

Nickel-Mediated Cross-Coupling of Unactivated Neopentyl Iodides with Organozincs

Kwangyong Park, Kaixu Yuan, and William J. Scott*¹

Department of Chemistry, The University of Iowa, Iowa City, Iowa 52242

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(dppf)NiCl₂ catalyzes the cross-coupling of unactivated primary neopentyl iodides with diorganozinc reagents. The zinc nucleophiles are formed by the treatment of ZnCl₂-dioxane with 2 mol equiv of a Grignard reagent in an ethereal solvent. The cross-coupling works optimally for diorganozincs formed from aryl chlorides or CH₃MgCl. Use of aryl bromides can cause reduction and/or reductive dimerization of the electrophile. The analogous reaction with (CH₃)₂CuMgCl in either the presence or the absence of Group 10 metal catalysts failed to afford reasonable yields of cross-coupled products. The diorganozinc methodology overcomes many of the side reactions observed with the (dppf)-NiCl₂-mediated cross-coupling of Grignard reagents.

Introduction

Carbon-carbon bond-forming reactions are among the most useful tools in the arsenal of the organic chemist. Palladium and nickel catalysts have become increasingly popular for mediating the coupling reactions of organic halides or pseudohalides which contain sp or sp² carbons at or immediately adjacent to the electrophilic center.² Presumably, the π -systems play an important role by precomplexing with the catalyst prior to oxidative addition. Until recently, few reports on the use of Group 10 transition-metal complexes to mediate the cross-coupling reactions of unactivated sp³ electrophiles had appeared. This can be attributed to the lack of reactivity of the catalysts and to the expectation of the formation of side products. Pearson showed that low-valent palladium species react with methyl iodide or methyl tosylate at relatively slow rates,³ indicating that oxidative addition of unactivated electrophiles may be a difficult process. Even if oxidative addition occurs, the newly formed alkyl metal species may undergo β -hydride elimination in competition with desired reaction processes. It has been commonly assumed that β -hydride elimination is a rapid process and that cross-coupling cannot normally compete with olefin formation.²

For the development of a general reaction utilizing unactivated sp³-electrophiles, one must therefore employ a catalyst that possesses sufficient nucleophilicity to allow oxidative addition with the electrophile and with electronic or steric features that minimize β -hydride elimination by either the electrophile or the nucleophile. Suzuki has recently found that Pd(PPh₃)₄ will catalyze the cross-coupling of unactivated alkyl halides with 9-alkyl-9-BBN derivatives both in the presence and absence of carbon monoxide.⁴ Under these conditions β -hydride elimination is largely overcome, but reduction of the electrophile remains a serious problem.

During a program directed toward the development of Group 10 metal complexes that would catalyze carbon-carbon bond formation using primary neopentyl electrophiles, we discovered that dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium(II), (dppf)PdCl₂,⁵ effectively catalyzes the Grignard-mediated reduction of both primary neopentyl iodides and *n*-alkyl iodides in Et₂O.^{6,7} The neopentyl group was initially chosen both because carbon-carbon bond formation using neopentyl electrophiles remains a difficult synthetic problem and because use of these electrophiles would avoid problems due to competitive β -hydride elimination. It was also recognized that neopentyl electrophiles present a severe test of the ability of a transition metal catalyst to undergo oxidative addition in the absence of activation, due to the steric encumbrance about the site of the electrophile.

Because the palladium-catalyzed reduction appeared to circumvent the problems of slow oxidative addition and rapid β -hydride elimination inherent to Group 10 metal-catalyzed reactions of unactivated alkyl electrophiles, we investigated the mechanism of both the palladium-catalyzed reduction and the unrelated reduction.⁷ This study indicated a number of factors that must be considered for the successful cross-coupling of unactivated electrophiles with nucleophiles. The nucleophile must be sufficiently stable under the reaction conditions to avoid direct reduction of the electrophile and to resist hydride delivery to the catalyst. At the same time, the nucleophile must be reactive enough to allow the transmetalation step of the catalytic cycle to occur. The solvent must be optimized to minimize uncatalyzed interactions between the electrophile and the nucleophile. In this study⁷ and others,⁸ Et₂O appeared to be preferable to THF for these reasons. Finally, the catalyst must be sufficiently nucleophilic to allow the oxidative addition reaction to occur.

On the basis of these principles, we discovered that dichloro(1,1'-bis(diphenylphosphino)ferrocene)nickel-

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Table I. Catalyzed Reaction of 1-Phenyl-2,2-dimethyl-3-iodopropane (2, RI) with CH₃MgCl (R'MgCl) after Pretreatment with a Transmetalation Additive^a

entry	catalyst	transmetalation additive (additive-CH ₃ MgCl ratio)	solvent (t, °C)	GC yield (%)		
				RR' (3)	RH (4)	RR (5)
1	(dppf)NiCl ₂	ZnCl ₂ -dioxane (0.5)	Et ₂ O (35)	91	9	0
2	(dppf)NiCl ₂	none	Et ₂ O (35)	75	9	16
3	(dppf)NiCl ₂	ZnCl ₂ -dioxane (0.5) ^b	Et ₂ O (35)	93	7	0
4	(dppf)NiCl ₂	ZnCl ₂ -dioxane (1.0)	Et ₂ O (35)	79	5	0 ^d
5	(dppf)NiCl ₂	ZnCl ₂ (0.5)	Et ₂ O (35)	91	9	0
6	(dppf)NiCl ₂	ZnBr ₂ (0.5)	Et ₂ O (35)	81	13	6
7	(dppf)NiCl ₂	ZnCl ₂ -dioxane (0.5)	THF (67)	89	11	0
8	(dppf)NiCl ₂	ZnCl ₂ -dioxane (0.5)	Diox (101)	87	10	0 ^d
9	(dppf)NiCl ₂	ZnCl ₂ -dioxane (0.5)	Bu ₂ O (115)	66	33	0 ^d
10	(dppf)NiCl ₂	ZnCl ₂ -dioxane (0.5)	HMPA (25)	56	41	0 ^d
11	(dppf)NiCl ₂	ZnCl ₂ -dioxane (0.5)	tol (111)	62	38	0
12	none	ZnCl ₂ -dioxane (0.5)	Et ₂ O (35)	0	92	0 ^d
13	Ni(acac) ₂	ZnCl ₂ -dioxane (0.5)	Et ₂ O (35)	0	81	0 ^d
14	(dppf)Ni(0) ^c	ZnCl ₂ -dioxane (0.5)	Et ₂ O (35)	77	23	0
15	(dppf)NiCl ₂	CuI (0.5)	Et ₂ O (35)	67	16	17

^a A slurry of transmetalation additive in solvent (0.19 M) was treated with CH₃MgCl (0.38 M Et₂O, 3.0 mmol) and transferred via cannula directly into a mixture of iodide 2 (1.0 mmol), GC standard, and catalyst (10 mol %) in solvent (0.1 M in 2) at the indicated temperature. The mixture was stirred at that temperature for 36 h, quenched by the addition of a 1% HCl solution, and analyzed by GC. ^b The CH₃MgCl/ZnCl₂ mixture was transferred via cannula to a sintered glass funnel containing a bed of dry Celite and filtered directly into the reaction mixture. ^c The (dppf)NiCl₂ was reduced with 20 mol % DIBAL prior to the addition of iodide 2. ^d The remaining material isolated was unreacted iodide 2.

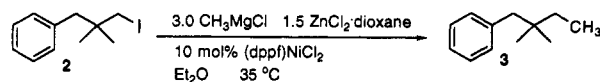
(II), (dppf)NiCl₂,⁹ will catalyze the cross-coupling of primary unactivated neopentyl electrophiles with aryl, heteroaryl, and naphthyl Grignard reagents,¹⁰ the first general case of the Group 10 metal-mediated cross-coupling of a nucleophile with unactivated electrophiles.¹¹ The nickel catalyst was chosen in order to increase the nucleophilicity of the catalyst¹² while retaining the steric and electron-donating effects of the dppf ligand. (dppf)-NiCl₂ (1) had previously been used to catalyze the reactions of 5-alkyl-2,3-dihydrofurans,¹³ allylic esters and sulfones,¹⁴ silyl enol ethers,¹⁵ β-bromostyrene,¹⁶ and 2-(methylthio)-4,4-dimethyl-2-oxazoline.¹⁷ However, there had been no previous reports of its use to catalyze reactions of unactivated electrophiles. Unfortunately, the reaction mixture from the Grignard reagent cross-coupling occasionally contained side products including those resulting from reduction and reductive dimerization of the neopentyl electrophile, making purification of the product difficult and lowering the yield of cross-coupled product.

The observation of products due to the reductive dimerization of the electrophile suggested that a radical process might be on-going. Radical-based side reactions might be suppressed in several ways, including varying the catalyst, the electrophile, or the nucleophile. Having previously conducted some preliminary catalyst and electrophile studies,¹⁸ the latter possibility seemed most intriguing. Negishi pioneered the cross-coupling of organozincs with electrophiles.¹⁹ He found that substitution of very hard nucleophiles, such as organolithiums and Grignard reagents, with the softer organozincs minimizes side products in cross-coupling reactions, often avoiding them altogether.²⁰ Such a tactic has also been used in the palladium-mediated coupling of electrophiles with organostannanes and organoborates.²¹ Thus, it seemed plausible that use of softer nucleophiles in place of Grignard reagents might reduce radical-based reactions such as dimerization and also minimize transmetalation of the alkyl halide, which leads to reduction.

Results

Previously, CH₃MgX had been shown to cross-couple poorly with neopentyl halides.¹⁰ The ability of (dppf)-

NiCl₂ to catalyze cross-coupling reactions of neopentyl iodides with organozinc reagents was therefore initially examined with methyl nucleophiles. Treatment of a mixture of 1-iodo-2,2-dimethyl-3-phenylpropane (2) and



(dppf)NiCl₂ (10 mol %) with dimethylzinc, formed *in situ* by treatment of CH₃MgCl (3 equiv) with ZnCl₂-dioxane²² (1.5 equiv), gave 1-phenyl-2,2-dimethylbutane (3, 91%) along with 1-phenyl-2,2-dimethylpropane (4, 9%), the product of reduction of the electrophile (Table I, entry 1). No 1,6-diphenyl-2,2,5,5-tetramethylhexane (5), the product of reductive dimerization of iodide 2, was detected. In the absence of ZnCl₂-dioxane the reaction afforded lower amounts of cross-coupled product and increased amounts

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Table II. Effect of Varying the Halide in the Coupling of 1-Phenyl-2,2-dimethyl-3-iodopropane (2, RI) with CH_3MgX and PhMgX ($\text{R}'\text{MgX}$) after Pretreatment with ZnCl_2 -dioxane^a

entry	Grignard reagent	GC yield (%)			
		RI (2)	RR' (3)	RH (4)	RR (5)
1	CH_3MgCl	0	93	7	0
2	CH_3MgBr	0	92	8	0
3	CH_3MgI	26	69	5	0
4	PhMgCl	0	90	10	0
5	PhMgBr	0	48	6	0 ^b
6	PhMgI	0	19	48	0 ^b

^a A slurry of ZnCl_2 -dioxane (1.5 mmol, 1.5 equiv) in Et_2O (0.19 M) was treated with Grignard reagent (3.0 mmol, 3.0 equiv) and filtered through a bed of dry Celite directly into a mixture of iodide 2 (1.0 mmol), GC standard, and catalyst (10 mol %) in Et_2O (0.1 M in 2). The mixture was stirred at the reflux temperature for 36 h, quenched by the addition of a 1% HCl solution, and analyzed by GC. ^b 2,2-Dimethyl-3-phenylpropanol was identified as the remaining constituent in the product mixture.

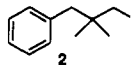
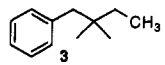
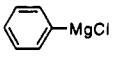
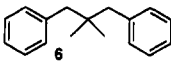
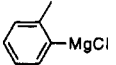
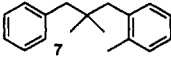
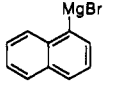
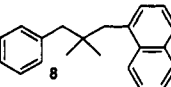
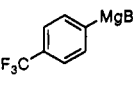
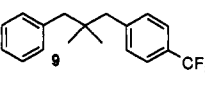
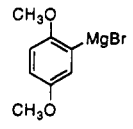
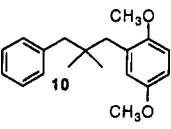

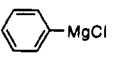

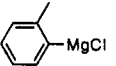
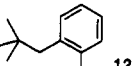
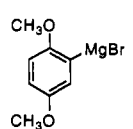
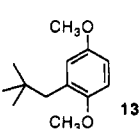
of dimerization (entry 2). Removal of precipitated magnesium salts prior to addition of the nucleophile had little effect on the course of the reaction (entry 3). Use of a 1:1 ratio of CH_3MgCl to ZnCl_2 -dioxane gave a product mixture similar to that formed in the absence of zinc (entry 4). Although unpurified zinc halides also led to reasonable product mixtures (entries 5 and 6), all further studies were conducted with the dioxane adduct. A brief solvent survey indicated that ethereal solvents afforded similar yields of products (entries 7–11). Thereafter, when necessary, THF was substituted for Et_2O for the formation of Grignard reagents.

(dppf) NiCl_2 was required for the reaction to proceed. In the absence of the catalyst no cross-coupling was observed (entry 12). Use of $\text{Ni}(\text{acac})_2$, a much less nucleophilic catalyst, failed to mediate cross-coupling (entry 13). Surprisingly, prereluction of (dppf) NiCl_2 to the Ni(O) state with DIBAL caused increased reduction of iodide 2 (entry 14). On treatment of iodide 2 with Me_2CuMgCl (formed *in situ* from MeMgCl and CuI) either in the presence of (dppf) NiCl_2 (entry 15) or (dppf) PdCl_2^{18} or in the absence of a Group 10 metal catalyst, dimerization and reduction were increased at the expense of cross-coupling. Thus, the neopentyl iodide cross-coupling could not have been simply achieved by use of an organocopper species.

Variation of the halide in the Grignard reagent caused interesting results. MeMgCl and MeMgBr gave almost identical product ratios (Table II, entries 1 and 2; see also Table I, entries 1, 5, and 6). On use of MeMgI , the catalyst appeared to be less stable and large amounts of starting material were returned unchanged (Table II, entry 3). Changing the halide in PhMgX from Cl to Br to I afforded decreasing yields of 2. In the latter two cases the crude product mixture also contained variable amounts of 2,2-dimethyl-3-phenylpropan-1-ol, identified by comparison with authentic material (GC, TLC, MS, ^1H and ^{13}C NMR). This suggests that a side reaction, possibly radical-mediated, is competitive with the desired cross-coupling. On the basis of these results, organomagnesium chlorides appear to be the reagents of choice. Because of variable difficulties in the formation of Grignard reagents from aryl chlorides, aryl bromides were employed for some of the ensuing synthetic studies in spite of the potential for lowered yields of cross-coupled products.

Optimization studies indicated that the best yields could be obtained on addition of 1–1.5 equiv of a diorganozinc

Table III. (dppf) NiCl_2 -Mediated Cross-Coupling of Neopentyl Iodides with Grignard Reagents in the Presence of ZnCl_2 -Dioxane

entry	neopentyl iodide	RMgX	cross-coupled product	isolated yield (%)
1		CH_3MgCl		83
2				81
3				83
4				88
5				86
6				80
7				72
8				73
9				84

reagent, prepared by treatment of a slurry of ZnCl_2 -dioxane (1–1.5 equiv) with a Grignard reagent (2–3 equiv) to a mixture of (dppf) NiCl_2 (10 mol %) and neopentyl iodide in Et_2O under reflux. As shown in Table III, methyl- and most arylorganozinc reagents gave very good yields of cross-coupled products under these conditions. In most cases studied yields were 10–30% higher than when cross-coupling was attempted in the absence of ZnCl_2 . In these cases no significant amount of byproducts relating to the electrophile was observed. The major impurity in the reaction mixtures was the biaryl compound obtained during the formation of the arylmagnesium halide. In most cases, purification could be achieved by column chromatography or spinning band distillation.

In some cases the aryl- or alkylzinc reagents gave disappointing results. (dppf) NiCl_2 -mediated reaction of neopentyl iodide 2 with either 1-octylmagnesium chloride, (*p*-chlorophenyl)magnesium bromide, or benzylmagnesium chloride after transmetalation with ZnCl_2 -dioxane afforded cross-coupled products (24%, 47%, and 54% GC ratios, respectively) mixed with significant amounts of reduction of the electrophile (76%, 53%, and 22% GC ratios, respectively) and in the latter case dimerization (24%) of the electrophile. Cross-coupling of iodide 2 with the organozinc reagents generated from cyclopentylmagnesium chloride, (*p*-methoxyphenyl)magnesium bromide, or 2-thienylmagnesium bromide returned iodide 2 and gave

reduced electrophile **4** with only minor amounts of cross-coupled products observed. It had been shown that the latter two aryl Grignard reagents coupled in good yields in the absence of zinc salts without competitive reduction or dimerization of the electrophile, thus showing the complementary nature of the zinc and magnesium nucleophiles.¹⁰

In summary, we have found that the (dppf)NiCl₂-mediated cross-coupling of neopentyl iodides with Grignard reagents generally proceeds in better yield in the presence of ZnCl₂-dioxane. Transmetalation of the nucleophile to the more stable diorganozinc acts to minimize reduction and dimerization of the electrophile. Generally, aryl Grignard reagents undergo the cross-coupling reaction in better yield than does CH₃MgCl, which couples better than alkyl Grignard reagents. To date, synthetically useful conditions for the cross-coupling of the latter reagents (RMgCl, R = Et-, C₆H₅CH₂-, c-C₅H₁₁-) have not been developed. The (dppf)NiCl₂-mediated cross-coupling of diorganozincs displays a significant halogen effect with organomagnesium chlorides affording highest yields. All cases of significant side-product formation when using aryl Grignard reagents as organozinc precursors occurred with aryl bromides. Because yields are typically 10–30% higher and reaction mixtures are typically cleaner than with the Grignard cross-coupling, the use of zinc nucleophiles should prove to be a useful approach for building carbon-carbon bonds to neopentyl electrophiles.

Experimental Section

¹H NMR spectra were obtained using a Bruker AC-300 spectrometer (300 MHz) with (CD₃)₂CO or CDCl₃ as solvent and tetramethylsilane (δ 0.00) or acetone (δ 2.04) as internal standard. ¹³C NMR spectra were obtained at 75 MHz using (CD₃)₂CO (δ 29.8) or CDCl₃ (δ 77.0) as solvent and internal standard. ¹⁹F NMR were taken using a Bruker AC-300 (282 MHz) using CFC₃ (δ 0.00) as internal standard. Capillary gas chromatographic analyses were run on a Hewlett-Packard 5890A gas chromatograph equipped with 12.5-m \times 0.25-mm cross-linked methyl silicone column and a flame ionization detector. Low-resolution GCMS were obtained on a VG TRIO1 instrument at an ionization potential of 70 eV. Flash column chromatography was performed with 40- μ m Baker silica gel. Radial chromatography was performed on a Harrison Research chromatotron with silica gel 60 PF₂₅₄ containing gypsum. Thin-layer chromatography was performed with EM silica gel 60F-254 plates. Spinning band distillations were conducted with an Ace/Bowdoin microscale spinning band column (10 cm). Distillations were conducted using a bulb-to-bulb apparatus (Aldrich Kugelrohr); ot refers to the Kugelrohr oven temperature range over which distillation occurred. Because bulb-to-bulb distillations occur below the boiling points of compounds, ot ranges were typically below ranges reported for boiling points. All glassware was oven-dried at 140 °C overnight. Bis(diphenylphosphino)ferrocene (dppf)²³ and dichloro(1,1'-bis(diphenylphosphino)ferrocene)nickel(II), **1**,^{9,16} were prepared following literature procedures. ZnCl₂-dioxane was obtained by recrystallizing ZnCl₂ from dioxane in the presence of Zn powder.²² 1-Iodo-2,2-dimethyl-3-phenylpropane, **2**, was prepared using a modification of a literature procedure.²⁴ 1-Iodo-2,2-dimethylpropane, 1-bromonaphthalene, 4-bromo-1-(trifluoromethyl)benzene, 2-bromo-1,4-dimethoxybenzene, 4-bromoanisole, 2-bromothiophene, and 2,2-dimethyl-3-phenylpropanol were obtained commercially. Alkyl iodides were passed through a short column of neutral alumina just prior to use. Methyl-, phenyl-, *o*-tolyl-, octyl-, cyclopentyl-, and benzylmagnesium chloride and (4-chlorophenyl)magnesium bromide were obtained

commercially. Other Grignard reagents were prepared by the reaction of magnesium turnings with the organic halide in THF or Et₂O. After the reaction was complete, the resulting ethereal solution was transferred via cannula through a small pad of Celite in a type C sintered glass funnel directly into a dry storage bottle. All Grignard reagents were titrated immediately prior to use employing a modification of the procedure of Watson and Eastham.²⁵ Tetrahydrofuran (THF) was doubly distilled from potassium. Et₂O was distilled from sodium and benzophenone. All reactions were conducted under an inert atmosphere.

General Procedure. To ZnCl₂-dioxane (1.5 mmol, 1.5 equiv) which had been placed under N₂ using two cycles of an evacuate/quench protocol was added sufficient Et₂O to afford a final volume of 8 mL after the addition of the Grignard reagent. This mixture was cooled to 0 °C, treated with Grignard reagent (3.0 mmol, 3.0 equiv), stirred for 15 min at 0 °C and for 45 min at room temperature, and then transferred via cannula through a sintered glass funnel containing a small pad of dry Celite directly into a flask containing a mixture of the neopentyl iodide (1.0 mmol, 1.0 equiv) and (dppf)NiCl₂ (0.1 mmol, 0.1 equiv) at room temperature. An additional amount of Et₂O (2 mL) was transferred via cannula through the Celite filter and into the reaction mixture. The mixture was heated at the reflux temperature for 36 h, allowed to cool to room temperature, diluted with pentane (60 mL), and quenched by the addition of a 1% HCl solution (40 mL). The organic layer was washed with a 1% HCl solution ((3–7) \times 25 mL), water (3 \times 25), and a saturated NaCl solution (2 \times 25 mL), dried (MgSO₄), and concentrated by distillation through a 130-mm Vigreux column. Volatiles were further removed by spinning band distillation and the remaining oil was purified by either bulb-to-bulb distillation or chromatography.

(2,2-Dimethylbutyl)benzene (3; Table III, Entry 1). Bulb-to-bulb distillation of the remaining oil gave **3** as a clear oil (0.13 g, 83%): ot (bulb-to-bulb) 165–190 °C (760 mmHg) [lit.^{26a} bp 212 °C (742 mmHg)]; TLC *R_f* (hexane) 0.35; ¹H NMR (CDCl₃) δ 0.83 (s, 6H), 0.89 (t, *J* = 7.5 Hz, 3H), 1.25 (q, *J* = 7.5 Hz, 2H), 2.49 (s, 2H), 7.10–7.30 (m, 5H); ¹³C NMR (CDCl₃) δ 8.54, 26.2 (2C), 29.4, 34.3, 48.0, 125.7, 127.6 (2C), 130.6 (2C), 139.6; LRMS *m/z* (rel abundance) 162 (8).

The ¹H NMR spectrum of **3** was consistent with that reported.^{26c}

2,2-Dimethyl-1-phenylpropane (4; Table III, Entry 7). Bulb-to-bulb distillation of the remaining oil gave **4** as a clear oil (0.11 g, 72%) contaminated with a small amount of biphenyl: ot (bulb-to-bulb) 160–180 °C (760 mmHg) [lit.^{28a} bp 176.5–178 °C (760 mmHg), lit.^{28b} bp 185.6–186.0 °C (758 mmHg)]; TLC *R_f* (hexane) 0.45; ¹H NMR (CDCl₃) δ 0.90 (s, 9H), 2.50 (s, 2H), 7.15–7.32 (m, 5H); ¹³C NMR (CDCl₃) δ 29.4 (3C), 31.7, 50.3, 125.7, 127.6 (2C), 130.4 (2C), 139.6; LRMS *m/z* (rel abundance) 148 (12).

The ¹H NMR spectrum of **4** was consistent with that reported.^{28a,d}

1,3-Diphenyl-2,2-dimethylpropane (6; Table III, Entry 2). Bulb-to-bulb distillation of the remaining oil gave **6** as a white solid (0.18 g, 81%) contaminated with a small amount of biphenyl: ot (bulb-to-bulb) 175–200 °C (760 mmHg) [lit.²⁷ bp 293–294 °C (760 mmHg)]; mp 66–66.5 °C [lit.²⁷ mp 68–69 °C]; TLC *R_f* (hexane) 0.47; ¹H NMR (CDCl₃) δ 0.83 (s, 6H), 2.58 (s, 4H), 7.12–7.30 (m, 10H); ¹³C NMR (CDCl₃) δ 26.1 (2C), 35.4, 49.4 (2C), 125.8 (2C), 127.7 (4C), 130.7 (4C), 139.0 (2C); LRMS *m/z* (rel abundance) 224 (4); HRMS calcd for C₁₇H₂₀ 224.1565, found 224.1575.

1-(2,2-Dimethyl-3-phenylpropyl)-2-methylbenzene (7; Table III, Entry 3). Bulb-to-bulb distillation of the remaining oil

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gave **7** as a clear oil (0.20 g, 83%) contaminated with a small amount of 2,2'-dimethylbiphenyl: *ot* (bulb-to-bulb) 100–120 °C (0.5 mmHg); TLC R_f (2.5% EtOAc/hexane) 0.45; ^1H NMR (CDCl_3) δ 0.85 (s, 6H), 2.28 (s, 3H), 2.62 (s, 2H), 2.64 (s, 2H), 7.08–7.28 (m, 9H); ^{13}C NMR (CDCl_3) δ 20.6, 26.2 (2C), 36.8, 44.9, 49.8, 125.0, 125.8, 125.9, 127.6 (2C), 130.4, 130.8 (2C), 131.8, 137.2, 137.5, 139.1; LRMS m/z (rel abundance) 238 (2); HRMS calcd for $\text{C}_{18}\text{H}_{22}$ 238.1722, found 238.1720.

1-(2,2-Dimethyl-3-phenylpropyl)naphthalene (8; Table III, Entry 4). The remaining oil was purified using radial chromatography (SiO_2 , pentane). Fractions were concentrated to approximately 3 mL by distillation using a 130-mm Vigreux column. Volatiles were further removed by spinning band distillation followed by brief treatment under reduced atmosphere (0.8 mmHg) to give **8** as a clear oil (0.24 g, 88%): TLC R_f (2.5% EtOAc/hexane) 0.39; ^1H NMR (CDCl_3) δ 0.85 (s, 6H), 2.67 (s, 2H), 3.08 (s, 2H), 7.10–7.26 (m, 2H), 7.32–7.55 (m, 6H), 7.68–8.03 (m, 4H); ^{13}C NMR (CDCl_3) δ 26.8 (2C), 36.7, 44.0, 50.0, 124.9, 125.1 (2C), 125.3, 125.9, 126.8, 127.7 (2C), 128.6, 129.1, 130.8 (2C), 133.4, 133.9, 135.7, 139.1; LRMS m/z (rel abundance) 274 (14); HRMS calcd for $\text{C}_{21}\text{H}_{22}$ 274.1722, found 274.1730.

1-(2,2-Dimethyl-3-phenylpropyl)-4-(trifluoromethyl)benzene (9; Table III, Entry 5). The remaining oil was purified using radial chromatography (SiO_2 , pentane). Fractions were concentrated to approximately 3 mL by distillation using a 130-mm Vigreux column. Volatiles were further removed by spinning band distillation followed by brief treatment under reduced atmosphere (0.8 mmHg) to afford **9** as a white solid (0.25 g, 86%): mp 41.5–42.5 °C; ^1H NMR (acetone- d_6) δ 0.83 (s, 6H), 2.62 (s, 2H), 2.71 (s, 2H), 7.15–7.30 (m, 5H), 7.39 (d, $J = 7.8$ Hz, 2H), 7.61 (d, $J = 7.7$ Hz, 2H); ^{13}C NMR (CDCl_3) δ 26.0 (2C), 35.5, 48.9, 49.5, 124.4 (q, $^1J_{\text{CF}} = 271.6$ Hz), 124.6 (q, $^3J_{\text{CF}} = 3.8$ Hz, 2C), 126.0, 127.8 (2C), 128.3 (q, $^2J_{\text{CF}} = 32.1$ Hz), 130.7 (2C), 130.9 (2C), 138.7, 143.3; ^{19}F NMR (CDCl_3) δ -62.8 (s, 3F); TLC R_f (2.5% EtOAc/hexane) 0.45; LRMS m/z (rel abundance) 292 (2); HRMS calcd for $\text{C}_{18}\text{H}_{18}\text{F}_3$ 292.1439, found 292.1423. Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{F}_3$: C, 73.95; H, 6.55. Found: C, 73.93; H, 6.57.

1,4-Dimethoxy-2-(2,2-dimethyl-3-phenylpropyl)benzene (10; Table III, Entry 6). The remaining oil was purified using radial chromatography (SiO_2 , pentane, 5% Et_2O /pentane) to afford **10** as a colorless oil (0.23 g, 80%) mixed with a small amount

of 1,4-dimethoxybenzene: TLC R_f (10% EtOAc/hexane) 0.43; ^1H NMR (acetone- d_6) δ 0.81 (s, 6H), 2.60 (s, 2H), 2.62 (s, 2H), 3.71 (s, 3H), 3.73 (s, 3H), 6.65–6.90 (m, 3H), 7.12–7.30 (m, 5H); ^{13}C NMR (acetone- d_6) δ 26.4 (2C), 36.5, 42.7, 49.6, 55.6, 55.8, 112.0, 112.1, 119.3, 126.4, 128.3 (2C), 129.2, 131.4 (2C), 140.1, 153.2, 153.8; LRMS m/z (rel abundance) 284 (36); HRMS calcd for $\text{C}_{19}\text{H}_{24}\text{O}_2$ 284.1776, found 284.1774. Anal. Calcd for $\text{C}_{19}\text{H}_{24}\text{O}_2$: C, 80.24; H, 8.51. Found: C, 80.09; H, 8.45.

1-(2,2-Dimethylpropyl)-2-methylbenzene (12; Table III, Entry 8). The crude oil was purified using flash chromatography (SiO_2 , pentane) followed by concentration to approximately 3 mL by distillation using a 130-mm Vigreux column. Volatiles were further removed by spinning band distillation to afford **12** as a colorless oil (0.12 g, 73%): *ot* (bulb-to-bulb) 165–190 °C (760 mmHg) [lit.^{28a} bp 216–218 °C (760 mmHg)]; ^1H NMR (acetone- d_6) δ 0.93 (s, 9H), 2.31 (s, 3H), 2.57 (s, 2H), 7.04–7.15 (m, 4H); ^{13}C NMR (acetone- d_6) δ 20.7, 30.1 (3C), 33.6, 46.1, 125.9, 126.8, 131.2, 132.4, 137.6, 138.7.

The ^1H NMR spectrum of **12** was consistent with those reported.^{26c,28a}

1,4-Dimethoxy-2-(2,2-dimethylpropyl)benzene (13; Table III, Entry 9). The crude oil was purified using flash chromatography (SiO_2 , pentane) followed by concentration to approximately 3 mL by distillation using a 130-mm Vigreux column. Volatiles were further removed by spinning band distillation to afford **13** as a colorless oil (0.18 g, 84%): TLC R_f (10% EtOAc/hexane) 0.48; ^1H NMR (acetone- d_6) δ 0.89 (s, 9H), 2.52 (s, 2H), 3.71 (s, 3H), 3.73 (s, 3H), 6.66 (d, $J = 3.1$ Hz, 1H), 6.72 (dd, $J = 3.1, 8.8$ Hz, 1H), 6.84 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (acetone- d_6) δ 29.8 (3C), 32.8, 43.3, 55.7, 55.8, 112.0 (2C), 119.2, 129.8, 153.2, 153.9; LRMS m/z (rel abundance) 208 (78); HRMS calcd for $\text{C}_{13}\text{H}_{20}\text{O}_2$ 208.1463, found 208.1471.

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