Directed Lithiation/Transmetalation Approach to Palladium-Catalyzed Cross-Coupling Acylation Reactions

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The directed *ortho*-lithiation method of electrophilically functionalizing a variety of substrates has become a very powerful synthetic tool for target-directed synthesis. Indeed, since its conception by Gilman and Wittig over 50 years ago there has been widespread development in this area.[1] The early work of Gilman and Hauser provided the impetus for the subsequent contributions from a number of groups which have expanded the scope of the reaction to a variety of substituted aromatic and olefinic substrates, in addition to providing important mechanistic information.[2] This area of investigation has been reviewed on several occasions and has become a sophisticated method in organic synthesis.[3] An array of directing groups have emerged which are capable of enhancing *ortho*-deprotonations and have a hierachial order of directing ability. This allows rational prediction of the reactivity of a particular substrate, which may be explained in terms of a complimentary interplay between inductive and complexation effects. Indeed, the ability of a species to effect the nature of a substituent in close proximity has been rationalized in terms of the *complex-induced proximity effect* (CIPE) proposed by Beak and Meyers.[4]

Recent reports on the palladium- and nickel-catalyzed cross-coupling reactions of aryl and vinyl triflates with organozinc reagents[5,6] which were prepared *via* directed lithiation/transmetalation prompted us to publish our results on the corresponding acylation reactions. We report the palladium-catalyzed cross-coupling of a variety of acyl chlorides with organozinc reagents derived from *ortho*-metalation followed by transmetalation. Carbanion-mediated acylation reactions with acyl halides are particularly problematic owing to competitive addition of the carbanion to the newly formed aryl ketone and/or enolization. Negishi provided a practical solution to this problem by employing the organozinc species, formed *via* the transmetalation of the organolithium, in a palladium-catalyzed cross-coupling reaction with a variety of acyl chlorides to afford the corresponding ketones.[7] Organozinc reagents are particularly useful and have found widespread application to complex synthetic problems owing to their versatility and inherent tolerance of sensitive functionality.[8] This paper describes the first example of the combination of these methodologies for the preparation of a variety of aryl ketones.

Scheme 1

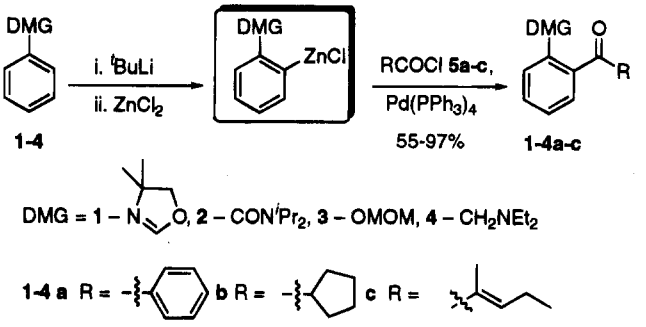

Table 1. Optimization of the Palladium-Catalyzed Cross-Coupling of the Oxazoline 1 with Acid Chloride 5b

entry	oxazoline 1[a] (equiv)	^{t}BuLi[b] (equiv)	$ZnCl_2$[c] (equiv)	acid chloride[d] **5b** (equiv)	$Pd(PPh_3)_4$ (mol %)	yield[e] (%)
1	1.1	1.1	1.1	1.0	5	50
2	1.5	1.5	1.5	1.0	5	78
3	1.5	1.5	1.5	1.0	2	71
4	1.5	1.5	1.5	1.0	0	4
5	1.0	1.1	1.1	1.1	5	50

[a] Reactions carried out on a 1 mmol reaction scale in diethyl ether. [b] The oxazoline **1** was deprotonated at −78 °C. [c] Zinc chloride added at −78 °C and allowed to warm to room temperature. [d] Acyl chloride **5b** added at 0 °C, allowed to warm to room temperature, and stirred for 4 h. [e] Isolated yields.

Table 1 summarizes the results for the optimization study using the oxazoline **1** and cyclopentanecarbonyl chloride **5b**. Treatment of acid chloride **5b** with 1.1 equiv of the organozinc reagent derived from the directed lithiation/transmetalation of the oxazoline **1** under palladium catalysis gave the aryl ketone **1b** in 50% yield (entry 1). Increasing the amount of the organozinc species to 1.5 equiv furnished the aryl ketone **1b** in an improved 78% yield (entry 2). Excess organozinc reagent was necessary owing to its reduced reactivity which may be attributed to the formation of a stable chelate with the directing group. However, despite the fact that an excess of the oxazoline **1** has to be employed, the excess reagent may be recovered from the reaction. Reduction in the palladium catalyst to 2 mol % had a minimal effect on the reaction (entry 3), but when the reaction was carried out in the absence of the palladium catalyst only a trace amount of the aryl ketone **1b** was obtained (entry 4). Finally, when the stoichiometry of the reaction was reversed with that of entry 1 and the acid chloride **5b** was used in excess, a similar yield of the aryl ketone **1b** was obtained (entry 5). Therefore, the reactions were normally carried out using an excess of the directing group owing to its relative ease of recovery from the reaction mixture (entry 2).

Table 2 summarizes the results of the application of the directed lithiation/transmetalation cross-coupling reaction to the aryl directing groups **1**–**4** with the acid chlorides **5a**–**c**. Interestingly, the success of the reaction was dependent upon the nature of the directing group.[9]

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(3) For recent reviews, see: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (b) Snieckus, V. *Heterocycles* **1980**, *14*, 1649. (c) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. (d) Snieckus, V. *Lect. Heterocycl. Chem.* **1984**, *7*, 95. (e) Snieckus, V. *Bull. Soc. Chim. Fr.* **1988**, 67. (f) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

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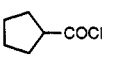
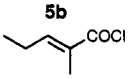
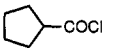
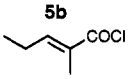
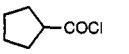
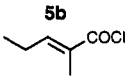
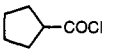
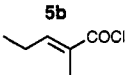
Table 2. Palladium Catalyzed Cross-Coupling of the Aryl DMG Groups 1–4 with the Acyl Chlorides 5a–c

entry	directing group DMG[a]	acid chloride RCOCl **5a–c**[e,f]	temp[g]	solvent	product	yield[j] (%)
1	oxazoline **1**[b]	PhCOCl **5a**	rt	Et_2O	**1a**	92
2	**1**[b]	 **5b**	rt	Et_2O	**1b**	86
3	**1**[b]	 **5c**	rt	Et_2O	**1c**	83
4	CON^iPr_2 **2**[b]	PhCOCl **5a**	rt	Et_2O/THF (10:1)[h]	**2a**	95
5	**2**[b]	 **5b**	rt	Et_2O/THF (10:1)[h]	**2b**	94
6	**2**[b]	 **5c**	rt	Et_2O/THF (10:1)[h]	**2c**	76[k]
7	OMOM **3**[c]	PhCOCl **5a**	rt	Et_2O	**3a**	97
8	**3**[c]	 **5b**	rt	Et_2O	**3b**	93
9	**3**[c]	 **5c**	rt	Et_2O	**3c**	75
10	CH_2NEt_2 **4**[d]	PhCOCl **5a**	Δ	Et_2O/THF (1:1)[i]	**4a**	69
11	**4**[d]	 **5b**	Δ	Et_2O/THF (1:1)[i]	**4b**	55
12	**4**[d]	 **5c**	Δ	Et_2O/THF (1:1)[i]	**4c**	57

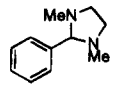
[a] 1.5 equiv of the DMG group. [b] ^{t}BuLi at −78 °C, 1 h; $ZnCl_2$, −78 °C to rt. [c] ^{t}BuLi at 0 °C, 1 h; $ZnCl_2$, 0 °C to rt. [d] ^{t}BuLi at 0 °C for 1 h; $ZnCl_2$, −78 °C to rt. [e] 5 mol % of $Pd(PPh_3)_4$. [f] All the reactions were carried out based on 5 mmol of the acyl chlorides **5a–c**. [g] The acyl chloride was added at 0 °C and then warmed to the temperature indicated. [h] 10:1 Et_2O/THF was required to solubilize **2**. [i] An equivalent amount of THF was added to elevate the reflux temperature. [j] Isolated yields. [k] GC yield.

The reaction was also particularly sensitive to the reaction scale, in that it was significantly more efficient on a 5 mmol verses a 1 mmol reaction scale. The *ortho*-deprotonations were carried out in ethereal solutions, except for **2** (entries 4–6) where solubility problems were encountered, as indicated in Table 2. This allowed clean metalation and avoided the use of additives such as TMEDA, which retards the cross-coupling reaction.[10] Directed lithiations that are carried out in tetrahydrofuran can have regioselectivity problems, especially in more highly functionalized substrates.[6] Treatment of the *ortho*-directing groups **1–4** with *tert*-butyllithium in ether affords the *ortho*-carbanion[11–14] which undergoes smooth transmetalation with zinc chloride to furnish the intermediary organozinc species (Scheme 1). Treatment of the organozinc species with the acid chlorides **5a–c** under palladium(0) catalysis afforded the corresponding aryl ketones **1–4a–c** in good to excellent yield.

The electronic nature of the acyl chloride was found to have a minimal effect on the reaction. However, the α,β-unsaturated acid chloride **5c** gave the corresponding ketones in slightly lower yields, probably due to their inherent reduced reactivity and/or potential to polymerize (entries 3, 6, 9, and 12). However, these effects obviously play a minimal role in the outcome of the reaction.

The diethylamine directing group proved particularly resistant to ketone formation, presumably due to the formation of a chelated and unreactive organozinc species as a result of the lone pair basicity of the diethylamine directing group. In order to achieve synthetically useful yields an equivalent amount of tetrahydrofuran was added in order to elevate the reflux temperature of the

(9) However, our investigations with the imidazolidine **6**,[15] cyclohexylimine **7**[16] and sulfonamide **8**[17] directing groups under a variety of reaction conditions proved problematic. The organozinc species derived from the *ortho*-lithiated imidazolidine **6** was less reactive than that from the diethylamine directing group, presumably due to the formation of a highly chelated organozinc species which proved particularly resistant to acylation. The imine **7** also proved to be unsuitable, since it does not undergo clean acylation. The sulfonamide **8** undergoes clean metalation; however, the transmetalation was particularly problematic leading to the formation of many products prior to the addition of the catalyst and acyl chloride.



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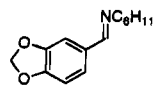

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8

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(12) For lead references on the diisopropyl amide directing group, see: Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.

(13) For lead references on the methoxymethyl ether directing group, see: Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101.

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reaction (entries 10–12). In each case, significant amounts of unreacted diethylamine **1d** was recovered from the reaction. Therefore, basic nitrogen directing groups retard the cross-coupling reaction.

In conclusion, we have demonstrated the first example of the directed lithiation/transmetalation approach to palladium-catalyzed cross-coupling acylation reactions. The reaction provides an efficient and regioselective method of aryl acylation. However, it is particularly sensitive to the nature of the directing group. Application of this methodology to target-directed synthesis should find general synthetic utility.

Experimental Section

General. ^{1}H NMR and ^{13}NMR were recorded on a Bruker AM-250 spectrometer. Chemical shifts are reported relative to tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR. High-resolution mass spectra (HRMS) were obtained on a VG 70-70 mass spectrometer. Diethyl ether and tetrahydrofuran were distilled from sodium, using benzophenone ketyl as an indicator. Analytical TLC was carried out on precoated 0.2 mm thick Merck 60 F_{254} silica plates. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh). *tert*-Butyllithium, zinc chloride in diethyl ether, and tetrakis(triphenylphosphine)palladium(0) were obtained from Aldrich Chemical Co. and used without further purification. The acid chlorides **5a–c** were freshly distilled and the cross-coupling reactions carried out under an atmosphere of nitrogen.

2-(2-Benzoylphenyl)-4,4-dimethyl-2-oxazoline (1a). The oxazoline **1** (1.331 g, 7.596 mmol) was dissolved in anhydrous diethyl ether (22 mL) and cooled with stirring to −78 °C. *tert*-Butyllithium (4.5 mL, 7.6 mmol; 1.7 M solution in pentane) was then added dropwise, keeping the internal temperature ≤−70 °C, and stirred for 1 h forming a yellow anion. Zinc chloride solution (7.6 mL, 7.6 mmol; 1.0 M solution in diethyl ether) was added dropwise, again keeping the internal temperature ≤−70 °C. The reaction mixture was then allowed to warm to room temperature during which time a white precipitate formed. After 1 h the reaction mixture was cooled to 0 °C, and tetrakis-(triphenylphosphine) palladium(0) (0.29 g, 5 mol %) was added followed by the dropwise addition of benzoyl chloride **5a** (0.716 g, 5.094 mmol) in anhydrous ether (22 mL) *via* Teflon cannula. The reaction mixture was then allowed to warm to room temperature and stirred for *ca.* 4 h affording a yellow solution, which was poured into a mixture of saturated $NaHCO_3$ solution (100 mL) and diethyl ether (50 mL), shaken, and separated. The organic phase was then back-extracted with diethyl ether (2 × 50 mL). The organic layers were combined, washed with saturated NaCl solution (100 mL), dried over anhydrous Na_2SO_4, and filtered and the solvent removed *in vacuo* to afford a crude oil. Purification by flash chromatography on silica gel (eluting with 1:9, 1:4, 3:7 diethyl ether/hexane) furnished **1a** (1.314 g, 92%) as a pale yellow low-melting solid: IR ($CHCl_3$) 3033, 3017, 2969, 1669, 1653 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.93–7.90 (1H, m), 7.38 (2H, dd, J = 7.6, 1.2 Hz), 7.61–7.47 (4H, M), 7.42–7.36 (2H, m), 3.58 (2H, s), 1.02 (6H, s); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 196.60 (e), 161.02 (e), 139.61 (e), 137.64 (e), 132.50 (o), 130.98 (o), 129.94 (o), 129.04 (o), 128.80 (o), 128.36 (o), 128.24 (o), 127.01 (e), 79.13 (e), 67.68 (e), 27.60 (o); HRMS (EI) calcd for $C_{18}H_{17}NO_2$ 279.1259, found 279.1255.

2-[2-(Cyclopentylmethanoyl)phenyl]-4,4-dimethyl-2-oxazoline (1b): IR ($CHCl_3$) 3017, 2967, 2871, 1695, 1653 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.84–7.80 (1H, m), 7.49–7.38 (2H, m), 7.33–7.29 (1H, m), 4.04 (2H, s), 3.34 (1H, quintet, J = 7.7 Hz), 1.94–1.54 (8H, m), 1.34 (6H, s); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 208.79 (e), 161.18 (e), 142.49 (e), 130.61 (o), 129.31 (o), 129.25 (o), 126.63 (o), 125.45 (e), 79.34 (e), 67.99 (e), 51.22 (o), 29.75 (e), 28.11 (o), 25.98 (e); HRMS (EI) calcd for $C_{17}H_{21}NO_2$ 271.1572, found 271.1594.

2-[2-(2-Methyl-(2*E*)-pent-2-enoyl)phenyl]-4,4-dimethyl-2-oxazoline (1c): IR ($CHCl_3$) 3017, 2971, 2935, 1653 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.88–7.85 (1H, m), 7.52–7.40 (2H, m), 7.33–7.30 (1H, m), 5.91 (1H, dt, J = 7.3, 1.2 Hz), 3.94 (2H, s), 2.16 (2H, quintet, J = 7.5 Hz), 1.91 (3H, s), 1.28 (6H, s), 0.92 (3H, t, J = 7.6 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 199.08 (e), 161.33 (e), 146.88 (o), 140.45 (e), 137.94 (e), 130.60 (o), 129.06 (o), 128.78 (o), 127.88 (o), 126.53 (e), 79.29 (e), 67.71 (e), 27.98 (o), 22.18 (e), 12.83 (o), 11.28 (o); HRMS (EI) calcd for $C_{17}H_{21}NO_2$ 271.1572, found 271.1563.

2-Benzoyl-1-(diisopropylamido)benzene (2a). The diisopropylamide **2** (1.571 g, 7.63 mmol) was dissolved in a mixture of anhydrous diethyl ether and tetrahydrofuran (42.5 mL; 9:1) and cooled with stirring to −78 °C. *tert*-Butyllithium (4.5 mL, 7.6 mmol; 1.7 M solution in pentane) was then added dropwise, keeping the internal temperature ≤−70 °C, and the reaction stirred for 1 h forming a pale lemon suspension. Zinc chloride solution (7.6 mL, 7.6 mmol; 1.0 M solution in diethyl ether) was added dropwise, keeping the internal temperature ≤−70 °C. The reaction mixture was then allowed to warm to room temperature, affording a colorless solution. After 1 h the reaction mixture was cooled to 0 °C, and tetrakis(triphenylphosphine)-palladium(0) (0.295 g, 5.0 mol %) was added followed by the dropwise addition of benzoyl chloride **5a** (0.718 g, 5.1 mmol) in anhydrous diethyl ether (8 mL) *via* Teflon cannula. The reaction mixture was then allowed to warm to room temperature and stirred for *ca.* 12 h affording a yellow solution, which was poured into a mixture of saturated $NaHCO_3$ solution (200 mL) and diethyl ether (100 mL), shaken, and separated. The organic phase was then back-extracted with diethyl ether (2 × 100 mL). The organic layers were combined, washed with saturated NaCl solution (100 mL), dried over anhydrous Na_2SO_4, and filtered and the solvent removed *in vacuo* to afford a crude oil. Purification by flash chromatography on silica gel (eluting with 2%–10% acetone/hexane in 2% increments) furnished **2a** (1.497 g, 95%) as a pale yellow oil: IR ($CHCl_3$) 3020, 1663, 1625 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.78 (2H, dd, J = 7.1, 1.5 Hz), 7.56–7.28 (7H, m), 3.82 (1H, septet, J = 6.7 Hz), 3.42 (1H, septet, J = 6.8 Hz), 1.41 (6H, d, J = 6.7 Hz), 1.17 (6H, d, J = 6.6 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 196.47 (e), 169.43 (e), 139.69 (e), 137.24 (e), 136.55 (e), 132.71 (o), 130.62 (o), 130.18 (o), 129.82 (o), 128.11 (o), 127.39 (o), 125.95 (o), 51.18 (o), 45.57 (o), 20.25 (o), 20.07 (o); HRMS (EI) calcd for $C_{20}H_{23}NO_2$ 309.1729, found 309.1751.

2-(Cyclopentylmethanoyl)-1-(diisopropylamido)benzene (2b): IR ($CHCl_3$) 3016, 2971, 2872, 1684, 1624 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.71 (1H, dd, J = 7.6, 1.3 Hz), 7.44 (1H, dt, J = 7.5, 1.4 Hz), 7.36 (1H, dt, J = 7.5, 1.5 Hz), 7.17 (1H, dd, J = 7.4, 1.4 Hz), 3.63–3.51 (2H, m), 3.46 (1H, quintet, J = 6.9 Hz), 1.91–1.54 (8H, m), 1.53 (6H, d, J = 6.8 Hz), 1.09 (6H, d, J = 6.7 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 203.77 (e), 170.13 (e), 139.27 (e), 135.91 (e), 131.25 (o), 128.47 (o), 127.75 (o), 126.13 (o), 50.93 (o), 47.79 (o), 45.41 (o), 29.46 (e), 26.00 (e), 20.14 (o); HRMS (EI) calcd for $C_{19}H_{27}NO_2$ 301.2042, found 301.2026.

2-(2-Methyl-(2*E*)-pent-2-enoyl)-1-(diisopropylamido)benzene (2c): IR ($CHCl_3$) 3017, 2973, 2936, 2876, 1628 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43–7.23 (3H, m), 7.20 (1H, d, J = 7.3 Hz), 6.34 (1H, t, J = 7.2 Hz), 3.70 (1H, septet, J = 6.5 Hz), 3.42 (1H, septet, J = 6.7 Hz), 2.23 (2H, quintet, J = 7.4 Hz), 1.87 (3H, s), 1.44 (6H, d, J = 6.6 Hz), 1.11 (6H, d, J = 6.3 Hz), 0.99 (3H, t, J = 7.6 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 198.71 (e), 170.08 (e), 151.42 (o), 138.72 (e), 137.58 (e), 136.10 (e), 129.73 (o), 129.02 (o), 127.39 (o), 125.75 (o), 51.12 (o), 45.61 (o), 22.64 (e), 20.32 (o), 12.77 (o), 11.55 (o); HRMS (EI) calcd for $C_{19}H_{27}NO_2$ 301.2042, found 301.2038.

2-Benzoyl-1-[(methoxymethyl)oxy]benzene (3a). The MOM ether **3** (1.012 g, 7.30 mmol) was dissolved in anhydrous diethyl ether (22 mL) and cooled with stirring to 0 °C. *tert*-Butyllithium (4.3 mL, 7.3 mmol, 1.7 M solution in pentane) was then added dropwise, keeping the internal temperature ≤0 °C, and stirred for 1 h, forming a cream-colored suspension. Zinc chloride solution (7.3 mL, 7.3 mmol; 1.0 M solution in diethyl ether) was added dropwise, keeping the internal temperature ≤0 °C. The reaction mixture was then allowed to warm to room temperature during which time a white precipitate formed. After 1 h the reaction mixture was cooled to 0 °C, and tetrakis-(triphenylphosphine)palladium(0) (0.282 g, 5 mol %) was added followed by the dropwise addition of benzoyl chloride **5a** (0.686 g, 4.88 mmol) in anhydrous ether (21.5 mL) *via* Teflon cannula. The reaction mixture was then allowed to warm to room temperature and stirred for *ca.* 12 h affording a yellow solution, which was poured into a mixture of saturated $NaHCO_3$ solution (200 mL) and diethyl ether (100 mL), shaken, and separated.

The organic phase was then back-extracted with diethyl ether (2 × 100 mL). The organic layers were combined, washed with saturated NaCl solution (100 mL), dried over anhydrous Na_2SO_4, and filtered and the solvent removed *in vacuo* to afford a crude oil. Purification by flash chromatography on silica gel (eluting with hexane/dichloromethane 1:1) furnished **3a** (1.145 g, 97%) as a pale lime oil; IR ($CHCl_3$) 3018, 1664, 1600 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.81 (2H, dd, J = 7.5, 0.9 Hz), 7.54 (1H, t, J = 7.2 Hz), 7.46–7.34 (4H, m), 7.19 (1H, d, J = 8.3 Hz), 7.08 (1H, t, J = 7.5 Hz), 5.03 (2H, s), 3.27 (3H, s); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 196.03 (e), 154.58 (e), 137.61 (e), 132.73 (o), 131.51 (o), 129.68 (e), 129.48 (o), 129.08 (o), 128.03 (o), 121.51 (o), 114.81 (o), 94.34 (e), 55.89 (o); HRMS (EI) calcd for $C_{15}H_{14}O_3$ 242.0943, found 242.0943.

2-(Cyclopentanylmethanoyl)-1-[(methoxymethyl)oxy]-benzene (3b): IR ($CHCl_3$) 3018, 2960, 2871, 1675, 1598 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.48 (1H, dd, J = 7.7, 1.7 Hz), 7.40–7.33 (1H, m), 7.14 (1H, d, J = 8.4 Hz), 7.01 (1H, t, J = 7.5 Hz), 5.21 (2H, s), 3.66 (1H, quintet, J = 7.8 Hz), 3.47 (3H, s), 1.88–1.81 (4H, m), 1.77–1.51 (4H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 206.41 (e), 155.07 (e), 132.18 (o), 130.22 (e), 129.42 (o), 121.53 (o), 114.65 (o), 94.43 (e), 56.10 (o), 51.03 (o), 29.39 (e), 25.89 (e); HRMS (EI) calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1286.

2-(2-Methyl-(2*E*)-pent-2-en-1-oyl)-1-[(methoxymethyl)-oxy]benzene (3c): IR ($CHCl_3$) 3018, 2971, 2936, 1653, 1636, 1600 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 7.18–7.17 (2H, m), 7.08–7.06 (1H, m), 6.82–6.76 (1H, m), 6.28 (1H, dt, J = 7.3, 1.3 Hz), 4.79 (2H, s), 3.10 (3H, s), 1.97 (3H, s), 1.88 (2H, quintet, J = 7.5 Hz), 0.65 (3H, t, J = 7.6 Hz); ^{13}C NMR (62.5 MHz, C_6D_6) δ 197.40 (e), 154.70 (e), 148.65 (o), 137.82 (e), 131.65 (e), 130.47 (o), 128.82 (o), 121.55 (o), 115.24 (o), 94.59 (e), 55.67 (o), 22.49 (e), 12.79 (o), 11.10 (o); HRMS (EI) calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1237.

2-Benzoyl-1-[(diethylamino)methyl]benzene (4a). The diethylamine **4** (1.229 g, 7.528 mmol) was dissolved in anhydrous diethyl ether (22 mL) and cooled with stirring to −5 °C . *tert*-Butyllithium (4.4 mL, 7.5 mmol; 1.7 M solution in pentane) was then added dropwise, keeping the internal temperature ≤0 °C. The reaction mixture was stirred at 0 °C for 1 h, forming a yellow colored anion, and then cooled to −78 °C for the dropwise addition of zinc chloride solution (7.5 mL, 7.5 mmol; 1.0 M solution in diethyl ether), keeping the internal temperature ≤−70 °C. The reaction mixture was then allowed to warm to room temperature during which time a white precipitate formed. After 1 h the reaction mixture was cooled to 0 °C, and tetrakis-(triphenylphosphine) palladium(0) (0.29 g, 5 mol %) was added followed by the dropwise addition of benzoyl chloride **5a** (0.714 g, 5.08 mmol) in anhydrous tetrahydrofuran (30 mL) *via* Teflon cannula. The reaction mixture was allowed to warm to room temperature and heated at reflux for *ca.* 16 h affording a yellow solution. The reaction mixture was then cooled to ambient temperature and poured into a mixture of saturated $NaHCO_3$ solution (100 mL) and diethyl ether (50 mL), shaken, and separated. The organic phase was then back-extracted with diethyl ether (2 × 50 mL). The organic layers were combined, washed with saturated NaCl solution (100 mL), dried over anhydrous Na_2SO_4, and filtered and the solvent removed *in vacuo* to afford a crude oil. Purification by flash chromatography on silica gel (eluting with 1:4 ethyl acetate/hexane) furnished **4a** (0.936 g, 69%) as a pale yellow oil: IR ($CHCl_3$) 3065, 3016, 2971, 2818, 1661, 1598 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.73 (2H, dd, J = 7.0, 1.6 Hz), 7.65–7.27 (7H, m), 3.51 (2H, s), 2.20 (4H, q, J = 7.2 Hz), 0.68 (6H, t, J = 7.1 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 197.11 (e), 140.09 (e), 139.28 (e), 137.88 (e), 132.15 (o), 129.20 (o), 128.95 (o), 128.07 (o), 127.97 (o), 126.54 (o), 55.81 (e), 44.79 (e), 9.90 (o); HRMS (EI) calcd for $C_{18}H_{21}NO$ 267.1623, found 267.1620.

2-(Cyclopentylmethanoyl)-1-[(diethylamino)methyl]benzene (4b): IR ($CHCl_3$) 3016, 2969, 2872, 2805, 1684 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.43–7.21 (4H, m), 3.65 (2H, s), 3.49–3.36 (1H, m), 2.43 (4H, q, J = 7.1 Hz), 1.91–1.54 (8H, m), 0.92 (6H, t, J = 7.2 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 208.49 (e), 140.86 (e), 139.39 (e), 129.80 (o), 129.48 (o), 126.87 (o), 126.41 (o), 55.71 (e), 50.10 (o), 46.05 (e), 29.56 (e), 26.16 (e), 10.86 (o); HRMS (EI) calcd for $C_{17}H_{25}NO$ 259.1936, found 259.1939.

2-(2-Methyl-(2*E*)-pent-2-enoyl)-1-[(diethylamino)methyl]-benzene (4c): IR ($CHCl_3$) 3024, 3013, 2970, 2876, 2803, 1635 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.39–7.14 (4H, m), 6.09–6.03 (1H, m), 3.50 (2H, bs), 2.45–2.25 (4H, m), 2.27–2.15 (2H, m), 1.90 (3H, s), 0.96 (3H, t J = 7.6 Hz), 0.98–0.81 (6H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 199.98 (e), 147.03 (o), 139.90 (e), 138.95 (e), 137.35 (e), 128.91 (o), 128.68 (o), 127.90 (o), 126.27 (o), 55.93 (e), 45.44 (e), 22.31 (e), 12.96 (o), 11.08 (o), 10.56 (o); HRMS (EI) calcd for $C_{17}H_{25}NO$ 259.1936, found 259.1916.

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Supplementary Material Available: Spectra for compounds **1–4a–c** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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