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Ligand Exchange Reaction of Sulfoxides in Organic Synthesis: A Versatile Procedure for One-Carbon Homologation of Methylesters to Esters, Thioesters, Carboxylic Acids and Amides

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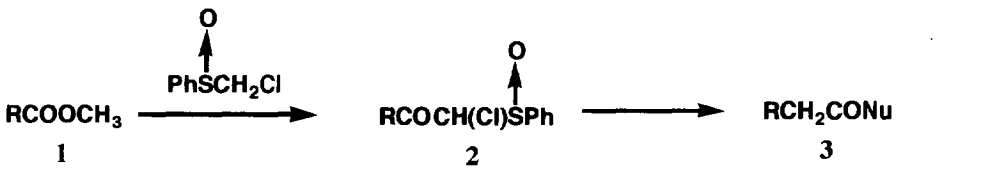
Abstract: *A novel two-step procedure for one-carbon homologation of methylesters to esters, thioesters, carboxylic acids and amides is described. Methylesters are reacted with lithium carbanion of chloromethyl phenyl sulfoxide to give α-chloro α-sulfinyl ketones in 70 to 90% yields. Potassium enolate of the α-chloro α-sulfinyl ketone was treated with tert-butyllithium at -78 °C to give alkynolate via alkylidene carbenoid. This intermediate was treated with alcohols, thioles, 5% aqueous NaOH, and amine hydrochlorides to afford one-carbon homologated esters, thioesters, carboxylic acids and amides, respectively, in good to excellent yields.* © 1997 Elsevier Science Ltd.

Carboxylic acids and their derivatives are obviously among the most important and fundamental compounds in organic chemistry.[1] Innumerable studies on the preparation and chemistry of carboxylic acids and their derivatives have already been reported; however, in view of the importance of these compounds in organic chemistry, new synthetic methods are still eagerly sought.

The homologation of carbonyl compounds from lower carbonyl compounds by a carbon-carbon coupling reaction is an attractive way for obtaining the desired carbonyl compounds.[2] However, while the homologation of aldehydes and ketones has been widely studied, only Arndt-Eistert reaction[3a,b] and Kowalski's work[3c-f] are published on the homologation of carboxylic acids. Further, these works only mentioned about the homologation of carboxylic acids or esters into **esters**.



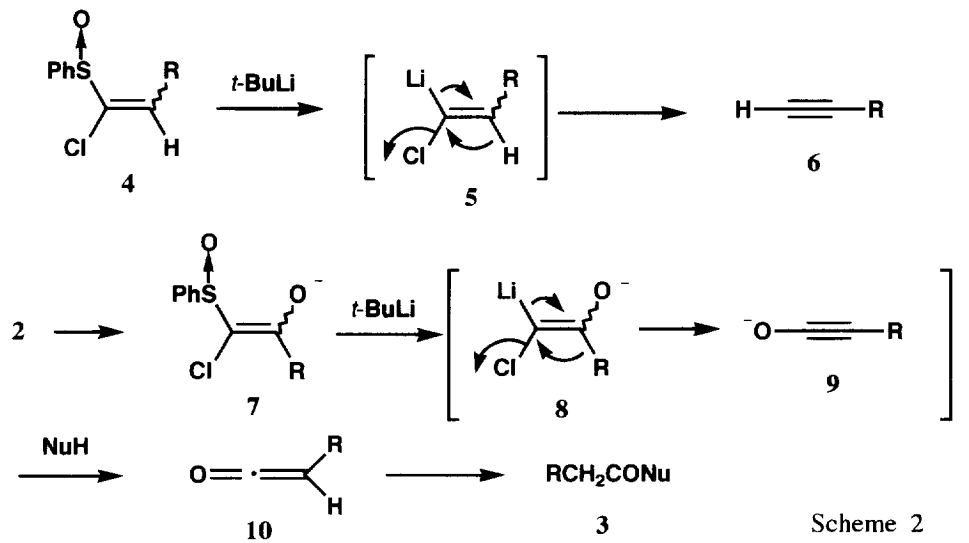
Scheme 1

Recently, we reported a novel procedure for the one-carbon homologation of methylesters **1** to carboxylic acids **3** (Nu=OH) via α-chloro α-sulfinyl ketones **2**.[4] In this paper, we describe the detailed results of the one-

carbon homologation of methylesters **1** into esters, thioesters, carboxylic acids and amides **3** through α-chloro α-sulfinyl ketones **2**.

Results and Discussion

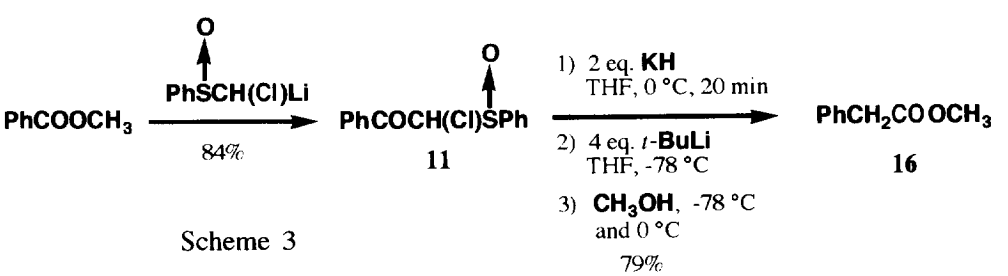
In our previous paper, we reported a novel method for generation of alkylidene carbenoid **5** from α-chloro vinyl sulfoxide **4** through the ligand exchange reaction of sulfoxide[5] with alkyllithium. The generated cabenoid **5** rearranged to give acetylene **6** in high yield (Scheme 2).[6] Analogously, we thought that the enolate **7** derived from α-chloro α-sulfinyl ketone **2** must react with *tert*-butyllithium (*t*-BuLi) to afford alkylidene carbenoid **8**, which rearranges into alkynolate **9**. Protonation of **9** in the presence of nucleophiles would give carboxylic acid and/or its derivatives **3** via ketene **10**.[7]



Scheme 2

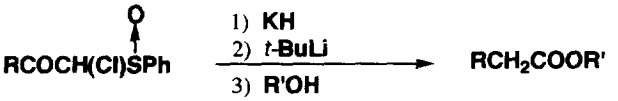
Synthesis of Esters

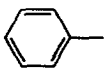
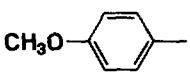
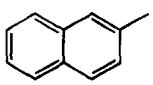
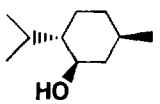
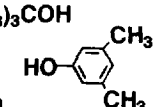
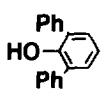
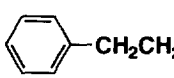
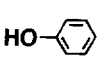
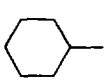
First, formation of the enolate of the α-chloro α-sulfinyl ketone **11**, which was synthesized from methyl benzoate and lithium carbanion of chloromethyl phenyl sulfoxide at low temperature in 84% yield,[8] was investigated (Scheme 3). After some investigation, potassium hydride (KH) was found to be a superior base for the enolization of α-chloro α-sulfinyl ketone **11**. In THF at 0 °C, **11** (and all α-chloro α-sulfinyl ketones **12**-**15** used in this paper) was enolized completely within 20 min with evolution of hydrogen.



Scheme 3

Table 1. Synthesis of Esters from α-Chloro α-Sulfinyl Ketones



Entry	α-Chloro α-Sulfinyl Ketone R	R'OH	Conditions[a]	Ester (yield/%)[b]
1	 **11**	CH_3OH	A	**16** (79)
2		C_2H_5OH	A	**17** (66)
3		$PhCH_2OH$	A	**18** (80)
4		$(CH_3)_2CHOH$	A	**19** (79)
5		$(CH_3)_3COH$	A	**20** (59)
6	 **12**	CH_3OH	A	**21** (83)
7	 **13**	CH_3OH	A	**22** (81)
8		C_2H_5OH	A	**23** (83)
9		$(CH_3)_2CHOH$	A	**24** (76)
10			B	**25** (73)
11			B	**26** (76)
12		$(CH_3)_3COH$	A	**27** (68)
13			B	**28** (44)
14			B	**29** (47)
15	 **14**	CH_3OH	C	**30** (81)
16		$(CH_3)_2CHOH$	C	**31** (66)
17		$(CH_3)_3COH$	C	**32** (73)
18			C	**33** (53)
19	 **15**	$PhCH_2OH$	A	**34** (76)

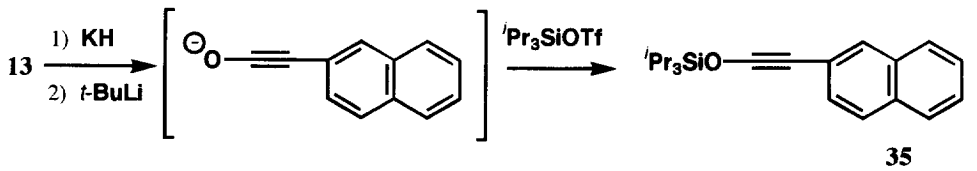
a) Conditions: A: *t*-BuLi (4 eq.) was added to the enolate at -78 °C. The reaction mixture was stirred for 15 min, then large excess alcohol was added at -78 °C and stirred for 15 min at -78 °C, then at 0 °C for 50 min. B: Eight equivalents of alcohol was used. C: See text. b) Isolated yield after silica gel column chromatography.

Next, the solution of the enolate was cooled to -78 °C and 4 equivalents of *t*-BuLi was added dropwise. After 20 min, excess methanol was added and quenched by saturated aqueous NH_4Cl to give the desired methyl phenylacetate **16** in 57% yield. The yield was improved by adding large excess methanol at -78 °C and stirring was continued for 15 min at -78 °C, then at 0 °C for 50 min to give **16** in 79% yield (Scheme 3).

This procedure for the synthesis of esters was applied to various α-chloro α-sulfinyl ketones (**11**-**15**) with various alcohols and phenols and the results are summarized in Table 1. The reaction conditions are almost the same as described above, except in the case of **14** (entries 15-18, vide infra). As shown in Table 1, α-chloro α-sulfinyl ketones derived from aryl-carboxylic esters (**11**-**13**) and alkyl-carboxylic esters (**14** and **15**) indicated quite similar results. Primary, secondary and even tertiary alcohols gave the corresponding esters in good yields. In the case of alcohols having high boiling point (entries 10 and 19) and an expensive alcohol (entry 11), eight equivalents of the alcohol was used. Even in these cases the reaction gave good yields of esters. In the case where the alcohol was L-menthol, we investigated the recovery of unused alcohol and over 97% of L-menthol was recovered after column chromatography (entry 11). As shown in entries 13, 14 and 18, though the yields of the phenol esters were moderate, the highly hindered phenol ester could be obtained (entry 14).

The reaction of α-chloro α-sulfinyl ketone **14** was problematical. Under the same conditions described above, over 90% of the starting material **14** was recovered. In this particular case the potassium enolate of **14** precipitated as a white solid at below 0 °C and did not react with *t*-BuLi at -78 °C. To overcome this problem, the reaction mixture was gradually warmed from -78 to 0 °C during 2 h. In this treatment the precipitated enolate slowly reacted with *t*-BuLi to give the alkynolate as a reddish-black transparent solution. The reaction mixture was again cooled to -78 °C and alcohol was added. The yields of the esters were 53-81% (entries 15-18).

As mentioned above, this reaction was thought to proceed through alkynolate (**9**, Scheme 2).[9] In order to get proof for the alkynolate intermediate, the potassium enolate of **13** was treated with *t*-BuLi followed by excess triisopropylsilyl trifluoromethanesulfonate.[9b] The reaction cleanly gave the silyltriflate **35**. Isolation of **35** was unsuccessful due to the unstableness of **35** on silica gel. However, the crude product showed strong and sharp absorption at 2264 cm^{-1} (IR; triple-bond).[9b] GC-MS showed *m/z* 324 ($C_{21}H_{28}OSi$) as the main peak (Scheme 4).

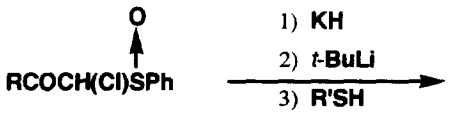


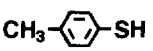
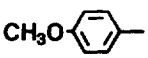
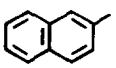
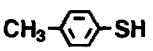
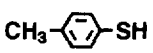
Scheme 4

Synthesis of Thioesters

The above-mentioned procedure was extended to the synthesis of thioesters. The optimized reaction conditions are as follows. To the potassium enolate at -78 °C was added 4-equivalents of *t*-BuLi. After stirring at -78 °C for 15 min, 8-equivalents of thiol was added and the reaction mixture was stirred at -78 °C for 15 min, then at 0 °C for 30 min. The results are summarized in Table 2. The yields of the thioesters are similar to the corresponding esters or slightly better. Interestingly, alkyl-thiol gave better yields (entries 1, 3 and 4) than aryl-thiol (entries 2, 5 and 6). Compared to the phenol in Table 1, aryl-thiol gave much better yields of thioester.

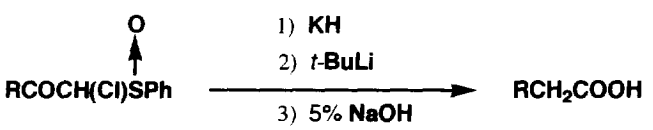
Table 2. Synthesis of Thioesters from α-Chloro α-Sulfinyl Ketones

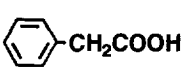
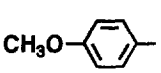
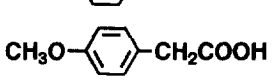
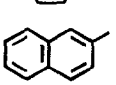
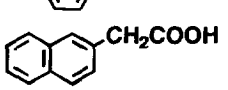
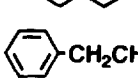
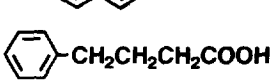
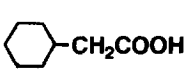


Entry	α-Chloro α-Sulfinyl Ketone R		R'SH	Thioester (Yield/%)[a]
1		11	$PhCH_2SH$	**36** (95)
2				**37** (79)
3		12	$PhCH_2SH$	**38** (83)
4		13	$PhCH_2SH$	**39** (85)
5				**40** (71)
6		15		**41** (79)

a) Isolated yield after silica gel column chromatography.

Table 3. Synthesis of Carboxylic Acids from α-Chloro α-Sulfinyl Ketones



Entry	α-Chloro α-Sulfinyl Ketone R		Carboxylic Acid (Yield/%)[a]
1		11	 (85)
2		12	 (70)
3		13	 (82)
4		14	 (74)
5		15	 (82)

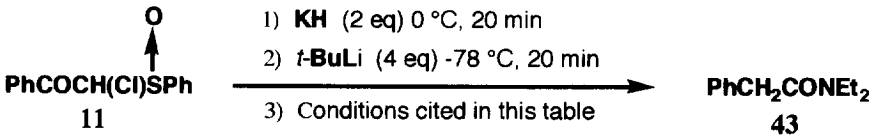
a) Isolated yield after silica gel column chromatography or recrystallization. All carboxylic acids are commercially available compounds.

Synthesis of Carboxylic Acids and Amides

In the above reaction, upon treatment of the alkynolate intermediate with 5% aqueous sodium hydroxide at -78 °C, we were able to obtain the one-carbon homologated carboxylic acids. The results are summarized in Table 3. The yields of the homologated carboxylic acids were usually very good.

In order to synthesize the one-carbon homologated amides, the alkynolate intermediate was treated with diethylamine (Table 4, entry 1). However, the treatment gave a rather complex mixture, from which only 30% yield of the desired *N,N*-diethyl phenylacetamide **43** was obtained. Longer reaction time gave a slightly better yield (entry 2). For purpose of protonation of the alkynolate intermediate, water or aqueous hydrogen chloride was added to the reaction mixture at -78 °C. These treatments were not effective (entries 3 and 4). Next, we tried to use diethylamine hydrochloride in this reaction.

Table 4. Improvement for the Synthesis of *N,N*-Diethyl Phenylacetamide from α-Chloro α-Sulfinyl Ketone **11**

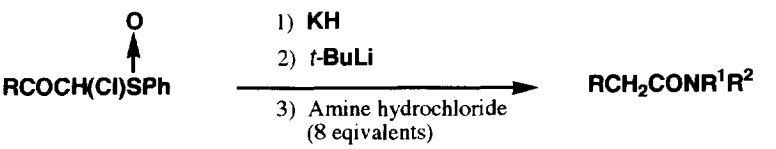


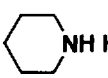
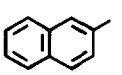
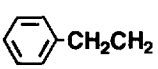
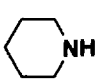
Entry	Diethylamine or Diethylamine hydrochloride	Conditions	*N,N*-Diethyl phenylacetamide (Yield / %)[d]
1	**Et_2NH (5 eq)**	-78 °C, 20 min	(30)
2	**Et_2NH (8 eq)**	-78 °C to 0 °C, 14 h	(37)
3	**Et_2NH (5 eq) and H_2O (40 eq)**	-78 °C, 15 min	(0)
4	**Et_2NH (25 eq) and HCl**[a]	-78 °C 1 h, then 0 °C 1 h	(20)
5	**Et_2NH HCl (8 eq)**[b]	-78 °C, 1 h	(69)
6	**Et_2NH HCl (8 eq)**[b]	0 °C, 1 h	(43)
7	**Et_2NH HCl (8 eq) and Et_2NH (4 eq)**	-78 °C, 1 h	(72)
8	**Et_2NH HCl (8 eq)**[c]	-78 °C, 1 h	(77)
9	**Et_2NH HCl (8 eq)**[c]	-78 °C to 0 °C, 12 h	(77)

a) 36% aqueous HCl (0.1 ml) was added to the reaction mixture (0.4 mmol scale). b) Commercially available diethylamine hydrochloride was used without any pretreatment. c) The diethylamine hydrochloride used in this experiment was finely ground and dried under vacuum. d) Isolated yield after silica gel column chromatography.

As diethylamine hydrochloride does not dissolve in THF, the crystals were added directly to the reaction mixture at -78 °C, and it was found that this was the optimal condition for this reaction (entry 5). The best result was obtained when finely ground and dried diethylamine hydrochloride was used (entry 8). These conditions were used for the formation of various one-carbon homologated amides and the results are summarized in Table 5. As can be seen in the table, the reactions were very clean and the yields of amides are good to excellent. Primary and seconary amides and also anilide (entry 1) were obtained without any problem.

Table 5. Synthesis of Amides from α-Chloro α-Sulfinyl Ketones



Entry	α-Chloro α-Sulfinyl Ketone R		Amine hydrochloride	Amide (Yield/%)[a]
1		**11**	$PhNH_2$ HCl	**42** (89)
2			Et_2NH HCl	**43** (77)
3			 NH HCl	**44** (89)
4	CH_3O- 	**12**	Et_2NH HCl	**45** (78)
5		**13**	$PhCH_2NH_2$ HCl	**46** (89)
6			Et_2NH HCl	**47** (83)
7		**14**	 NH HCl	**48** (65)
8		**15**	$PhCH_2NH_2$ HCl	**49** (71)

a) Isolated yield after silica gel column chromatography.

In conclusion, we have established a novel and versatile procedure for one-carbon homologation of esters to carboxylic acid derivatives. The whole sequence is in two-steps, and no expensive reagent is required. The yields are usually good to excellent. We believe that this procedure is one of the best methods for synthesizing carboxylic acids, esters, thioesters and amides with one-carbon homologation.

Experimental Section

^{1}H NMR spectra were measured in a $CDCl_3$ solution with JEOL GX-270 spectrometer. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion. Silica gel BW-127 ZH (Fuji-Silicia) containing 0.5% fluorescence reagent 254 and a quartz column were used for column chromatography and the products having UV absorption were detected by UV irradiation. In experiments requiring a dry solvent, THF was distilled from diphenylketyl; hexane was distilled from CaH_2. Potassium hydride (KH): Commercially available KH (30% oil suspension) was washed three times with dry hexane in a flame-dried flask by decantation to remove the mineral oil. Finally, the hexane was evaporated under vacuum to leave a light-gray powder, which was stored in a desiccator with a glass stopper.

2-Chloro-1-cyclohexyl-2-(phenylsulfinyl)-1-ethanone (15). A solution of chloromethyl phenyl sulfoxide (873 mg; 5 mmol) in 2 ml of dry THF was added dropwise to a solution of LDA (10 mmol) in 15 ml of dry THF at -78 °C. The mixture was stirred for 5 min. The solution turned yellow in color. Methyl cyclohexanecarboxylate (0.86 ml; 6 mmol) was added to the solution and the reaction mixture was stirred at -78 °C for 30 min. The reaction was quenched by adding sat. aq. NH_4Cl and the whole was extracted with $CHCl_3$. The product was purified by silica gel column chromatography (Hexane:AcOEt=5:1) to afford **15** (1.13 g; 79%) as colorless oil (about 2:3 diastereomeric mixture). IR (neat) 1716 (CO), 1090, 1057 cm^{-1}; ^{1}H NMR δ 1.1-2.0 (10H, m), 2.65 (1H, m), 5.04 (0.4H, s), 5.11 (0.6H, s), 7.5-7.7 (5H, m); MS *m/z* (%) 284 (M^+, 5), 157 (8), 125 (100). Calcd for $C_{14}H_{17}ClO_2S$: M, 284.1637. Found: *m/z* 284.1638.
α-Chloro α-sulfinyl ketones **11-14**; see lit. 8.

General Procedure for Synthesizing Esters. Synthesis of **methyl phenylacetate (16)** from **11** is described as a typical procedure. In a 30-ml flame-dried flask were added KH (32 mg; 0.8 mmol) and 3 ml of dry THF. This suspension was cooled in an ice bath and to this was added a solution of **11** (112 mg; 0.4 mmol) in 1 ml of dry THF. The reaction mixture was stirred at 0 °C for 20 min. The enolization was monitored by evolution of hydrogen gas. The reaction mixture was cooled to -78 °C and *t*-BuLi (1.64 M in pentane; 0.98 ml; 1.6 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred at -78 °C for 15 min, then 0.5 ml of methanol was added dropwise with stirring to the mixture. The reaction mixture was stirred at -78 °C for 15 min and at 0 °C for 50 min. Saturated aqueous NH_4Cl (10 ml) was added to the reaction mixture and the whole was extracted with ether-hexane. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The product was purified by silica gel column chromatography to give 47 mg (79%) of methyl phenylacetate **16**[10] as colorless oil.

Esters in Table 1, except **30-33**, were synthesized in a similar manner as described above.

Benzyl phenylacetate (18). Colorless oil; IR (neat) 1736 (CO), 1259, 1147 cm^{-1}; ^{1}H NMR δ 3.66 (2H, s), 5.12 (2H, s), 7.2-7.4 (10H, m). MS *m/z* (%) 226 (M^+, 10), 91 (100). Calcd for $C_{15}H_{14}O_2$: M, 226.0992. Found: *m/z* 226.0963.

Isopropyl phenylacetate (19). Colorless oil; IR (neat) 1732 (CO), 1262, 1107 cm^{-1}; ^{1}H NMR δ 1.22 (6H, d, *J*=6.3 Hz), 3.57 (2H, s), 5.01 (1H, septet, *J*=6.3 Hz), 7.28 (5H, m). MS *m/z* (%) 178 (M^+, 25), 91 (100). Calcd for $C_{11}H_{14}O_2$: M, 178.0993. Found: *m/z* 178.1005.

***tert*-Butyl phenylacetate (20).** Colorless oil; IR (neat) 1732 (CO), 1257, 1144 cm^{-1}; ^{1}H NMR δ 1.43 (9H, s), 3.52 (2H, s), 7.27 (5H, m). MS *m/z* (%) 192 (M^+, 2), 91 (60), 57 (100). Calcd for $C_{12}H_{16}O_2$: M, 192.1149. Found: *m/z* 192.1161.

Isopropyl 2-naphthylacetate (24). Colorless crystals; mp 45-47 °C (MeOH-H_2O); IR (KBr) 1730 (CO), 1194, 1105 cm^{-1}; ^1H NMR δ 1.20 (6H, d, *J*=6.3 Hz), 3.74 (2H, s), 5.03 (1H, septet, *J*=6.3 Hz), 7.4-7.8 (7H, m). MS *m/z* (%) 228 (35), 141 (100). Calcd for $C_{15}H_{16}O_2$: M, 228.1149. Found *m/z* 228.1149.

Cyclohexyl 2-naphtylacetate (25). Colorless oil; IR (neat) 1728 (CO), 1259, 1163 cm^{-1}; ^1H NMR δ 1.2-1.9 (10H, m), 3.75 (2H, s), 4.79 (1H, m), 7.4-7.8 (7H, m). MS *m/z* (%) 268 (M^+, 45), 186 (12), 141 (100). Calcd for $C_{18}H_{20}O_2$: M, 268.1463. Found: *m/z* 268.1463.

L-Menthyl 2-naphthylacetate (26). Colorless oil; IR (neat) 1728 (CO), 1261, 1161 cm^{-1}; ^1H NMR δ 0.67 (3H, d, *J*=6.9 Hz), 0.80 (3H, d, *J*=6.5 Hz), 0.87 (3H, d, *J*=6.6 Hz), 0.8-2.1 (9H, m), 3.75 (2H, s), 4.69 (1H, m), 7.4-7.8 (7H, m). MS *m/z* (%) 324 (M^+, 38), 186 (48), 141 (87), 83 (100). Calcd for $C_{22}H_{28}O_2$: M, 324.2087. Found: *m/z* 324.2081.

***tert*-Butyl 2-naphthylacetate (27).** Colorless low melting solid; IR (KBr) 1716 (CO), 1279, 1132 cm^{-1}; ^1H NMR δ 1.44 (9H, s), 3.68 (2H, s), 7.3-7.8 (7H, m). MS *m/z* (%) 242 (M^+, 30), 141 (73), 57 (100). Calcd for $C_{16}H_{18}O_2$: M, 242.1305. Found: *m/z* 242.1293.

3,5-Dimethylphenyl 2-naphtylacetate (28). Colorless oil; IR (neat) 1755 (CO), 1236, 1138 cm^{-1}; ^1H NMR δ 2.27 (6H, s), 3.99 (2H, s), 6.67 (2H, s), 6.83 (1H, s), 7.4-7.9 (7H, m). MS *m/z* (%) 290 (M^+, 20), 168 (99), 141 (100). Calcd for $C_{20}H_{18}O_2$: M, 290.1307. Found: *m/z* 290.1299.

2,6-Diphenylphenyl 2-naphthylacetate (29). Colorless crystals; mp 118-121 °C (AcOEt-hexane); IR (KBr) 1747 (CO), 1240, 1188, 1130 cm^{-1}; ^1H NMR δ 3.49 (2H, s), 6.95 (1H, dd, *J*=8.3, 1.7 Hz), 7.2-7.8 (19H, m). MS *m/z* (%) 414 (M^+, 8), 246 (30), 168 (100). Anal. Calcd for $C_{30}H_{22}O_2$: C, 86.93; H, 5.35. Found: C, 86.41; H, 5.17.

Methyl 4-phenylbutyrate (30). In a 30-ml flame-dried flask were added KH (32 mg; 0.8 mmol) and dry THF (3 ml). This suspension was cooled in an ice bath and to this was added a solution of **14** (117 mg; 0.4 mmol) in 1 ml of THF with stirring. After 20 min, the suspension was cooled to -78 °C and *t*-BuLi (1.6 mmol) was added dropwise with stirring. The temperature of the reaction mixture was gradually allowed to warm to 0 °C for 2 h. The solution turned reddish-black in color. Then, the reaction mixture was recooled to -78 °C and MeOH (0.5 ml) was added. The reaction mixture was again allowed to warm to 0 °C for 2 h. The reaction was quenched by sat. aq. NH_4Cl and the whole was extracted with ether-hexane. The product was purified by silica gel column chromatography to give 58 mg (81%) of **30** as colorless oil. IR (neat) 1740 (CO), 1203 cm^{-1}; ^1H NMR δ 1.96 (2H, quintet, *J*=7.6 Hz), 2.33 (2H, t, *J*=7.6 Hz), 2.65 (2H, t, *J*=7.6 Hz), 3.66 (3H, s), 7.1-7.4 (5H, m). MS *m/z* (%) 178 (M^+, 50), 147 (40), 104 (100). Calcd for $C_{11}H_{14}O_2$: M, 178.0993. Found: *m/z* 178.0996.

The esters **31**-**33** were synthesized in a similar way as described above.

Isopropyl 4-phenylbutyrate (31). Colorless oil; IR (neat) 1732 (CO) 1109 cm^{-1}; ^1H NMR δ 1.23 (6H, d, *J*=6.3 Hz), 1.94 (2H, m), 2.29 (2H, t, *J*=7.4 Hz), 2.64 (2H, t, *J*=7.6 Hz), 5.01 (1H, septet, *J*=6.3 Hz), 7.15-7.31 (5H, m). MS *m/z* (%) 206 (M^+, 35), 164 (30), 163 (35), 147 (70), 117 (50), 104 (100). Calcd for $C_{13}H_{18}O_2$: M, 206.1307. Found: *m/z* 206.1316.

***tert*-Butyl 4-phenylbutyrate (32).** Colorless oil; IR (neat) 1732 (CO), 1259, 1143 cm^{-1}; ^1H NMR δ 1.37 (9H, s), 1.83 (2H, m), 2.16 (2H, t, *J*=7.4 Hz), 2.56 (2H, t, *J*=7.6 Hz), 7.1-7.3 (5H, m). MS *m/z* (%) 220 (M^+, 2), 164 (65), 147 (75), 104 (65), 91 (60), 57 (100). Calcd for $C_{14}H_{20}O_2$: M, 220.1464. Found: *m/z* 220.1457.

Phenyl 4-phenylbutyrate (33). Colorless oil; IR (neat) 1761 (CO), 1196, 1128 cm^{-1}; ^1H NMR δ 2.08 (2H, quintet, *J*=7.5 Hz), 2.58 (2H, t, *J*=7.4 Hz), 2.74 (2H, t, *J*=7.6 Hz), 7.0-7.4 (10H, m). MS *m/z* (%) 240 (M^+, 20), 147 (100). Calcd for $C_{16}H_{16}O_2$: M, 240.1151. Found: *m/z* 240.1134.

Benzyl cyclohexylacetate (34). Colorless oil; IR (neat) 1736 (CO), 1288, 1161 cm^{-1}; ^1H NMR δ 0.8-1.9 (11H, m), 2.24 (2H, d, *J*=6.9 Hz), 5.11 (2H, s), 7.35 (5H, m). MS *m/z* (%) 232 (M^+, 15), 141 (16), 123 (22), 108 (23), 91 (100). Calcd for $C_{15}H_{20}O_2$: M, 232.1461. Found: *m/z* 232.1460.

General Procedure for Synthesizing Thioesters. A synthesis of ***S*-benzyl (2-naphthyl)-ethanethioate (39)** from **13** is described as a typical procedure. To a suspension of KH (16 mg; 0.4 mmol) in 2 ml of dry THF was added dropwise a solution of **13** (66 mg; 0.2 mmol) in 1 ml of THF with stirring at 0 °C. The mixture was stirred at 0 °C for 20 min, then it was cooled to -78 °C. *t*-BuLi (0.8 mmol) was added dropwise to the reaction mixture and the solution was stirred for 15 min. Benzyl mercaptan (0.19 ml; 1.6 mmol) was added to the reaction mixture and the solution was stirred at -78 °C for 15min, then at 0 °C for 30 min. The reaction mixture was diluted with ether-hexane and sat. aq. NH_4Cl (10 ml) was added. The whole was extracted with ether-hexane. The organic layer was washed twice with 2.5% NaOH (10 ml x 2) followed by sat. aq. NH_4Cl. The product was purified by silica gel column chromatography to afford 50 mg (85%) of **39** as colorless crystals. Mp 84-85 °C (AcOEt-hexane); IR (KBr) 1682 (CO), 999 cm^{-1}; ^1H NMR δ 3.99 (2H, s), 4.11 (2H, s), 7.25 (5H, m), 7.4-7.8 (7H, m). Anal. Calcd for $C_{19}H_{16}OS$: C, 78.05; H, 5.52; S, 10.96. Found: C, 77.76; H, 5.33; S, 10.66.

***S*-Benzyl phenylethanethioate (36)**. Colorless low melting solid; IR (KBr) 1682 (CO), 1022 cm^{-1}; ^1H NMR δ 3.83 (2H, s), 4.10 (2H, s), 7.2-7.4 (10H, m). MS *m/z* (%) 242 (M^+, 12), 91 (100). Calcd for $C_{15}H_{14}OS$: M, 242.0764. Found: *m/z* 242.0765.

***S*-(4-Methyphenyl) phenylethanethioate (37)**. Colorless crystals; mp 63-64.5 °C (AcOEt-hexane); IR (KBr) 1693 (CO), 1047 cm^{-1}; ^1H NMR δ 2.35 (3H, s), 3.90 (2H, s), 7.2-7.4 (9H, m). Anal. Calcd for $C_{15}H_{14}OS$: C, 73.65; H, 5.30; S, 14.04. Found: C, 73.89; H, 5.81; S, 13.44.

***S*-Benzyl (4-methoxyphenyl)ethanethioate (38)**. Colorless crystals; mp 57-58 °C (AcOEt-hexane); IR (KBr) 1680 (CO), 1034, 1005 cm^{-1}; ^1H NMR δ 3.77 (2H, s), 3.79 (3H, s), 4.09 (2H, s), 6.86 (2H, m), 7.18 (2H, m), 7.25 (5H, m). MS *m/z* (%) 272 (M^+, 16), 121 (100). Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.56; H, 5.92; S, 11.77. Found: C, 70.21; H, 5.79; S, 12.04.

***S*-(4-Methylphenyl) (2-naphthyl)ethanethioate (40)**. Colorless crystals; mp 114-116 °C (AcOEt-hexane); IR (KBr) 1686 (CO), 1041 cm^{-1}; ^1H NMR δ 2.35 (3H, s), 4.06 (2H, s), 7.20 (4H, m), 7.4-7.9 (7H, m). MS *m/z* (%) 292 (M^+, 15), 168 (34), 141 (100). Anal. Calcd for $C_{19}H_{16}OS$: C, 78.05; H, 5.52; S, 10.96. Found: C, 77.77; H, 5.37; S, 10.89.

***S*-(4-Methylphenyl) cyclohexylethanethioate (41)**. Colorless oil; IR (neat) 1709 (CO), 999 cm^{-1}; ^1H NMR δ 0.8-1.9 (11H, m), 2.37 (3H, s), 2.51 (2H, d, *J*=6.9 Hz), 7.1-7.4 (4H, m). MS *m/z* (%) 248 (M^+, 15), 125 (96), 97 (100). Calcd for $C_{15}H_{20}OS$: M, 248.1234. Found: *m/z* 248.1235.

General Procedure for Synthesizing Carboxylic Acids. A synthesis of **cyclohexylacetic acid** (Table 3, entry 5) from **15** is described as a typical procedure. To a suspension of KH (24 mg; 0.6 mmol) in 3 ml of dry THF was added dropwise with stirring a solution of **15** (85 mg; 0.3 mmol) in 0.5 ml of THF at 0 °C. The suspension was stirred at 0 °C for 15 min, then the solution was cooled to -78 °C. *t*-BuLi (1.2 mmol) was added to the reaction mixture and the solution was stirred for 20 min. To this was added 5% NaOH (0.5 ml) and the reaction mixture was stirred at -78 °C for 10 min, and at 0 °C for 10 min. To the reaction mixture were

added 5 ml of 5% NaOH and a mixture of ether-benzene (20 ml). The whole was stirred vigorouly on a magnetic stirrer. The solution was transferred into a separatory funnel and the aqueous layer was separated. The organic layer was extracted once with 5% NaOH (5 ml). The combined aqueous layer was acidified with 10% HCl and extracted with ether-benzene. The organic layer was washed once with sat. aq. NH_4Cl and dried over $MgSO_4$. Evaporation of the solvent gave pure cyclohexylacetic acid (35 mg, 82%) as a colorless, low-melting solid.

General Procedure for Synthesizing Amides. A synthesis of *N,N*-diethyl (2-naphthyl)ethanamide (**47**) from **13** is described as a typical procedure. To a suspension of KH (16 mg; 0.4 mmol) in 2 ml of dry THF was added dropwise a solution of **13** (66 mg; 0.2 mmol) in 1 ml of dry THF with stirring at 0 °C. The suspension was stirred at 0 °C for 20 min. The reaction mixture was then cooled to -78 °C and *t*-BuLi (1.6 mmol) was added dropwise with stirring. After 15 min, finely ground and dried diethylamine hydrochloride (175 mg; 1.6 mmol) was added and the reaction mixture was stirred at -78 °C for 1 h. The color of the reaction mixture slowly turned from reddish-brown to light yellow. The reaction was quenched with sat. aq. NH_4Cl and the whole was extracted with $CHCl_3$. The product was purified by silica gel column chromatography (hexane:AcOEt=1:1) to give **47** (40 mg; 83%) as colorless oil. IR (neat) 1641 (CO) cm^{-1}; ^1H NMR δ 1.08 (3H, t, *J*=7.3 Hz), 1.13 (3H, t, *J*=7.3 Hz), 3.30 (2H, q, *J*=7.3 Hz), 3.40 (2H, q, *J*=7.3 Hz), 3.85 (2H, s), 7.4-7.8 (7H, m). MS *m/z* (%) 241 (M^+, 17), 141 (25), 100 (100). Calcd for $C_{16}H_{19}NO$: M, 241.1464. Found: *m/z* 241.1464.

***N*-Phenyl phenylethanamide (42)**. Colorless crystals; mp 104-106 °C (AcOEt-hexane); IR (KBr) 1659 (CO) cm^{-1}; ^1H NMR δ 3.73 (2H, s), 7.0-7.5 (11H, m). Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.23; H, 6.20; N, 6.54.

***N,N*-Diethyl phenylethanamide (43)**. Colorless oil; IR (neat) 1639 (CO) cm^{-1}; ^1H NMR δ 1.07, 1.12 (each 3H, t, J=7 Hz), 3.28, 3.37 (each 2H, q, *J*=7 Hz), 3.68 (2H, s), 7.24 (5H, m). MS *m/z* (%) 191 (M^+, 42), 100 (100). Calcd for $C_{12}H_{17}NO$: M, 191.1309. Found: *m/z* 191.1299.

***N*-(Phenylethanoyl)piperidine (44)**. Colorless oil; IR (neat) 1637 (CO) cm^{-1}; ^1H NMR δ 1.34 (2H, m), 1.5-1.6 (4H, m), 3.36 (2H, t, *J*=5.4 Hz), 3.56 (2H, t, *J*=5.4 Hz), 3.72 (2H, s), 7.2-7.3 (5H, m). MS *m/z* (%) 203 (M^+, 40), 112 (100). Calcd for $C_{13}H_{17}NO$: M, 203.1309. Found: *m/z* 203.1314.

***N,N*-Diethyl (4-methoxyphenyl)ethanamide (45)**. Colorless oil; IR (neat) 1639 (CO), 1514, 1248 cm-1; 1H NMR d 1.09, 1.12 (each 3H, t, J=7.3 Hz), 3.30, 3.38 (each 2H, q, J=7.3 Hz), 3.63 (2H, s), 3.78 (3H, s), 6.86, 7.16 (each 2H, m). MS m/z (%) 221 (M+, 21), 121 (46), 100 (100). Calcd for $C_{13}H_{19}NO$: M, 221.1414. Found: *m/z* 221.1407.

***N*-Benzyl (2-naphthyl)ethanamide (46)**. Colorless crystals; mp 170-174 °C ($CHCl_3$-hexane); IR (KBr) 1637 (CO) cm^{-1}; ^1H NMR δ 3.78 (2H, s), 4.41 (2H, d, *J*=5.9 Hz), 5.76 (1H, bs, NH), 7.1-7.9 (12H, m). MS *m/z* (%) 275 (M^+, 52), 141 (100). Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.90; H, 6.16; N, 4.98.

***N*-(4-Phenylbutanoyl)piperidene (48)**. Colorless oil; IR (neat) 1643 (CO); ^1H NMR δ 1.5-1.7 (6H, m), 1.9-2.1 (2H, m), 2.32, 2.68 (each 2H, t, *J*=7.5 Hz), 3.31, 3.54 (each 2H, t, *J*=5.2 Hz), 7.1-7.4 (5H, m). MS *m/z* (%) 231 (M^+, 15), 127 (100). Calcd for $C_{15}H_{21}NO$: M, 231.1623. Found: *m/z* 231.1616.

***N*-Benzyl cyclohexylethanamide (49)**. Colorless crystals; mp 131-133 °C (AcOEt-hexane); IR (KBr) 1635 (CO) cm^{-1}; ^1H NMR δ 0.8-1.4 (5H, m), 1.6-1.9 (6H, m), 2.07 (2H, d, *J*=6.9 Hz), 4.44 (2H, d, *J*=5.6

Hz), 5.72 (1H, bs, NH), 7.2-7.4 (5H, m). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.84; H, 8.99; N, 5.97.

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