper catalyst system seemed

(3) (a) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7777–7782. Following the submission of this manuscript, a communication appeared that demonstrated the efficient transfer of a butyl group to benzoyl chloride and 2-cyclohexenone from mixed β-silyl cuprates: Bertz, S. H.; Eriksson, M.; Miao, G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906–10907.

(4) (a) Tamura, M.; Kochi, J. K. *J. Organomet. Chem.* **1972**, *14*, 205–228. (b) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788–7800 and references contained therein.

(5) Burns, D. H.; Miller, J. D. *Tetrahedron Lett.* **1994**, *35*, 5189–5192

(6) Burns, D. H.; Miller, J. D.; Santana, J. *J. Org. Chem.* **1993**, *58*, 6526–6528.

\* Corresponding author. E-mail: burns@wsuhub.uc.twsu.edu.

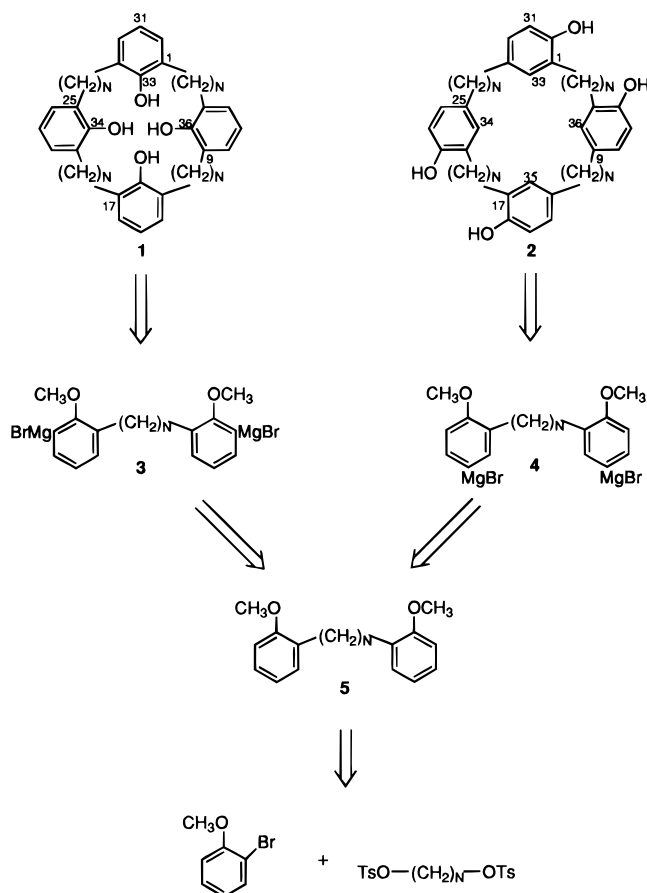
† Undergraduate researcher.

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(1) The term “higher order” cuprates, as used in this paper, is meant to imply only a stoichiometric relationship within the cuprate. For recent information on the structure of “higher order” cuprates, see: (a) Stemmler, T. L.; Barnhart, T. M.; Penner-Hahn, J. E.; Tucker, C. E.; Knochel, P.; Böhme, M.; Frenking, G. *J. Am. Chem. Soc.* **1995**, *117*, 12489–12497. (b) Snyder, J. P.; Bertz, S. H. *J. Org. Chem.* **1995**, *60*, 4312–4313. (c) Barnhart, T. M.; Huang, H.; Penner-Hahn, J. E. *J. Org. Chem.* **1995**, *60*, 4310–4311. (d) Snyder, J. P.; Spangler, D. P.; Behling, J. R. *J. Org. Chem.* **1995**, *59*, 2665–2667.

(2) For reviews on the substitution chemistry of cuprates, see: (a) Lipshutz, B. H. *Org. React.* (N. Y.) **1992**, *41*, 135–631. (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005–5038. (c) Posner, G. H. *Org. React.* (N. Y.) **1975**, *22*, 253–400.

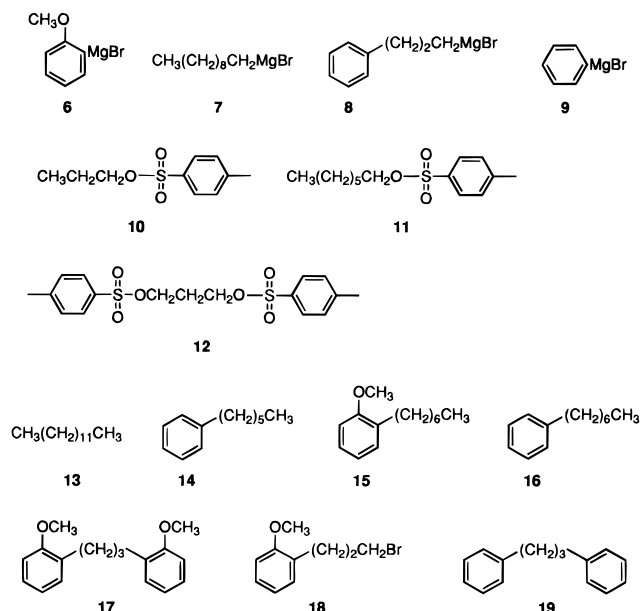
**Scheme 1.** Retrosynthetic Analysis of Metacyclophanes **1** and **2** from 2-Bromoanisole via Common Intermediate **5** (Numbering Schemes for **1** and **2** Are When  $N = 3$ , OTs = tosylate)



the most efficient pathway so as to minimize the waste of Grignard reagents in the preparation of **1** and **2** (Scheme 1).

The soluble copper reagent  $\text{Li}_2\text{CuCl}_4$  is known to couple  $\alpha,\omega$ -bromides with 2 equiv of Grignard reagent.<sup>7,8</sup> With the preparation of bis-anisole **5** in mind, the coupling of 2 equiv of (2-methoxyphenyl)magnesium bromide (**6**) with 1,3-dibromopropane was attempted using  $\text{Li}_2\text{CuCl}_4$  (6 mol %, THF, 0–18 °C, 48 h)<sup>8</sup> as the catalyst, while  $\text{CuBr}$  (12 mol % in a refluxing solution of THF and 6% v/v HMPA, 24 h)<sup>9,10</sup> was used for comparison. Utilization of both of these common catalyst systems led to poor yields of bis-anisole **17** based on the Grignard reagent (Figure 1). The use of  $\text{CuBr}$  led to good yields of **17** only when several equivalents of the Grignard reagent were employed, and when the soluble catalyst was used, greater than 80% of the product was the mono-coupled anisole **18**. Changing the electrophile from 1,3-dibromopropane to 1,3-bis-[4-methylbenzenesulfonyloxy]propane (**12**) further increased the amount of **17** to 15–20% of the product mixture.<sup>3,11</sup>

Since the above pathways produced bis-anisole **17** in a decidedly inefficient manner, an attempt was made to prepare a more active soluble  $\text{Cu(II)}$  catalyst by exchanging the  $\text{Cl}^-$  ligands with  $\text{Br}^-$ ,  $\text{I}^-$ , and/or  $\text{SPh}^-$  because these ligands stabilize



**Figure 1.** Primary alkyl and aryl Grignard reagents (**6–9**) and primary tosylates (**10–12**) used in the catalyst comparison, along with their coupled products (**13–19**).

$\text{Cu(I)}$ ,<sup>4b,12</sup> the active coupling agent in the reaction mixture.<sup>2a,4a</sup> As reported earlier,<sup>5</sup> two distinct rates of reaction (as followed by  $^1\text{H}$  NMR) were observed during the coupling reaction that furnished **18** when  $\text{Li}_2\text{CuCl}_4$  was used as a catalyst. After 0.5 h the rate quickly slowed 5-fold to a second rate that held constant for several hours. It was hypothesized that the stabilizing ligands perhaps would keep the more active species present in the reaction mixture for longer periods of time. Mixtures of  $\text{CuBr}_2$  and 2 equiv of  $\text{LiBr}$  or  $\text{LiI}$  remained soluble in THF (0.1 M solution). The former solution was olive green, while the latter solution became a deep red; both solutions presumably contained  $\text{Li}_2\text{CuX}_2\text{Y}_2$  ( $\text{X} = \text{Y} = \text{Br}$ ;  $\text{X} = \text{Br}$ ,  $\text{Y} = \text{I}$ ). When either solution was used as a catalyst, **17** was furnished in 10–15% yield when **6** was coupled with the bis-bromide and 50–60% when **6** was coupled with the bis-tosylate **12**. While these results were an improvement, the latter yields were attained only when the reactions were run for 3–4 days and 12–15% of catalyst was used.

As we communicated earlier,<sup>5</sup> a yellow solid was formed which contained a  $\text{Cu(I)}$  species when  $\text{CuBr}_2$  was mixed with 2 equiv of  $\text{LiSPh}$  in THF at room temperature. The initial  $\text{Cu(II)}$  was reduced by the thiophenol, and the latter oxidized to the disulfide. To avoid problems with stoichiometry (i.e., how much of the thiophenol was acting as a ligand and what part was involved in the redox event), a  $\text{Cu(I)}$  catalyst was prepared by mixing 1 equiv of  $\text{CuBr-SMe}_2$  with 1 equiv each of  $\text{LiBr}$  and  $\text{LiSPh}$  in THF. This conceivably would produce the same number of components as in the above  $\text{Cu(II)}$  catalysts, i.e., two sulfur and two bromide ligands with two lithium cations. Once again a yellow suspension formed over a 15–30 min time period. However, when the reactants were mixed at 0 °C, no precipitate was formed for several hours. When this 0 °C solution of soluble catalyst (or the  $\text{Cu(I)}$  suspension) was used in the reaction, the coupling of 2 equiv of (2-methoxyphenyl)magnesium bromide with 1 equiv of 1,3-bis[4-methylbenzenesulfonyloxy]propane (**12**) (THF, 0–18 °C over 24 h, 6 mol % catalyst) furnished **17** in 80% yield (85% if the reaction were run for 48 h) based on the Grignard reagent. The new soluble copper catalyst thus proved much more effective at coupling the stabilized aromatic Grignard reagent with the bis-tosylate

(7) Drouin, J.; Leyendecker, F.; Conia, J. M. *Tetrahedron* **1980**, *36*, 1195–1201.

(8) Kakhodayan, M.; Singleton, T.; Heldrich, F. O. *Synth. Commun.* **1984**, *14*, 707–712.

(9) Wuping, M.; Wilcoxon, K. M.; Szewczyk, J. W.; Ibers, J. A. *J. Org. Chem.* **1995**, *60*, 8081–8083.

(10) Zhang, H.-Y.; Blaskó, A.; Yu, J.-Q.; Bruice, T. C. *J. Am. Chem. Soc.* **1992**, *114*, 6621–6630.

(11) Fouquet, G.; Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 82–83.

(12) Hathaway, B. J. Copper. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon: New York, 1987; Vol. 5, pp 536–538.

than Li<sub>2</sub>CuCl<sub>4</sub>, CuBr or the other two modified Cu(II) catalysts. This initial success prompted us to examine the scope and utility of our copper catalyst in the coupling of Grignard reagents with electrophiles and to determine the general reaction conditions required for optimum yields. In this report, we detail the findings of our study on this new copper reagent that catalyzes the substitution reaction of alkyl sulfonates with 1 equiv of Grignard reagent in good to excellent yield, within the temperature range 0–67 °C. Our results show that our catalyst is not only more reactive than other copper catalysts to date, it is in fact more reactive in coupling reactions than comparable Gilman reagents, and without the inherent waste of starting material.










## Results and Discussion

**Optimum Reaction Conditions for the Catalyst.** To investigate the scope and limitations of our catalyst, we embarked upon a model study which compared the performance of our catalyst with two copper catalysts commonly used with Grignard reagents: the THF soluble Li<sub>2</sub>CuCl<sub>4</sub> (catalyst A)<sup>13</sup> and refluxing CuBr in THF/HMPA (catalyst B).<sup>9,10</sup> As usual, our copper catalyst was prepared in THF with CuBr–SMe<sub>2</sub>, LiBr, and LiSPh (catalyst C). Besides the nature of the catalyst, the study also examined variation in the nature of the electrophile, the nature of the Grignard reagent, variation in equivalents of Grignard reagent used, the mode of addition of copper catalyst, the reagent concentration, and variations in temperature and solvent. Additionally, we compared the use of washed and dried solid catalyst C, the catalyst C suspension prepared in THF at room temperature, and the soluble catalyst C prepared in THF at 0 °C, on their outcome of the coupling reaction.

The initial procedure was to add 1.0 equiv of the Grignard reagent dropwise over the course of 0.5 h to a 0 °C THF solution containing 6 mol % copper catalyst and 1.0 equiv of the electrophile. The reaction mixture was allowed to slowly warm from 0 to 16–18 °C overnight. After workup, the crude reaction mixture was purified by chromatography filtration and probed by GC and GC/MS to determine product species and their yields in the product mixtures (yields were based on the amount of alkyl or aryl halide used to make the Grignard reagent). It was found that the reaction of 1.0 equiv of decylmagnesium bromide (**7**) with 1 equiv of a 1-halopropane resulted in the lowest yields of coupled product, consistent with results already observed in the cyclophane synthesis. Thus, when 1-iodopropane or 1-bromopropane was used as the electrophile, the Li<sub>2</sub>CuCl<sub>4</sub> catalyst produced tridecane (**13**) in 52–54% yield, and with catalyst C, product **13** was furnished in 57–60% yield (Table 1). When propyl tosylate (**10**) was used as the electrophile, Li<sub>2</sub>CuCl<sub>4</sub> and catalyst C produced coupled product **13** in yields of 70% and 77%, respectively (Table 1). Wurtz-type dimers (0–10%),<sup>14</sup> the substitution product formed from the reaction of thiophenol with the electrophile (0–3%), and quenched Grignard reagent were the general byproducts of the reaction, all easily discernible by GC/MS and removable with chromatography and/or recrystallization.











Utilizing the above results as a reference point, the reaction parameters were examined for those that produced optimal yields when the tosylate was used as the electrophile. Increasing the equivalent ratio of Grignard reagent to tosylate from 1:1 to 1:25 and 1:5, respectively, did not substantially increase the yield of coupled product from that of a 1:1 ratio. Best results were attained when the reaction solvent was THF, rather than diethyl ether, dioxane, or combinations of THF/dioxane. For all

**Table 1.** Initial Optimization of the Coupling Reaction Utilizing Soluble Copper Catalysts A and C

entry	RMgX	R'Y	catalyst <sup>a</sup>	RR' (% yield)	conditions <sup>b</sup>
1	<b>7</b>		A	<b>13</b> (54)	nc
2	<b>7</b>		A	<b>13</b> (57)	nc
3	<b>7</b>		A	<b>13</b> (70)	nc
4	<b>7</b>		C	<b>13</b> (57)	nc
5	<b>7</b>		C	<b>13</b> (59)	nc
6	<b>7</b>		C	<b>13</b> (77)	nc
7	<b>7</b>		C	<b>13</b> (60)	1.0 M <sup>c</sup>
8	<b>7</b>		C	<b>13</b> (75)	0.1 M <sup>c</sup>
9	<b>7</b>		C	<b>13</b> (31)	0.05 M <sup>c</sup>

<sup>a</sup> Catalyst A, Li<sub>2</sub>CuCl<sub>4</sub>/THF; catalyst B, CuBr/HMPA/67 °C; catalyst C, CuBr·SMe<sub>2</sub>·LiBr·LiSPh/THF. <sup>b</sup> nc = normal conditions: 0–18 °C, 0.5 M Grignard in THF, 1:1 RMgX:R'Y, 6% catalyst, 24 h. <sup>c</sup> M = molarity of Grignard reagent in THF; all other conditions same as nc.

**Table 2.** Effectiveness of Catalysts under Differing Temperatures, with and without HMPA as Co-solvent

entry	RMgX	R'Y	catalyst <sup>a</sup>	RR' (% yield)	conditions <sup>b</sup>
1	<b>7</b>		A	<b>13</b> (52)	25 °C
2	<b>7</b>		C	<b>13</b> (55)	25 °C
3	<b>7</b>		A	<b>13</b> (21)	45 °C
4	<b>7</b>		C	<b>13</b> (33)	45 °C
5	<b>7</b>		C	<b>13</b> (57)	0 °C, 6% HMPA
6	<b>7</b>		A	<b>13</b> (78)	25 °C, 6% HMPA
7	<b>7</b>		C	<b>13</b> (87)	25 °C, 6% HMPA
8	<b>7</b>		A	<b>13</b> (80)	67 °C, 6% HMPA
9	<b>7</b>		C	<b>13</b> (80)	67 °C, 6% HMPA
10	<b>7</b>		B	<b>13</b> (44)	67 °C, 6% HMPA

<sup>a</sup> Catalyst A, Li<sub>2</sub>CuCl<sub>4</sub>/THF; catalyst B, CuBr/HMPA/67 °C; catalyst C, CuBr·SMe<sub>2</sub>·LiBr·LiSPh/THF. <sup>b</sup> Conditions are 0.5 M Grignard in THF, 1:1 RMgX:R'Y, 6% catalyst, 24 h. Temperature and addition of co-solvent are noted.

practical purposes, there was no difference in the outcome of the coupling reaction whether washed and dried solid catalyst C, the room temperature catalyst C suspension, or the soluble catalyst C prepared in THF at 0 °C was utilized. Since the latter system was the most convenient from the standpoint of syringe technique, it was the one generally employed. Occasionally, very good yields were obtained when the catalyst was added over time (0.5% every 45 min up to 6% total) instead of in one lump sum. However, this was not a consistent finding, and the latter (and easier) method of addition was employed for the data presented in this paper. Finally, data in Table 1 shows that best yields resulted when the Grignard reagent concentration was kept between 0.1 and 0.5 M.

Results in Table 2 show the sensitivity of catalysts A and C to changes in temperature. When the catalysts were used in THF alone, a precipitous drop in yield was recorded if the temperature was increased from the 0 to 18 °C warm-up protocol (77% yield, catalyst C) to 25 °C (55% yield, catalyst C) to 45

(13) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303–305.

(14) Wurtz dimers refers to homocoupled Grignard reactants. In this paper, the yields and identities of the Wurtz byproducts eicosane, 1,6-diphenylhexane, and biphenyl were determined from authenticated samples and GC/MS.

°C (33% yield, catalyst C). With the use of both catalysts, temperatures much below 0 °C only slowed the reaction down and did not improve overall yields. When hexamethylphosphoramide (HMPA) was added as a co-solvent (6% by volume), however, a dramatic improvement in product yields was seen at temperatures greater than or equal to 25 °C. For example, the product yield of the substitution reaction between the decyl Grignard **7** and propyl tosylate (**10**) was increased 8–10% when the reaction was run at room temperature with the addition of HMPA as a co-solvent (entries 6 and 7 in Table 2 compared to entries 3 and 6 in Table 1). Generally, product yields varied little when reactions were run between room temperature and 67 °C. Where cuprates are generally only stable at temperatures of 0 °C or lower,<sup>2,3,4b</sup> our copper catalyst was active and effective at higher temperature with addition of co-solvent. Unlike Li<sub>2</sub>CuCl<sub>4</sub> (vide supra), catalyst C showed little drop-off in reaction rate with time, and as the reaction temperature was increased, so did the rate of the reaction. Apparently, as with Posner's cuprate,<sup>4b</sup> the thiol helped stabilize the Grignard/catalyst system at temperatures where the substitution reaction was most active. Whereas the formation of bis-anisole **17** in 80% yield took 24 h with the 0–18 °C warm-up protocol, the reaction reached the same stage of completion in 3–4 h at 67 °C. Interestingly, addition of HMPA to a reaction held at 0 °C resulted in substantially lowered yields compared to those run at 0 °C without the co-solvent. Thus, HMPA was not just acting in its usual role as a polar, aprotic solvent but also acting to stabilize the catalyst system at elevated temperatures.

**Synthetic Scope of the Catalyst.** With optimized reaction parameters in hand, the Grignard reagent and tosylate were varied to determine the general synthetic usefulness of the catalyst beyond what we had previously found for our cyclophane synthesis. To first verify the above results, a different primary alkyl Grignard reagent [(3-phenylpropyl)magnesium bromide (**8**), Figure 1] was prepared. The new Grignard reagent contained a chromophore so that the coupled product would be easy to purify with chromatography, and the phenyl group also acted as a useful <sup>1</sup>H NMR probe. Yields of hexylbenzene (**14**) from the coupling of **8** with **10** ranged from 77 to 80% when Li<sub>2</sub>CuCl<sub>4</sub> was used and 80–87% when catalyst C was used at reaction temperatures that varied between 0 and 67 °C (Table 3). In general, the best product yields resulted when the reaction mixture was made up of a 0.5 M solution of Grignard and tosylate (1:1 equivalent ratio) in THF (6% HMPA v/v) containing 6 mol % of catalyst, and the reaction was allowed to stir at room temperature for 18–24 h. However, when the Grignard reagent and sulfonate contained primary alkyl groups, the difference in yield between the reactions run at room temperature (with addition of HMPA) and the 0–18 °C warm-up protocol (without addition of HMPA) was minimal.

Thus, of the two soluble catalysts, ours showed a small but definitive edge in reactivity when coupling 1 equiv of a primary Grignard reagent with 1 equiv of a primary alkyl tosylate or halide (vide supra). For an additional comparison, a 12% CuBr suspension (6% v/v HMPA, 67 °C) was used as a catalyst to couple 1 equiv of decyl Grignard **7** with 1 equiv of propyl tosylate **10**, and tridecane (**13**) was furnished in only 44% yield (Table 2). The above results proved the efficacy of our new catalyst when only 1 equiv of Grignard reagent was used.

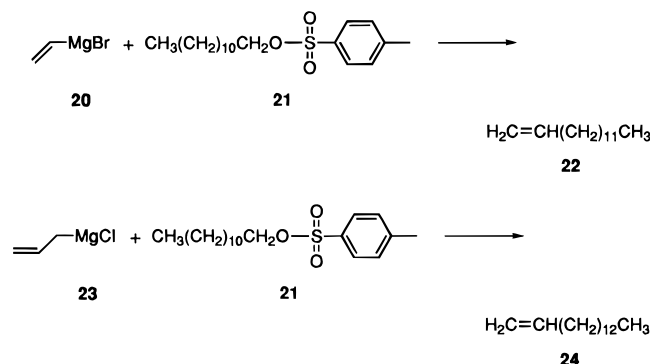
Further variation of the Grignard reagent demonstrated that our catalyst was significantly more reactive and furnished more consistent yields than catalyst A or B. The coupling of 1 equiv of (2-methoxyphenyl)magnesium bromide (**6**) or phenylmagnesium bromide (**9**) and 1 equiv of heptyl tosylate (**11**) furnished 2-heptylanisole (**15**) and heptylbenzene (**16**) in 94% and 85% yields, respectively, with catalyst C (entries 6 and 9, Table 3).

**Table 3.** Effectiveness of Catalysts A, B, and C in the Coupling of Primary, Aromatic, Vinyl, and Allylic Grignard Reagents with Primary Tosylates

entry	RMgX	R'Y	catalyst <sup>a</sup>	RR' (% yield)	conditions <sup>c</sup>
1	<b>8</b>	<b>10</b>	A	<b>14</b> (77–80)	0–67
2	<b>8</b>	<b>10</b>	B	<b>14</b> (49)	67
3	<b>8</b>	<b>10</b>	C	<b>14</b> (80–87)	0–67
4	<b>6</b>	<b>11</b>	A	<b>15</b> (71–74)	0–67
5	<b>6</b>	<b>11</b>	B	<b>15</b> (84)	67
6	<b>6</b>	<b>11</b>	C	<b>15</b> (90–94)	0–67
7	<b>9</b>	<b>11</b>	A	<b>16</b> (68–77)	0–67
8	<b>9</b>	<b>11</b>	B	<b>16</b> (70)	67
9	<b>9</b>	<b>11</b>	C	<b>16</b> (82–85)	0–67
10	<b>6</b>	<b>12</b>	A	<b>17</b> (17–55)	0–67
11	<b>6</b>	<b>12</b>	B	<b>17</b> (<5)	67
12	<b>6</b>	<b>12</b>	C	<b>17</b> (70–80)	0–67
13	<b>9</b>	<b>12</b>	A	<b>19</b> (32–64)	0–67
14	<b>9</b>	<b>12</b>	B	<b>19</b> (53)	67
15	<b>9</b>	<b>12</b>	C	<b>19</b> (73–76)	0–67
16	<b>20</b>	<b>21</b>	A	<b>22</b> (0)	25
17	<b>20</b>	<b>21</b>	B	<b>22</b> (2) <sup>b</sup>	25
18	<b>20</b>	<b>21</b>	C	<b>22</b> (57)	25
19	<b>23</b>	<b>21</b>	A	<b>24</b> (60)	0–18
20	<b>23</b>	<b>21</b>	B	<b>24</b> (0) <sup>b</sup>	0–18
21	<b>23</b>	<b>21</b>	C	<b>24</b> (90)	0–18

<sup>a</sup> Catalyst A, Li<sub>2</sub>CuCl<sub>4</sub>/THF; catalyst B, CuBr/12% v/v HMPA/67 °C; catalyst C, CuBr·SMe<sub>2</sub>·LiBr·LiSPH/THF. <sup>b</sup> Reactions run with catalyst B at 67 °C furnished the same yields. <sup>c</sup> Conditions are 0.5 M Grignard in THF, 1:1 RMgX:R'Y, 6% catalyst, and 24 h reaction time. The range of yields listed are those found within the range of temperatures noted (0–67 °C: reactions were run at 0–18, 25, 45, and 67 °C, and each set was repeated at least once). All reactions run at or above 25 °C contained 6% v/v HMPA.

### Scheme 2



These yields were superior (by 8–20%) to those found when either Li<sub>2</sub>CuCl<sub>4</sub> or CuBr was utilized as the catalyst (Table 3). Disubstitution of the primary  $\alpha,\omega$ -bis-tosylate (**12**) with 2 equiv of either **6** or **9** to furnish coupled product **17** or **19**, respectively, proceeded in excellent yield with the use of soluble catalyst C (entries 12 and 15, Table 3). Yields were consistent from one reaction to the next and varied little between 0 and 67 °C with the use of catalyst C. Interestingly, this was not true for the above reactions when utilizing catalyst A or B, where yields were not consistent and varied greatly depending on the temperature of the reaction (Table 3, entries 10–15). A limitation of all the catalysts was their inability to couple primary alkyl or aromatic Grignard reagents with aromatic iodides or tosylates in good yield.<sup>2a</sup>

With catalyst C, both vinyl and allylic Grignard reagents coupled to dodecyl tosylate (**21**) in good to excellent yield, furnishing 1-tetradecene (**22**) in 57% yield and 1-pentadecene (**24**) in 90% yield, respectively (Scheme 2 and entries 18 and 21, Table 3). Yields varied greatly from 0 to 67 °C with the use of these Grignard reagents and catalyst C, and the best yields and temperatures at which they were obtained are supplied in Table 3. The same coupled products were furnished in very poor yields with catalysts A and B (Table 3). Furthermore,

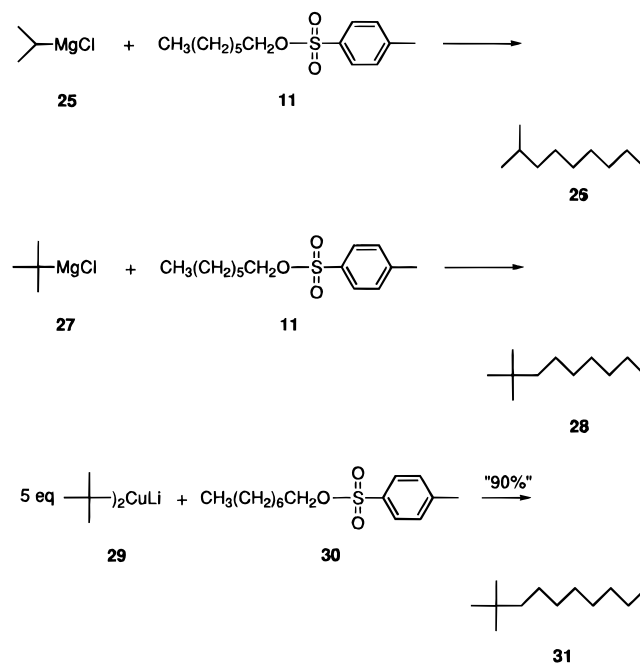
**Table 4.** Effectiveness of Catalysts A, B, and C in the Coupling of Primary, Secondary and Tertiary Grignard Reagents with Primary and Secondary Tosylates and Mesylates

entry	RMgX	R'Y	catalyst <sup>a</sup>	RR' (% yield)	conditions <sup>c</sup>
1	<b>25</b>	<b>11</b>	A	<b>26</b> (29)	24
2	<b>25</b>	<b>11</b>	B	<b>26</b> (29)	24
3	<b>25</b>	<b>11</b>	C	<b>26</b> (65)	24
4	<b>27</b>	<b>11</b>	A	<b>28</b> (16)	24
5	<b>27</b>	<b>11</b>	B	<b>28</b> (33)	24
6	<b>27</b>	<b>11</b>	C	<b>28</b> (50)	24
7	<b>7</b>	<b>32</b>	A	<b>33</b> (59)	24
8	<b>7</b>	<b>32</b>	B	<b>33</b> (07)	24
9	<b>7</b>	<b>32</b>	C	<b>33</b> (76)	24
10	<b>8</b>	<b>32</b>	A	<b>34</b> (17)	24
11	<b>8</b>	<b>32</b>	B	<b>34</b> (19)	24
12	<b>8</b>	<b>32</b>	C	<b>34</b> (80)	24
13	<b>8</b>	<b>35</b>	C	<b>36</b> (35)	48
14	<b>8</b>	<b>38</b>	C	<b>39</b> (28)	48
15	<b>8</b>	<b>37</b>	A	<b>36</b> (17)	48
16	<b>8</b>	<b>37</b>	B	<b>36</b> (30)	48
17	<b>8</b>	<b>37</b>	C	<b>36</b> (62)	48
18	<b>8</b>	<b>40</b>	A	<b>39</b> (0) <sup>b</sup>	48
19	<b>8</b>	<b>40</b>	B	<b>39</b> (25)	48
20	<b>8</b>	<b>40</b>	C	<b>39</b> (74)	48
21	<b>8</b>	<b>41</b>	C	<b>42</b> (71)	24 <sup>d</sup>

<sup>a</sup> Catalyst A, Li<sub>2</sub>CuCl<sub>4</sub>/THF; catalyst B, CuBr/HMPA/67 °C; catalyst C, CuBr·SMe<sub>2</sub>·LiBr·LiSPh/THF. <sup>b</sup> At 25 and 45 °C this catalyst produced **39** in 20–26% yield. <sup>c</sup> Conditions are 0.5 M Grignard in THF, 1:1 RMgX:R'Y, 6% catalyst, 6% v/v HMPA, 67 °C, and either 24 or 48 h reaction times as noted. <sup>d</sup> Reaction was run at room temperature.

vinyl and allyl lower order cuprates couple to iodo-electrophiles in similar (or worse) yields only with the use of 3–4 equiv of cuprate (i.e., 6–8 equiv of Grignard).<sup>15</sup>

The further examination of the less reactive secondary and tertiary Grignard reagents, and secondary alkyl sulfonates, along with an ester functionalized tosylate (vide infra) revealed the full scope and potential of our new catalyst. In each case, our catalyst exhibited greatly enhanced reactivity over that of Li<sub>2</sub>CuCl<sub>4</sub> and CuBr. *Indeed, the reactivity was equal to or greater than that of a comparable Gilman reagent, and as before, good product yields occurred without the need for excess Grignard reagent.* When (1-methylethyl)magnesium chloride (**25**) was reacted with heptyl tosylate (**11**), 2-methylnonane (**26**) was formed in 65% yield (67 °C, 6% HMPA v/v) (Scheme 3, Table 4, entry 3) with our soluble catalyst, compared to only 29% yield with the use of Li<sub>2</sub>CuCl<sub>4</sub> or with CuBr (Table 4, entries 1 and 2). The first yield is somewhat less than those found when Gilman reagents are used to transfer secondary R groups; however, where 3–5 equiv of the cuprate are required, only 1 equiv of the Grignard reagent was used.<sup>2,4</sup> In fact, the use of excess Grignard reagent in the coupling reaction utilizing catalyst C did not improve product yield. It was found necessary to prepare the Grignard reagent from 2-chloropropane rather than 2-bromopropane, for the substitution reaction was slow enough that exchange of bromide ion with the tosylate was a competing side reaction, and 1-bromoheptane does not efficiently couple with the secondary alkyl Grignard reagent. The coupling of 1 equiv of *t*-C<sub>4</sub>H<sub>9</sub>MgCl (**27**) with 1 equiv of tosylate **11** furnished coupled product **28** in 50% yield (Table 4, entry 6) with our catalyst compared to 16% yield with Li<sub>2</sub>CuCl<sub>4</sub> and 33% yield with CuBr (Table 4, entries 4–5). The 50% yield is substantially lower than when Johnson used (*t*-C<sub>4</sub>H<sub>9</sub>)<sub>2</sub>CuLi (**29**) to couple with octyl tosylate (**30**), furnishing 2,2-dimethyldecane (**31**) (Scheme 3) in 90% yield, based on tosylate.<sup>3</sup> However, it was necessary for the addition of 5 equiv of cuprate (10 equiv of Grignard reagents) to obtain that yield. Thus, our

**Scheme 3**

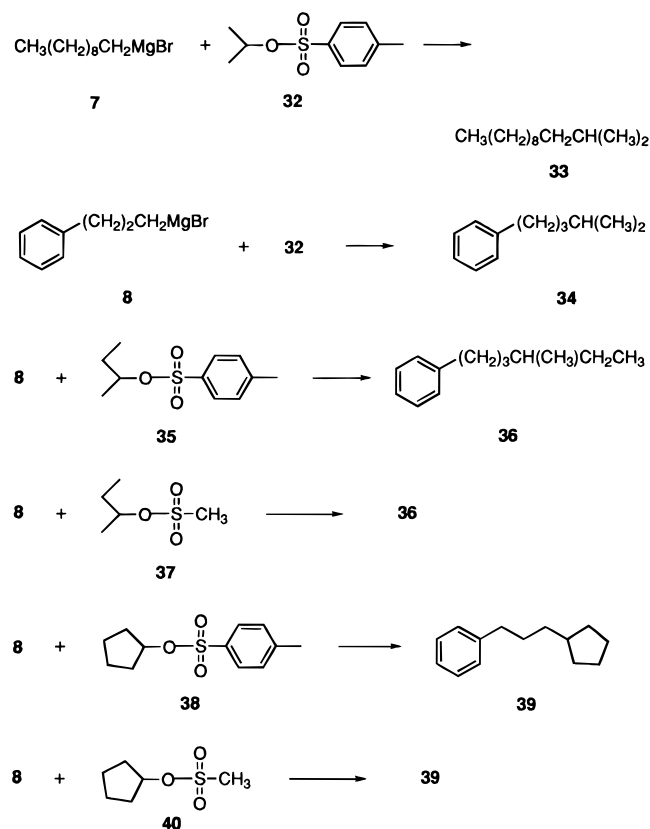
catalyst's ability to couple secondary and tertiary Grignard reagents to a primary tosylate far outweighs that of Li<sub>2</sub>CuCl<sub>4</sub> or CuBr and is certainly the system of choice even over a cuprate when the Grignard reagent (transfer group) is considered precious.

Lower order cuprates (or copper catalysts combined with Grignard reagents) do not effectively couple primary R groups (except methyl) to secondary alkyl halides or tosylates because the sterically hindered electrophiles are prone to elimination.<sup>2b</sup> The efficient substitution of secondary alkyl halides (tosylates are not as efficient<sup>2b</sup>) with an alkyl or allylic group has required the use of "higher order" cuprates. Therefore, we were pleasantly surprised to find that our copper catalyst coupled primary Grignard reagents with a range of secondary tosylates and mesylates at 67 °C in good yield (Scheme 4, Table 4). As before, the reaction utilized only 1 equiv of Grignard reagent, compared to the common use of 2 equiv of R<sub>2</sub>Cu(CN)Li<sub>2</sub> in the cuprate coupling reaction. Thus, the reaction of a 1:1 ratio of isopropyl tosylate **32** and decylmagnesium bromide (**7**) with our catalyst produced 2-methyldodecane (**33**) in 76% yield (Table 4, entry 9), compared to 59% yield with the use of Li<sub>2</sub>CuCl<sub>4</sub> and 7% yield with the use of CuBr (Table 4, entries 7 and 8). The addition of (3-phenylpropyl)magnesium bromide (**8**) to isopropyl tosylate (**32**) furnished 4-methyl-1-phenylpentane (**34**) in 80% yield with the use of catalyst C (Table 4, entry 12).

Attempted coupling of (3-phenylpropyl)magnesium bromide (**8**) and *sec*-butyl tosylate (**35**) or cyclopentyl tosylate (**38**) with our catalyst produced products in low yields (35%), while catalysts A and B produced no product. Much of the Grignard reagent remained after 24 h, as evidenced by the reaction quench. Allowing the reaction to reflux for longer periods increased the product yield only slightly. Lipshutz has demonstrated that the change from a sterically hindered secondary tosylate to a less hindered mesylate improved the coupling reaction yields of "higher order" cuprates.<sup>2b</sup> By utilizing this approach with our catalyst, we found that coupling **8** and *sec*-butyl mesylate (**37**) furnished 4-methyl-1-phenylhexane (**36**) in 62% yield, while little product was prepared with the use of catalysts A and B (Table 4, entries 15–17). With the same Grignard reagent, cyclopentyl mesylate (**40**) produced 1-cyclopentyl-3-phenylpropane (**39**) in 74% yield when our catalyst

(15) Bajgrowicz, J. A.; Hallaoui, A. E.; Jacquier, R.; Pigiere, C.; Viallefont, P. *Tetrahedron* **1985**, *41*, 1833–1843.

## Scheme 4

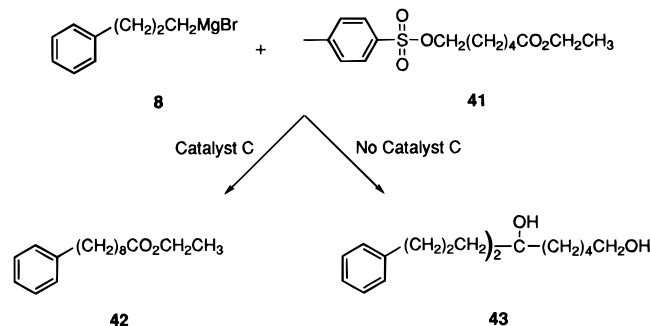


was used and again very poor yields with the use of catalysts A and B (Table 4, entries 18–20). Unfortunately, our catalyst was not able to efficiently couple (3-phenylpropyl)magnesium bromide with  $C_6H_{11}X$ , ( $X =$  iodine, tosylate, or mesylate), for 1-cyclohexyl-3-phenylpropane was never produced in more than 16% yield. Similar to the “higher order” cuprates, catalyst C was unable to couple secondary or aromatic Grignard reagents to secondary sulfonates. However, with its ability to couple primary Grignard reagents with several secondary alkyl sulfonates, our catalyst demonstrated greater reactivity than that of lower order cuprates, furnishing coupled products in good yields with the use of a 1:1 ratio of reactants.

In general, cuprates and Grignard reagents combined with  $Li_2CuCl_4$  and other nonsoluble catalysts exhibit compatibility with acid derivatives.<sup>16,17</sup> To test the carbonyl chemoselectivity of a Grignard reagent/catalyst C system, tosylate **41** was prepared from ethyl 6-hydroxyhexanoate. Reaction with Grignard **8** at room temperature furnished ethyl 9-phenylnonanoate (**42**) in 71% yield (Scheme 5, Table 4, entry 21). Addition of Grignard **8** to tosylate **41** without catalyst C under identical conditions produced little coupled product. Instead, bis-addition of the Grignard to the ester with formation of the tertiary alcohol **43** was observed, along with loss of the tosylate functional group, presumably via addition of ethoxide to the sulfonate. No products resulting from addition of **8** to the ester carbonyl (nor loss of the tosylate functional group) were detected when catalyst C was used. Thus, the catalyst C/Grignard reagent system exhibited not only a range of reactivity similar to the cuprates but also similar chemoselectivity as well.

**<sup>1</sup>H NMR and UV/Visible Spectral Characterization of “CuBr(SMe<sub>2</sub>)LiBr” and Catalyst C in Solution.** We previously reported the <sup>1</sup>H NMR of the washed and dried solid Cu(I)

## Scheme 5



catalyst (precipitated from THF at room temperature) which showed that THF,  $SMe_2$ , and SPh were Cu(I) ligands.<sup>5</sup> Atomic absorption spectroscopy has since shown that the precipitate also contained Li, Br, and Cu. It has not been possible to obtain a suitable crystal for single-crystal X-ray analysis, and it is not clear whether the catalyst in this precipitate forms a homogeneous mixture (elemental analyses of different precipitate mixtures do not coincide). However, we have used <sup>1</sup>H NMR spectrometry and UV/visible spectrophotometry to investigate the soluble copper catalyst and its component parts in an initial attempt to probe its solution structure.

Although  $CuBr-SMe_2$  was insoluble in THF, it was completely taken up into solution with the addition of 1 equiv of LiBr. This is similar to the solubilization of CuCN in THF with the addition of 2 equiv of LiCl.<sup>18</sup> We hypothesized that the LiBr allowed aggregates to form that could complex with THF, dissolving the copper salt, as is the case with CuCN and LiCl in THF.<sup>19,20</sup> At room temperature and above, the <sup>1</sup>H NMR of the  $CuBr-SMe_2-LiBr$  solution (THF- $d_8$ ) showed an extremely broad singlet centered at 2.1 ppm due to the methyl resonance. Presumably, different structures that contain dimethyl sulfide are in slow exchange in the NMR time scale, producing the broad singlet observed. Cooling the sample to temperatures between 0 and 10 °C showed the loss of the resonance signal into the baseline, and further cooling to -95 °C showed the growth of a singlet that greatly narrowed as the temperature was lowered (Figure 2). Over the entire temperature range, the methyl resonance signal shifted downfield as the signal became broader and the temperature was lowered to 0 °C, and then shifted back upfield with the re-emergence and narrowing of the signal as the solution was cooled below 0 °C. This shift may reflect a change in the distribution of species within the slow exchange region.

The change in distribution and very slow exchange of these precursor species between 0 and 10 °C might be a factor in the longer solubility times of catalyst C prepared in that temperature range. Examination of catalyst C (via addition of 1 equiv of LiSPh to  $CuBr-SMe_2-LiBr$  in THF- $d_8$ ) with <sup>1</sup>H NMR showed that the dimethyl sulfide signal sharpened to a narrow singlet whose methyl resonance was exactly that of uncomplexed dimethyl sulfide. On the other hand, the phenolic aromatic proton resonances changed dramatically upon the addition of the thiophenol salt, indicating that it was now bound to the copper. The three aromatic proton resonances at 7.25 ppm (d, 2H), 6.70 ppm (t, 2H), and 6.51 ppm (t, 1H) of LiSPh were transformed into a multiplet at 7.52–7.22 ppm (2H) and a broad singlet at 6.76 ppm (3H). The ligation of LiSPh was also substantiated by the change in the UV/visible spectrum of LiSPh

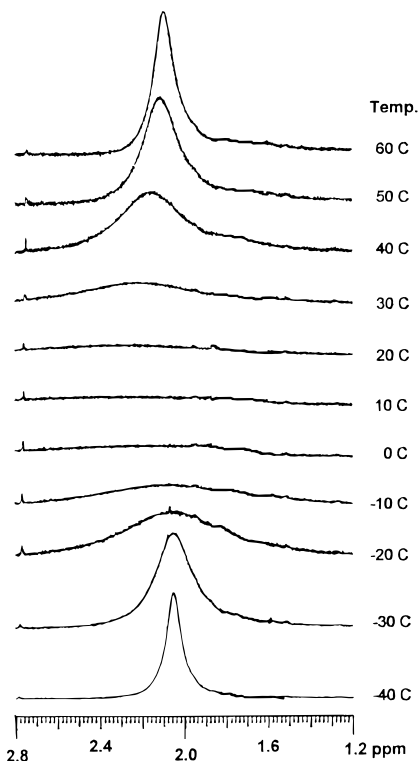
(18) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. J. *Org. Chem.* **1988**, *53*, 2390–2392.

(19) Lipshutz, B. H.; Stevens, K. L.; James, B.; Pavlovich, J. G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 6796–6797.

(20) Huang, H.; Alvarez, K.; Qiang, L.; Barnhart, T. M.; Snyder, J. P.; Penner-Hahn, J. E. *J. Am. Chem. Soc.* **1996**, *118*, 8808–8816.

(16) Nunomoto, S.; Kawakami, Y.; Yamashita, Y. *J. Org. Chem.* **1983**, *48*, 1912–1914.

(17) Normant, J. F.; Villieras, J.; Scott, F. *Tetrahedron Lett.* **1977**, 3263–3266.

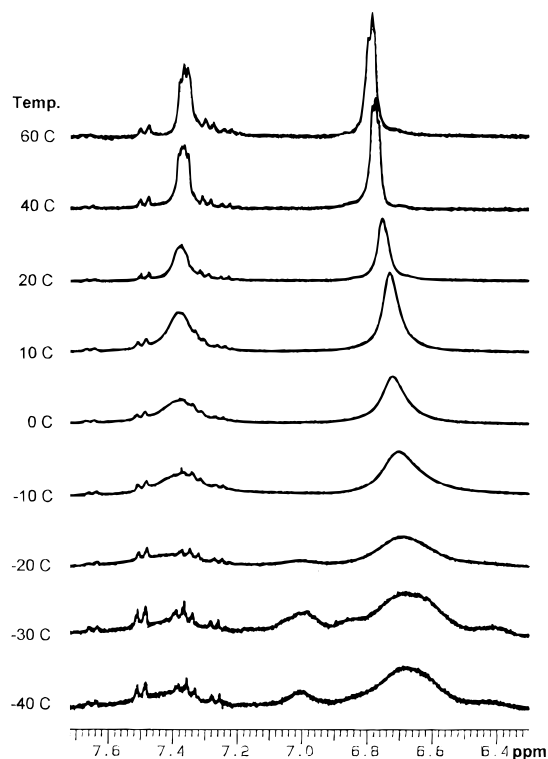


**Figure 2.** Variable-temperature  $^1\text{H}$  NMR (300 MHz) of 1:1 ratio of  $\text{CuBr-S(CH}_3)_2$  plus  $\text{LiBr}$  in  $\text{THF-d}_8$  (referenced to a THF resonance at 1.74 ppm that was removed for clarity).

as it was added to a THF solution of  $\text{CuBr-SMe}_2\text{-LiBr}$ , exhibiting a blue-shift (loss of 292 nm peak with concomitant increase in peak at 266 nm) as the free anion became a bound species.<sup>21</sup> Upon cooling of catalyst C from 20 to  $-10$  °C, the resonance at 6.76 ppm became a broad singlet that shifted upfield to 6.71 ppm, and the broad singlet at 7.39 broke up into several multiplet resonances (Figure 3). Unlike the precursor species, there was no dramatic change in the spectra within the above temperature range, although the resonances continued to broaden as the solution was cooled. Thus, in solution at 0–10 °C, catalyst C is made up of several copper species whose blend remains soluble for several hours and whose structures are most likely composed of metal and SPh, THF, Br, and Li.

## Conclusions

The scope and limitations of the new soluble copper catalyst “ $\text{CuBr-LiBr-LiSPh-THF}$ ” have been examined. The catalyst has been shown to be highly efficient at coupling primary, secondary, tertiary, aryl, vinyl, and allylic Grignard reagents to primary tosylates with the use of only 1 equiv of the Grignard reagent. Additionally, the catalyst couples primary Grignard reagents to secondary tosylates and mesylates in good to excellent yields, again with the use of 1 equiv of Grignard reagent. The catalyst has been shown to be more reactive than other copper catalysts to date and more efficient in the transference of secondary and tertiary alkyl groups than lower order cuprates and has demonstrated more reactivity than the lower order cuprates with its ability to couple primary Grignard reagents to secondary sulfonates. Rather than a cuprate, the copper catalyst method is the system of choice when a synthetically precious transfer group can be made into a Grignard reagent. The carbonyl chemoselectivity of a Grignard



**Figure 3.** Variable-temperature  $^1\text{H}$  NMR (300 MHz) of 1:1 ratio of  $\text{CuBr-S(CH}_3)_2$ ,  $\text{LiBr}$ , and  $\text{LiSPh}$  (catalyst C) in  $\text{THF-d}_8$  (referenced to a THF resonance at 1.74 ppm).

reagent/catalyst C system is similar to that of a cuprate, as it is compatible with an ester functionalized tosylate. Finally,  $^1\text{H}$  NMR of the catalyst precursor and catalyst C suggests that a complicated mixture of metal species are present in solution that are presumably ligated with thiophenol, THF, and  $\text{LiBr}$  in aggregated forms.

While cuprates are usually stable only below 0 °C, our system of Grignard reagent and copper catalyst demonstrated efficient coupling with alkyl sulfonates when the reaction was warmed from 0 to 18 °C and, with the addition of 6% v/v HMPA to the catalyst solution, demonstrated efficient coupling with alkyl sulfonates between 25 and 67 °C. Presumably the thiol and HMPA stabilized the Grignard/catalyst system at temperatures where the substitution reactions were most active. This was a particularly relevant finding for the synthesis of our cyclophanes, for previous syntheses of the macrocycles demonstrated that yields were greater at elevated temperatures. We are currently preparing a family of metacyclophanes (**1**, **2**) using the strategy presented in Scheme 1 and our newly developed copper catalyst, which will be reported in due course.

## Experimental Section

**Materials and General Procedures.** The following chemicals were obtained commercially and were dried and purified according to literature methods:<sup>22</sup> tetrahydrofuran (THF) was distilled from sodium and benzophenone; hexamethylphosphoramide (HMPA), bromobenzene, 2-bromoanisole, and pyridine were distilled from calcium hydride; 1-bromodecane, 1-bromoheptane, 1-bromo-3-phenylpropane, 2-bromopropane, and 1-bromopropane were dried over sodium sulfate and then fractionally distilled; 1-iodopropane was dried over sodium carbonate and then fractionally distilled; 2-chloropropane was fractionally distilled; 2-butanol, cyclopentanol, dodecanol, heptanol, 1-propanol, and 2-propanol were dried over sodium carbonate and then fractionally distilled;  $\text{Cu}^{\text{I}}\text{Br}$  was purified with refluxing THF via Soxhlet extraction. Lithium bromide, lithium chloride, cuprous bromide dimethyl sulfide,

(21) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; John Wiley and Sons, Inc.: New York, 1991; pp 306–307.

(22) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1988.

*para*-toluenesulfonyl chloride, and methanesulfonyl chloride were used as received from Aldrich. GC standard decane, dodecane, tridecane, eicosane, hexylbenzene, heptylbenzene, and propylbenzene were used as received from Aldrich. GC standard 1,3-bis(2-methoxyphenyl)propane was prepared by a previously reported method.<sup>5</sup> Allylmagnesium chloride and vinylmagnesium bromide were purchased from Aldrich and assayed by literature procedure.<sup>23</sup>

All melting points (Mel-Temp) and boiling points (micro boiling point apparatus) are uncorrected. <sup>1</sup>H NMR spectra were recorded at 300 MHz in CDCl<sub>3</sub> with Me<sub>4</sub>Si as an internal standard unless otherwise specified. Silica gel (Davisol 633) was used for column chromatography, and analytical thin layer chromatography was performed using precoated Analtech Uniplates (silica gel GF). Samples that underwent spectral and analytical analysis were purified by radial chromatography using a Chromatotron. Elemental analysis was done by Desert Analytics, Tucson, AZ. Gas chromatographs (GC) were obtained with a Hewlett Packard Series II 5890 GC, utilizing a J&W capillary column (DB5, 30 m) and FID detection, and chromatogram signals were integrated using Water's Baseline 810 software. Identities of known compounds in product mixtures were obtained either from GC by comparison with an authentic standard and/or GC/MS. An internal standard method<sup>24</sup> was used to determine yields by GC; standards used were dodecane, tridecane, heptylbenzene, propylbenzene, and 1,4-bis(2-methoxyphenyl)butane,<sup>25</sup> depending on the nature of the product mixtures. GC/MS were obtained with a Varian 3400 GC (SGE capillary column, BP1, 30 m) interfaced to a Finnigan Incos 50 mass spectrometer. All reactions were run under a nitrogen atmosphere obtained by passing the nitrogen through a drying tower containing 3 Å molecular sieves.

**Procedure for the Preparation of Tosylates.** *p*-Toluenesulfonyl chloride (6.7 g, 87.6 mmol) was added over a period of 30 min to a stirred solution of pyridine (27.7 g, 350 mmol) and *n*-propanol (6.32 g, 105 mmol) maintained at 0 °C (1.0 equiv of alcohol was used in the syntheses of the tosylates except for tosylates **10** and **32**, where 1.2 equiv of alcohol were used). The reaction mixture was allowed to stir an additional 3 h (6 h for secondary tosylates) and then quenched with H<sub>2</sub>O (150 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 60 mL), and the combined organic layers were washed with 3 M HCl (3 × 80 mL) followed by 10% NaHCO<sub>3</sub> (1 × 80 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum and the crude product purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>). Azeotrope distillation with benzene (tosylates **21**, **35**, and **38** were dried in a vacuum desiccator over P<sub>2</sub>O<sub>5</sub>) yielded 18.0 g (96%) of 4-methylbenzenesulfonic acid, propyl ester (**10**) as a clear oil: bp 153 °C (lit.<sup>26</sup> 154–156°); <sup>1</sup>H NMR δ 0.90 (t, 3H, *J* = 7.3 Hz), 1.62–1.73 (m, 2H), 2.45 (s, 3H), 3.99 (t, 2H, *J* = 7.2 Hz), 7.36 (d, 2H, *J* = 8.3 Hz), 7.90 (d, 2H, *J* = 8.3 Hz).

**4-Methylbenzenesulfonic Acid, Heptyl Ester (11).** Prepared as a clear oil in 88% yield: bp 201 °C (dec) (lit.<sup>27</sup> 92 °C, 3 mmHg); <sup>1</sup>H NMR δ 0.86 (t, 3H, *J* = 6.6 Hz), 1.18–1.35 (m, 10H), 1.59–1.69 (m, 2H), 2.45 (s, 3H), 4.02 (t, 2H, *J* = 6.6 Hz), 7.35 (d, 2H, *J* = 8.1 Hz), 7.79 (d, 2H, *J* = 8.4 Hz).

**4-Methylbenzenesulfonic Acid, Dodecyl Ester (21).** Prepared as a clear solid in 88% yield: mp 30 °C (lit.<sup>28</sup> 30 °C); <sup>1</sup>H NMR δ 0.857–0.903 (m, 3H), 1.18–1.35 (m, 18H), 1.59–1.68 (m, 2H), 2.45 (s, 3H), 4.02 (t, 2H, *J* = 6.6 Hz), 7.34 (d, 2H, *J* = 8.1 Hz), 7.79 (d, 2H, *J* = 8.4 Hz).

**4-Methylbenzenesulfonic Acid, Isopropyl Ester (32).** Prepared as a clear oil in 94% yield: bp 129 °C (dec) (lit.<sup>26</sup> mp 20 °C); <sup>1</sup>H NMR δ 1.27 (d, 6H, *J* = 6.6 Hz), 2.45 (s, 3H), 4.69–4.77 (m, 1H), 7.34 (d, 2H, *J* = 7.8 Hz), 7.79 (d, 2H, *J* = 8.7 Hz).

**4-Methylbenzenesulfonic Acid, *sec*-Butyl Ester (35).** Prepared as a clear oil in 99% yield: bp 109 °C (dec) (lit.<sup>29</sup> dec); <sup>1</sup>H NMR δ 0.815

(t, 3H, *J* = 7.5 Hz), 1.25 (d, 3H, *J* = 6.3 Hz), 1.52–1.67 (m, 2H), 2.45 (s, 3H), 4.51–4.50 (m, 1H), 7.32 (d, 2H, *J* = 8.1 Hz), 7.79 (d, 2H, *J* = 8.3 Hz).

**4-Methylbenzenesulfonic Acid, Cyclopentyl Ester (38).** Prepared as a clear solid in 91% yield: mp 26 °C (lit.<sup>26</sup> 28 °C); <sup>1</sup>H NMR δ 1.50–1.60 (m, 2H), 1.66–1.85 (m, 6H), 2.45 (s, 3H), 4.92–5.00 (m, 1H), 7.34 (d, 2H, *J* = 8.1 Hz), 7.79 (d, 2H, *J* = 8.4 Hz).

**6-[(4-Methylbenzenesulfonyloxy]hexanoic acid, ethyl ester (41).** Prepared as a clear oil in 84% yield: bp 246–247 °C. IR (cm<sup>-1</sup>) 2932, 2355, 1732, 1595, 1355, 1259, 1173, 1033, 1029, 949, 815; <sup>1</sup>H NMR δ 1.25 (t, 3H, *J* = 7.28 Hz), 1.31–1.39 (m, 2H), 1.55–1.60 (m, 2H), 1.64–1.69 (m, 2H), 2.23–2.28 (t, 2H, *J* = 7.6 Hz), 2.45 (s, 3H), 4.00–4.04 (t, 2H, *J* = 6.4 Hz), 4.08–4.15 (q, 2H, *J* = 7.22 Hz), 7.33–7.36 (d, 2H, *J* = 8.74), 7.78–7.80 (d, 2H, *J* = 8.36 Hz); <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>) δ 173.2, 144.6, 133.1, 129.7, 127.7, 77.4, 77.0, 76.6, 70.2, 60.1, 33.9, 33.8, 28.4, 28.3, 24.8, 24.7, 24.1, 21.5, 14.1; LRMS *m/z* 314 (M<sup>+</sup>), 269, 155, 143, 91. Anal. Calcd for C<sub>15</sub>H<sub>22</sub>O<sub>5</sub>S: C, 57.31; H, 7.05. Found: C, 57.14; H, 7.14.

**Procedure for the Preparation of Mesylates.** A stirred solution of CH<sub>2</sub>Cl<sub>2</sub> (240 mL), 2-butanol (6.02 g, 81 mmol), and triethylamine (12.33 g, 121.8 mmol) was cooled on an ice bath, and methanesulfonyl chloride (10.2 g, 89.3 mmol) was added via syringe at a rate of 0.23 mL/min. The reaction was allowed to stir for 1 h at this temperature and then quenched with 250 mL of ice-water. The mixture was washed successively with 1.5 M HCl (200 mL), 10% NaHCO<sub>3</sub> (200 mL), and brine (200 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The crude product was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>) and dried over P<sub>2</sub>O<sub>5</sub> in a vacuum desiccator for 24 h, furnishing 11.59 g (94%) of methanesulfonic acid, *sec*-butyl ester (**37**) as a clear oil: bp 235 °C (lit.<sup>30</sup> 61 °C, 0.5 Torr); <sup>1</sup>H NMR δ 0.99 (t, 3H, *J* = 7.5 Hz), 1.41 (d, 3H, *J* = 6.3 Hz), 1.62–1.80 (m, 2H), 3.01 (s, 3H), 4.72–4.80 (m, 1H).

**Methanesulfonic Acid, Cyclopentyl Ester (40).** Prepared as a clear oil in 91% yield: bp 232 °C (lit.<sup>31</sup> 71 °C, 1 Torr); <sup>1</sup>H NMR δ 1.62–1.70 (m, 2H), 1.75–1.85 (m, 2H), 1.90–2.01 (m, 4H), 3.00 (s, 3H), 5.15–5.19 (m, 1H).

**Synthesis of Catalyst A: Li<sub>2</sub>CuCl<sub>4</sub>.** Lithium chloride (0.0963 g, 1.29 mmol) and copper(II) chloride (0.1525 g, 1.29 mmol) were weighed into a 25 mL flask under nitrogen in a glovebag or a drybox. The flask was removed from the bag or box and cooled on an ice bath, and dry THF (11.40 mL) was then added. The mixture was allowed to stir for approximately 5 min or until all species were soluble in the resulting 0.1 M bright orange-red solution.

**Synthesis of Catalyst C: Li<sub>2</sub>CuBr<sub>2</sub>SM<sub>2</sub>SPh.** Lithium bromide (0.112 g, 1.29 mmol), lithium thiophenolate (0.150 g, 1.29 mmol), and copper(I) bromide dimethyl sulfide (0.266 g, 1.29 mmol) were weighed into a 50 mL flask in a glovebag or drybox under nitrogen. The flask was removed from the bag or box, placed in an ice bath to cool, and then THF (12.90 mL) was added. The mixture was allowed to stir until all species were soluble in the resulting 0.1 M clear yellow solution. The catalyst was kept in an ice bath and used within the first 2–3 h of its preparation: <sup>1</sup>H NMR (THF-*d*<sub>8</sub>) δ 2.04 (s, 6H), 6.65–6.83 (m, 3H), 7.30–7.52 (m, 2H); UV/visible (THF) λ<sub>max</sub> nm (ε) 216 (4.38 × 10<sup>5</sup>), 266 (2.49 × 10<sup>5</sup>).

**Lithium Thiophenolate (LiSPh).** Thiophenol (4.00 g, 36.30 mmol) was added to Et<sub>2</sub>O (42 mL) in a 100 mL Schlenk flask attached to a double-ended filter funnel, and the mixture was cooled with an ice bath. Methyllithium (39.93 mmol in 30.7 mL of Et<sub>2</sub>O) was added at a rate of 1.02 mL/min to the flask. The reaction was stirred overnight, gradually warming to room temperature. After 24 h, the apparatus was turned upside-down and the reaction mixture was vacuum filtered and the remaining white salt washed with Et<sub>2</sub>O (2 × 35 mL). The powdery white salt was dried under strong vacuum to remove any trace of solvent, yielding 4.11 g (98%) of lithiated thiophenol: <sup>1</sup>H NMR δ (THF-*d*<sub>8</sub>) δ 6.49–6.55 (m, 1H), 6.70 (t, 2H, *J* = 7.5 Hz), 7.25 (d, 2H, *J* = 7.4 Hz); UV/visible (THF) λ<sub>max</sub> nm (ε) 218 (9.14 × 10<sup>2</sup>), 292 (1.66 × 10<sup>3</sup>).

**Typical Procedure and Variations Used in the Copper-Catalyzed Substitution Reaction. Tridecane (13).** 1-Bromodecane (0.70 g, 3.17 mmol) in 3.4 mL of THF was added at a rate of 0.33 mL/min to Mg

(23) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–168.

(24) (a) Grant, D. W. *Capillary Gas Chromatography*; John Wiley and Sons, Inc.: New York, 1996; pp 235–252. (b) Schomburg, G. *Gas Chromatography*; VCH Publishers, Inc.: New York, 1990; pp 108–122.

(25) Unpublished work; this compound gave satisfactory spectral and elemental analysis.

(26) Drahowzal, F.; Klamman, D. *Monatsh. Chem.* **1951**, *82*, 452–459.

(27) Carman, R. M.; Kibby, J. J. *Aust. J. Chem.* **1976**, *26*, 1761–1767.

(28) Sekera, V. C.; Manel, C. S. *J. Am. Chem. Soc.* **1933**, *55*, 345–349.

(29) Gilman, H.; Beaber, N. J. *J. Am. Chem. Soc.* **1925**, *47*, 518–525.

(30) Helmkamp, R. *J. Org. Chem.* **1957**, *22*, 479–481.

(31) Mosher, H. S.; Williams, H. R. *J. Am. Chem. Soc.* **1954**, *76*, 2987–2990.



turnings (0.384 g, 15.8 mmol) in 3.0 mL of THF. The mixture was allowed to gently reflux for 2 h and cooled to ambient temperature, and the prepared Grignard reagent **7** was added at a rate of 0.33 mL/min to a solution containing propyl tosylate (**10**) (0.679 g, 3.17 mmol), 1.90 mL of a 0.1 M solution of catalyst C, and 0.56 mL of HMPA (6% v/v) that was maintained at room temperature. After 18 h the reaction was quenched with 100 mL of 1.5 M HCl and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 35 mL). The combined organic layers were washed again with 100 mL of 1.5 M HCl (to remove HMPA), and the acid wash was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 35 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum. The crude oil was purified by chromatography filtration (silica gel plug eluting with CH<sub>2</sub>Cl<sub>2</sub>), and the yields of tridecane (**13**), eicosane (Wurtz product), and decane (quenched Grignard reagent) were determined by GC analysis using dodecane as an internal standard. Identities of the peaks in the GC chromatogram were confirmed by co-injection with authentic standards. Yield of tridecane (**13**) was 0.502 g (2.73 mmol, 86%). Yields of all coupled products are presented in Tables 1–4. *Variants on the above procedure are as follows:* (1) with catalyst A, the above procedure was followed, but with the use of catalyst B, the reaction conditions employed refluxing THF/HMPA, and CuBr was used in 12 mol %, unless otherwise indicated; (2) reaction temperatures were also carried out at 0 °C (the reaction was allowed to warm slowly to 15–18 °C over the rest of the reaction time, and since no HMPA was added, only one acid wash was used in the workup), 45 and 67 °C, as noted in Tables 1–4; (3) reactions performed with secondary tosylates and mesylates were run for 48 h, as noted in Table 4; (4) new compounds were purified with chromatography (Chromatotron), and their reported yields in Tables 1–4 are purified yields; (5) 2-bromoanisole was allowed to react with Mg turnings for 3–4 h before their addition to the reaction mixture; (6) glassware that utilized catalyst C was washed with a 10% bleach solution to remove malodorous sulfur compounds.

The identities and yields of coupled products tridecane (**13**), hexylbenzene (**14**), and heptylbenzene (**16**) were determined from GC by co-injection with authenticated standards and by GC/MS. The identities and yields of the following coupled products, as well as reaction byproducts, were also established with GC and GC/MS. However, since the relevant literature is old enough so that there was no available NMR spectra, the reaction mixtures were purified so <sup>1</sup>H NMR could be presented. The new compounds, tosylate **41** and ester **42**, are presented with full analytical data (<sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, LRMS, and elemental analysis).

**2-Heptyl-1-methoxybenzene (15).** The crude product was purified by chromatography (Chromatotron, hexanes) which furnished **15** as a clear oil: bp 260–262 °C (lit.<sup>32</sup> 153–155 °C, 20 Torr); <sup>1</sup>H NMR δ 0.85–0.95 (m, 3H), 1.25–1.40 (m, 8H), 1.52–1.62 (m, 2H), 2.60 (t, 2H, *J* = 7.8 Hz), 3.82 (s, 3H), 6.81–6.91 (m, 2H), 7.10–7.20 (m, 2H). Anal. Calcd for C<sub>14</sub>H<sub>22</sub>O: C, 81.50; H, 10.75. Found: C, 81.48; H, 10.55.

**1,3-Diphenylpropane (19).** The crude product was purified by chromatography (Chromatotron, hexanes) which furnished **19** as a clear oil: bp 69–71 °C, 0.025 Torr (lit.<sup>33</sup> 123–124 °C, 1.7 Torr); <sup>1</sup>H NMR δ 1.90–2.01 (m, 2H), 2.65 (t, 4H, *J* = 7.6 Hz), 7.16–7.27 (m, 10 H).

**1-Tetradecene (22).** The crude product was purified by chromatography (Chromatotron, petroleum ether) which furnished **22** as a clear oil: bp 250 °C (lit.<sup>34</sup> 251 °C); <sup>1</sup>H NMR δ 0.86–0.90 (m, 3H), 1.20–1.30 (m, 20 H), 2.00–2.09 (m, 2H), 4.09–5.02 (m, 2H), 5.81–5.87 (m, 1H).

**1-Pentadecene (24).** The crude product was purified by chromatography (Chromatotron, petroleum ether) which furnished **24** as a clear oil: bp 267 °C, (lit.<sup>35</sup> 269 °C); <sup>1</sup>H NMR δ 0.86–0.89 (m, 3H), 1.20–1.30 (m, 22 H), 2.00–2.09 (m, 2H), 4.09–5.02 (m, 2H), 5.82–5.88 (m, 1H).

**2-Methylnonane (26).** The crude product was purified by chromatography (Chromatotron, petroleum ether,) which furnished **26** as a

clear oil: bp 165 °C (lit.<sup>36</sup> 166.8 °C); <sup>1</sup>H NMR δ 0.79–0.95 (m, 9H), 1.15–1.35 (m, 13H).

**2,2-Dimethylnonane (28).** The crude oil was purified by chromatography (Chromatotron, petroleum ether) which furnished **28** as a clear oil: bp 186 °C, (lit.<sup>37</sup> 186 °C); <sup>1</sup>H NMR δ 0.85–0.87 (br s, 12H), 1.20–1.34 (m, 12H).

**2-Methyldodecane (33).** The crude product was purified by chromatography (Chromatotron, petroleum ether) which furnished **33** as a clear oil: bp 233–235 °C (lit.<sup>38</sup> 103 °C, 10.5 Torr); <sup>1</sup>H NMR δ 0.85–0.87 (m, 9H), 1.26 (br s, 19H).

**4-Methyl-1-phenylpentane (34).** The crude product was purified by chromatography (Chromatotron, petroleum ether) which furnished **34** as a clear oil: bp 218 °C, (lit.<sup>39</sup> 219 °C); <sup>1</sup>H NMR δ 0.87 (d, 6H, *J* = 6.1 Hz), 1.2–1.3 (m, 2H), 1.5–1.66 (m, 3H), 2.58 (t, 2H, *J* = 8.0 Hz), 7.15–7.30 (m, 5H). Anal. Calcd for C<sub>12</sub>H<sub>18</sub>: C, 88.82; H, 11.18. Found: C, 88.56; H, 10.83.

**4-Methyl-1-phenylhexane (36).** The crude product was purified by chromatography (Chromatotron, hexanes) which furnished **36** as a clear oil: bp 248–249 °C, (lit.<sup>40</sup> 85–86 °C, 3.0 Torr); <sup>1</sup>H NMR δ 0.82–0.87 (m, 6H), 1.10–1.22 (m, 1H), 1.28–1.42 (m, 4H), 1.55–1.67 (m, 2H), 2.56–2.62 (m, 2H), 7.16–7.26 (m, 5H).

**3-Cyclopentyl-1-phenylpropane (39).** The crude product was purified by chromatography (Chromatotron, hexanes) which furnished **36** as a clear oil: bp 267 °C (lit.<sup>41</sup> 133 °C, 10 Torr). <sup>1</sup>H NMR δ 1.03–1.05 (m, 2H), 1.32–1.38 (m, 2H), 1.46–1.80 (m, 9H), 2.60 (t, 2H, *J* = 7.8 Hz), 7.14–7.30 (m, 5H). Anal. Calcd for C<sub>14</sub>H<sub>20</sub>: C, 89.30; H, 10.70. Found: C, 89.03; H, 10.56.

**9-Phenylnonanoic Acid, Ethyl Ester (42).** 1-Bromo-3-phenylpropane (0.780 g, 3.92 mmol) in THF (3.9 mL) was added at a rate of 0.33 mL/min to Mg turnings (0.476 g, 19.6 mmol) in THF (3.9 mL). The mixture was heated to reflux for 2.0 h and cooled, and the Grignard reagent was added at a rate of 0.33 mL/min to a solution of 6-[(4-methylbenzenesulfonyl)oxy]hexanoic acid, ethyl ester (1.232 g, 3.92 mmol), 2.35 mL of 0.1 M catalyst C, and HMPA (0.50 mL, 6% v/v). The reaction mixture was allowed to stir at room temperature for 18 h at which time it was quenched with 1.5 M HCl (100 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 35 mL). The combined organic layers were washed with 1.5 M HCl (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under vacuum. The crude product was subjected to chromatography (silica gel, hexane to elute propylbenzene and 90/10 hexane/ethyl acetate to elute product) which furnished 0.720 g (71%) of 9-phenylnonanoic acid, ethyl ester (**42**) as a clear oil: bp 322 °C. IR (cm<sup>-1</sup>) 2932, 2857, 1728, 1454, 1373, 1258, 1186, 1031; <sup>1</sup>H NMR δ 1.22–1.30 (m, 11H), 1.58–1.63 (m, 4H), 2.28 (t, 2H, *J* = 7.4 Hz), 2.59 (t, 2H, *J* = 7.9 Hz), 4.12 (q, 2H, *J* = 7.1 Hz), 7.15–7.27 (m, 5H); <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>) δ 14.3, 25.0, 29.1, 29.3, 31.4, 34.4, 36.0, 60.1, 76.6, 77.0, 77.4, 125.6, 128.2, 128.4, 142.6, 173.4; LRMS *m/z* 262 (M<sup>+</sup>), 217, 185, 171, 91. Anal. Calcd for C<sub>17</sub>H<sub>26</sub>O<sub>2</sub>: C, 77.82; H, 9.99. Found: C, 77.98; H, 9.90.

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(32) Klages, A. *Chem. Ber.* **1905**, *37*, 3987–4002.  
 (33) Sergian, K. T.; Wise, P. H. *J. Am. Chem. Soc.* **1951**, *73*, 4766.  
 (34) Dupont, G.; Dulou, R.; Chetieu-Bessière, Y. *C. R. Hebd. Seances Acad. Sci.* **1958**, *246*, 126.  
 (35) Schmidt, A. W.; Schoeller, V.; Eberlein, K. *Chem. Ber.* **1941**, *74*, 1313.

(36) Calingaert, G.; Sovaos, S. *J. Am. Chem. Soc.* **1936**, *58*, 635–636.  
 (37) Karapet'yants, K. M. *Zh. Fiz. Khim.* **1956**, *30*, 2218–2227.  
 (38) Petrov, A.; Sergienko, S. R.; Nechitailo, N. A.; Tsedilina, A. L. *Izv. Akad. Navk. SSSR, Otd. Khim. Nauk.* **1959**, 1091–1097.  
 (39) Pines, H.; Arrigo, J. T. *J. Am. Chem. Soc.* **1957**, *79*, 4958–4959.  
 (40) Young, W. G.; Kosmin, M.; Mixer, R. Y.; Campbell, T. W. *J. Am. Chem. Soc.* **1952**, *74*, 608–611.  
 (41) Evans, A.; Hibbard, R. R. *Anal. Chem.* **1951**, *23*, 1604–1610.