A New Method for Expeditious Ketone Synthesis from Acids via Acyl Hemiacetals

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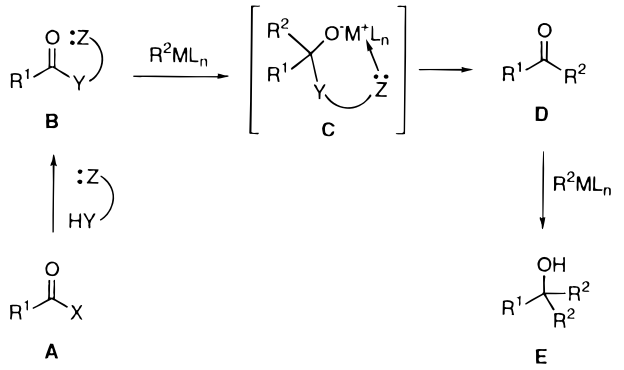
Since ketones are common and versatile functionalities in organic synthesis for both carbon−carbon bond formation and functional group interconversion, a large number of methods for their convergent construction has been developed. The synthesis of ketones from organometallic reagents and carboxylic acids and their derivatives has been explored exhaustively for a large variety of combinations.[1] However, acylation methods that are economical, efficient, and easily performed in a variety of applications are still being sought.[2]

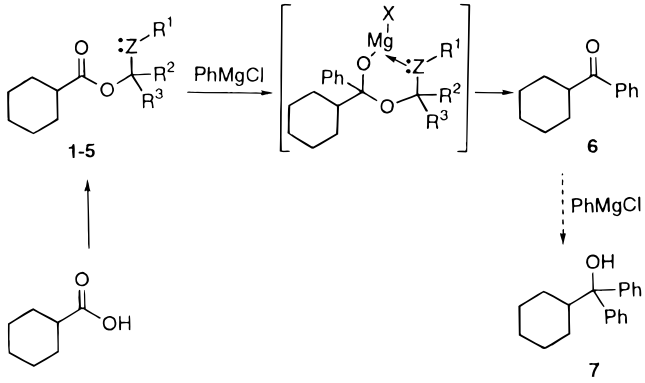
Most generally, the nucleophilic addition of organomagnesium and -lithium reagents to carboxylic acid derivatives generates the ketone, a reaction that is often complicated by a following rapid addition to form the tertiary alcohol.[3] The reaction of simple esters with Grignard reagents normally yields the tertiary alcohol products, not the ketone, and is also often complicated by enolization and the formation of reduction products.[3a] The development of heterosubstituted esters[4] (Scheme 1, **B**, Y = O, S) and amides[5] (**B**, Y = NR), which can chelate the metal in the initial addition product (**C**), thus preventing premature ketone liberation, has improved the selective formation of ketones. Addition of organomagnesium and -lithium reagents to *N*,*O*-dialkyl hydroxamates has become popular and is generally a very selective and high-yielding process,[5,6] although loss of alkoxide from the hydroxamate has been observed and can lead to byproducts.[2,5b,c] Also, another step for derivatization of the carboxylic acid (to **A**) and possible purification of the dialkyl hydroxamates may be required,[5,6] which can add to the cost.[7]

We sought a carboxylic acid derivative with similar chelation control that might be prepared more directly and efficiently from the carboxylic acid. The possible employment of acyl hemiacetal (AHA) derivatives[8] appeared attractive for their ready formation and easy removal[9] from the subsequent product mixture.

Scheme 1



Scheme 2. Reaction of Phenylmagnesium Chloride with Acyl Hemiacetals



Thus, an examination of five cyclohexanecarboxylic esters, chosen for their ease and economy of preparation, was conducted for possible ketone formation using phenylmagnesium chloride (Scheme 2). Straightforward preparation of the AHA esters **1**−**5** by reported methods does not require any prior activation of the carboxyl group and is generally high yielding (Table 1). The methoxymethyl ester **1** is readily made using procedures that do not involve MOM-Cl,[10] and the (methylthio)methyl ester **2** is made by alkylation[11] or mild Pummerer reaction[12] with the carboxylic acid. The other three esters (2-methoxy-2-propyl **3**, 2-tetrahydropyranyl **4**, 2-tetrahydrofuranyl **5**) are available using the corresponding enol ether[13−15] and a catalytic amount of methanesulfonic acid.

(1) (a) O'Neill, B. T. Nucleophilic Addition to Carboxylic Acid Derivatives. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, Chapter 1.13, p 397. (b) Jorgenson, M. J. *Org. React.* **1970**, *18*, 1. (c) Shirley, D. A. *Org. React.* **1954**, *8*, 28. (d) Cason, J. *Chem. Rev.* **1947**, *40*, 15.

(2) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

(3) (a) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: New York, 1954. (b) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: San Diego, 1995. (c) Wakefield, B. J. *Organolithium Methods in Organic Synthesis*; Academic Press: San Diego, 1988. (d) Use of lithium carboxylates with Grignard reagents has effectively formed ketones from substituted α-amino acids: Knudsen, C. G.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 2260.

(4) *S*-(2-Pyridyl) thioates and 2-pyridyl esters: (a) Araki, M.; Sakata, S.; Takei, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1777. (b) Reviewed in: Kim, S. *Org. Prep. Proc. Int.* **1988**, *20*, 145. Other heterosubstituted esters are noted in ref 1a, p 422.

(5) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. Reviewed in: Sibi, M. P. *Org. Prep. Proc. Int.* **1993**, *25*, 15. (b) Graham, S. L.; Scholz, T. H. *Tetrahedron Lett.* **1990**, *31*, 6269. (c) Acyl isoxazolidides: Lubell, W. D.; Jamison, T. F.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3511. (d) Acyl imidazolides: Staab, H. A.; Jost, E. *Liebigs Ann. Chem.* **1962**, *655*, 90.

(6) Sibi, M. P.; Stessman, C. C.; Schultz, J. A.; Christensen, J. W.; Lu, J.; Marvin, M. *Synth. Commun.* **1995**, *25*, 1255 and references cited therein. *N*,*O*-Dimethylhydroxamates have also been efficiently made from the methyl or ethyl esters: ref 2.

(7) *N*,*O*-Dimethylhydroxylamine hydrochloride, an expensive commercial reagent, can be easily prepared: Goel, O. P.; Krolls, U. *Org. Prep. Proc. Int.* **1987**, *19*, 75.

(8) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991; Chapter 5. (b) Kocienski, P. J. *Protecting Groups*; Thieme Verlag: New York, 1994.

(9) Mild acidic quench of the reaction mixture, followed by washing with mild aqueous base, removes the starting carboxylic acid. The more stable dialkylhydroxamates remain after quenching and washing.

(10) A procedure employing iodomethyl methyl ether was used: (a) Pankowski, J.; Winiarski, J. *Org. Prep. Proc. Int.* **1994**, *26*, 327. See also: (b) Dardoize, F.; Gaudemar, M.; Goasdoue, N. *Synthesis* **1977**, 567.

(11) Wade, L. G., Jr.; Gerdes, J. M.; Wirth, R. P. *Tetrahedron Lett.* **1978**, 731.

(12) (a) Dossena, A.; Palla, G.; Marchelli, R.; Lodi, T. *Int. J. Pept. Protein Res.* **1984**, *23*, 198. (b) Dossena, A.; Marchelli, R.; Casnati, G. *J. Chem. Soc., Chem. Commun.* **1979**, 370. (c) Ho, T.-L. *Synth. Commun.* **1979**, *9*, 267.

(13) 1-Methyl-1-methoxyethyl ether formation: Klug, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 7827.

(14) THP ester formation: Bernady, K. F.; Floyd, M. B.; Poletto, J. F.; Weiss, M. J. *J. Org. Chem.* **1979**, *44*, 1438.

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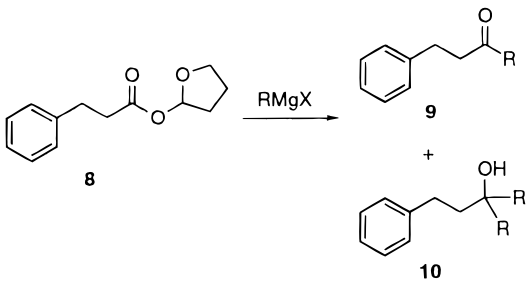
Simple isolation with an aqueous wash and drying yields each ester in high purity, sufficient to proceed into the acylation reaction.[16]

The AHA esters **1**−**4** reacted to form the tertiary alcohol **7**, even when using only 100 mol % of phenyl Grignard reagent (Table 1). The sulfur chelate, (methylthio)methyl ester **2**, cleanly produced only the tertiary alcohol.[17] Although the acyclic AHA ester **3** reacted poorly with decomposition, both of the cyclic AHA esters, 2-tetrahydropyranyl (THP) ester **4** and 2-tetrahydrofuranyl (THF) ester **5**, readily reacted with phenyl Grignard reagent. In comparison to esters **1**−**4**, the THF ester **5** produced the phenyl ketone **6** in higher ratios (4−6/1 in initial trials and 10/1 when reacted for 8 h at −8 °C). Also, isolation using aqueous washing of the organic phase removed the reaction byproducts derived from **5** (THF ester) somewhat better than those from **4** (THP ester). Thus, the 2-tetrahydrofuranyl ester was selected for our study with other Grignard reagents.

To survey the potential for formation of ketones with a variety of Grignard reagents, 2-tetrahydrofuranyl 3-phenylpropionate (**8**) was chosen as the model. Possible enolization and formation of Claisen products as competing side reactions are more fairly evaluated with the less hindered α-hydrogens of **8**. We employed reaction conditions of 100 mol %[18] of Grignard reagent in dichloromethane or THF from −20 °C to room temperature[19] to survey the reactions with THF ester **8** in the formation of ketones **9** and tertiary alcohols **10** (eq 1, Table 2).[20]



(eq. 1)

Alkyl Grignard reagents reacted very well with the THF ester **8**. Ethyl Grignard reagent gave usable formation of ketone **9a**. Also, the isopropyl and *tert*-butyl Grignard reagents reacted smoothly, despite the overwhelming precedence for enolization of esters with these Grignard reagents.[21,22]

Table 1. Reaction of Phenyl Grignard with Acyl Hemiacetal (AHA) Esters

AHA	Z	R^1	R^2	R^3	% yield, AHA	ratio[a] **6/7**
1	O	Me	H	H	90	1.5/1
2	S	Me	H	H	100	<1/50[b]
3	O	Me	Me	Me	84	3/1
4	O		$(CH_2)_4$	H	100	1/1.5
5	O		$(CH_2)_3$	H	100	4−10/1[c]

[a] ^{1}H NMR measured ratio of cyclohexyl phenyl ketone (**6**) to cyclohexyldiphenylmethanol (**7**) from reactions using 100 mol % PhMgCl in THF at −40 to 20 °C. [b] Less than 2% of the ketone was detected, while the remainder was ester **2**. [c] The higher ratios of ketone were obtained for reactions warmed more slowly (~8 h at −8 °C).

Table 2. Reaction of 2-Tetrahydrofuranyl Ester 8 with Grignard Reagents

entry	Grignard R	solvent[a]	ratio[b] **9**/**10**	ketone **9** (% yield)[c]
a-1	Et	THF	10/1	**9a** (83)
a-2	Et	CH_2Cl_2	>100/1	**9a** (88)
b	*i*-Pr	THF	>25/1	**9b** (82)
c	*t*-Bu	CH_2Cl_2	>100/1	**9c** (50)
d	allyl	either	<10% ketone	nd
e	Vinyl	either	<25% ketone	nd
f	Ph	CH_2Cl_2	4/1	**9f** (70)
g	*n*-BuC≡C	CH_2Cl_2	5/1	**9g** (75)

[a] Isolated THF ester in either THF or CH_2Cl_2 was treated with the Grignard reagent at −20 to 20 °C. [b] The raw product mixtures were analyzed by capillary GC and GC-MS.[20] [c] Isolated by silica gel chromatography.

Relatively electronegative groups in the Grignard reagent gave less favorable ketone formation. The phenyl, allyl, vinyl, and 1-hexynyl Grignard reagents gave less stable chelation in the proposed Mg-chelated intermediate (cf. Scheme 1, **C**). For the phenyl case the result was significant formation of tertiary alcohol. Both the allyl and vinyl Grignard reagents gave typical product distribution for reactions with conventional esters.[3a,23] Following collapse of intermediate **C**, the released conjugated enone (formed directly or following base-catalyzed isomerization) underwent further conjugate addition and tertiary alcohol formation. This collapse occurred despite the uniquely high reactivity of the allyl Grignard at −20 °C. Although the hexynyl group adds relatively slowly at room temperature (6 h, 25 °C), the formation of ketone remains controlled when 100 mol % of Grignard reagent is used.

In an effort to improve the reaction with phenylmagnesium chloride to produce ketone **9f**, a number of solvents and additives were surveyed (Table 3). Noncoordinating solvents (CH_2Cl_2 and toluene) gave the best results. Addition of any type of Lewis acid generally produced 2-phenyltetrahydrofuran, the side product of cleavage of the 3-phenylpropionate moiety.[24] Further trial reactions of ester **8** with *n*-BuLi (THF, −78 °C) alone or with $CeCl_3$[25] (100 mol %) or CuCN[26] (50 mol %)[27]

(15) (a) THF-esters from 2-chloro-tetrahydrofuran or 2-(diphenylacetyl)tetrahydrofuran: Kruse, C. G.; Jonkers, F. L.; Dert, V.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 371. (b) THF ethers from 2,3-dihydrofuran: Eliel, E. L.; Nowak, B. E.; Daignault, R. A.; Badding, V. G. *J. Org. Chem.* **1965**, *30*, 2441.

(16) These AHA esters are hygroscopic and readily hydrolyze at 20 °C; therefore, they should be used directly; if storage is required, it should be cold and dry.

(17) A partial explanation may lie in the stronger *σ*-donor character of the sulfur in thioether **2** versus the oxygen in ether **1**. As donation from Z to Mg in intermediate **C** increases (Scheme 1); the magnesium alkoxide bond is destabilized, and the electronegativity/leaving group ability of the ester is increased.

(18) The ratio of ketone/tertiary alcohol products may be increased by using less Grignard reagent, and the yield of ketones may be optimized by adjustment with a small excess of Grignard reagent. Our study, however, is a comparison of the relative performance of several Grignard reagents under fixed conditions.

(19) In the reaction of ester **5** with phenyl Grignard reagent, control of optimal monoaddition required fine tuning of the reaction temperature. The ratio of ketone/tertiary alcohol products is generally sensitive to the temperature and concentration.

(20) Authentic samples of ketone and tertiary alcohol products, **9** and **10**, respectively, were prepared from the corresponding *N*,*O*-dimethyl hydroxamate and methyl ester, respectively, of 3-phenylpropionic acid. As an example, phenyl Grignard reagent gave ketone **9f** to tertiary alcohol **10f** ratios of 32/1 and 1/49 with the hydroxamate and methyl ester, respectively.

(21) Zook, H. D.; McAleer, W. J.; Horwin, L. *J. Am. Chem. Soc.* **1946**, *68*, 2404. In our hands, these Grignard reagents gave significant enolization with the methyl 3-phenylpropionate.

(22) In no reaction was any product of Claisen (or aldol) condensation recovered.

(23) Watanabe, S.; Suga, K.; Fujita, T.; Saito, N. *Aust. J. Chem.* **1977**, *30*, 427.

(24) 2-Tetrahydrofuranyl substitution is exclusive in 2-tetrahydrofuranyl phenyl sulfone in the presence of the appropriate Lewis acids: Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293.

(25) (a) Imamoto, T. Organocerium Reagents. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, Chapter 1.8, p 231. (b) Mudryk, B.; Shook, C.; Cohen, T. *J. Am. Chem. Soc.* **1990**, *112*, 6389.

Table 3. Solvent and Additive Modifications of Phenyl Grignard Reaction with THF Ester 8

solvent	additive (100 mol %)	ratio **9f**/**10f**
THF		68/32
THF	$CeCl_3$	65/35[a]
THF	$ZnBr_2$	*b*
THF	Et_2AlCl	*b*
THF	$MgBr_2$	*b*
Et_2O		62/38
MeCN		55/45
CH_2Cl_2		80/20
CH_2Cl_2	$BF_3{\cdot}OEt_2$	73/27[c,d]
CH_2Cl_2	Me_3SiCl	81/19[d]
toluene		84/16[e]

[a] Reaction occurs at −15 to −10 °C. [b] The major product is 2-phenyltetrahydrofuran. [c] 2-Phenyltetrahydrofuran is observed. [d] Dehydration of **10f** observed. [e] Slow reaction requires warming to 30 °C.

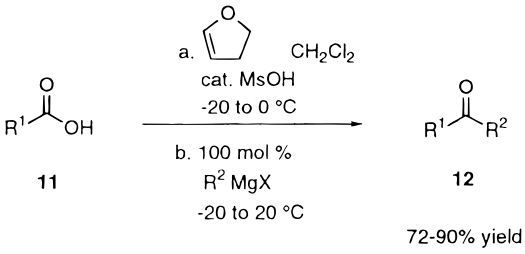
Table 4. Single Flask Formation and Reaction of THF Esters

entry	Grignard reagent, R^2	acid R^1	ketone/tertiary alcohol[a]	ketone (% yield)[b]
a	Et	$PhCH_2$	>80/1	**12a** (90)
b	*i*-Pr	$PhCH_2CH_2$	>40/1	**9b** (86)
c	*i*-Pr	$PhCH_2$	>80/1	**12b** (81)
d	*i*-Pr	Ph	8/1	**12c** (86)
e	*i*-Pr	3,4-$(MeO)_2C_6H_3$	>80/1	**12d** (72)

[a] The raw product mixtures were evaluated by capillary GC and GC−MS. [b] Isolated by silica gel chromatography.

produced only double addition or enolization products. Likewise, reaction of ester **8** with $LiAlH_4$ in THF or Et_2O produced only 3-phenylpropanol. Thus, selection of the metal counterion of the nucleophile is crucial to the strength of intermediate coordination and nucleophilic substitution ability of the 2-tetrahydrofuranyl group.

Finally, the culmination of our efforts was the single flask reaction with a variety of carboxylic acids. Formation of the intermediate THF ester was followed by direct addition of the Grignard reagent (eq 2). This simple



(eq. 2)

procedure does not involve any isolation of carboxylic acid derivatives and provides the ketone after simple aqueous workup. Ketones are formed in high yield with well-maintained control of double addition (Table 4). Remarkably, the more readily enolizable phenylacetate ester produced ketones **12a** and **12b** in good yields. In view of the results for **9f**, formation of the aryl isopropyl ketones **12c** and **12d** was well-controlled.[28]

Overall, the application of THF esters is an expeditious method for the controlled synthesis of a number of ketones. The 2-tetrahydrofuranyl ester effectively controls the single addition of Grignard reagents. Relatively weak chelation[29] in the intermediate adduct may be responsible for retaining ketone formation.[30] In each case, reaction parameters, as well as the interesting dependence on the nature of the nucleophilic reagent and counterion, may benefit from further experimentation.

Experimental Section

General Methods. Dichloromethane and dihydropyran were distilled from calcium hydride under nitrogen. Tetrahydrofuran and diethyl ether were distilled from sodium metal and benzophenone under nitrogen. Dihydropyran and dihydrofuran (Aldrich Chemical Co.) were stored over K_2CO_3. Cerium trichloride was dried as described.[25a] Zinc bromide was freshly prepared from 1,2-dibromoethane as a solution in tetrahydrofuran. Cyclohexanecarboxylic acid (Eastman Chemical Co.) was used as received, as were all other carboxylic acids and Lewis acids. Vinyl-, allyl-, and 1-hexynylmagnesium bromides were freshly prepared, while other Grignard reagents were used as received (Aldrich Chemical Co.). All Grignard reagents were titrated immediately before use.[31] NMR spectra (300 MHz for ^1H, 75 MHz for ^{13}C, unless otherwise noted) were obtained in $CDCl_3$ and are referenced to internal TMS; *J* values are in hertz.

Methoxymethyl Cyclohexanecarboxylate (1). Following the reported procedure,[10a] cyclohexanecarboxylic acid (2.57 g, 20.0 mmol) was esterified with iodomethylmethyl ether to yield 3.09 g (90%) of **1** as a yellow oil: ^1H NMR δ 1.14−1.95 (m, 10H), 2.30 (m, 1H), 3.40 (s, 3H), 5.18 (s, 2H); ^{13}C NMR δ 25.3, 25.6, 28.8, 43.1, 57.2, 89.9, 175.3. Anal. Calcd for $C_9H_{16}O_3$: C, 62.8; H, 9.4. Found: C, 62.6; H, 9.5.

(Methylthio)methyl Cyclohexanecarboxylate (2). The procedure of Dossena *et al.*[12a,b] was followed. To cyclohexanecarboxylic acid (2.57 g, 20.0 mmol) and $NaHCO_3$ (16.8 g, 200 mmol, 1000 mol %) under nitrogen were added dimethyl sulfoxide (200 mL) and, with vigorous stirring, 2-bromo-2-methylpropane (13.5 mL, 120 mmol, 600 mol %). The stirred reaction mixture was first warmed to 35 °C for 12 h and then to 45 °C for 1 h, whereupon gas evolution had ceased. The stirred reaction mixture was quenched at 20 °C with addition of H_2O (150 mL) and CH_2Cl_2 (250 mL). Separation and extraction of the aqueous phase with CH_2Cl_2 (3 × 75 mL) was followed by washing of the combined organic phases with saturated $NaHCO_3$ (2 × 75 mL) and saturated NaCl (1 × 150 mL, 4 × 75 mL), drying over Na_2SO_4, filtering, and evaporating in vacuo (40 °C bath). Addition and evaporation of heptane (2 × 25 mL) and application of full vacuum (2 h) yielded 3.82 g (100%) of a slightly yellow oil: ^1H NMR δ 1.16−1.96 (m, 10H), 2.20 (s, 3H), 2.31 (m, 1H), 5.10 (s, 2H); ^{13}C NMR δ 15.2, 25.3, 25.7, 28.8, 43.1, 67.6, 175.5. Anal. Calcd for $C_9H_{16}O_2S$: C, 57.4; H, 8.6. Found: C, 57.1; H, 8.6.

Formation of Esters of Cyclohexanecarboxylic Acid Using Enol Ethers. 2-(2-Methoxypropyl) Cyclohexanecarboxylate (3). To cyclohexanecarboxylic acid (2.57 g, 20.0 mmol) dissolved in CH_2Cl_2 (50 mL) was added 2-methoxypropene (2.3 mL, 24 mmol, 120 mol %) at 0 °C. To the stirred reaction mixture at −78 °C was added a solution of methanesulfonic acid (130 μL, 10% v/v in CH_2Cl_2, 0.20 mmol, 1.0 mol %) via syringe. The reaction mixture was stirred at −78 °C for 2.5 h and then warmed to −25 °C over 5 min. Addition of CH_2Cl_2 saturated with NH_3 (1.5 mL, −40 °C) to the reaction mixture at −78 °C, followed by washing of the organic phase at 5 °C with saturated aqueous $NaHCO_3$ (2 × 15 mL), 1/1/1 saturated $NaHCO_3$/saturated NaCl/H_2O, and saturated NaCl (14 mL), drying over Na_2SO_4, filtration through K_2CO_3, and evaporation in vacuo (37 °C bath), followed by addition and evaporation of heptane (2 × 15 mL) and application of full vacuum (2 h), yielded 3.34 g (84%) of **3** as a golden oil that slowly crystallized at 0 °C: mp 16−22 °C; ^1H NMR δ 1.12−1.45 (m, 6H), 1.56 (s, 6H) 1.69 (m, 2H), 1.85 (m, 2H), 2.20 (m, 1H), 3.29 (s, 3H); ^{13}C NMR (100 MHz) δ 24.4,

(26) Lipshutz, B. H. *Tetrahedron Lett.* **1983**, *24*, 127.

(27) Certain heteroatom-substituted esters can yield ketones with lower-order cuprates: Humphrey, S. A.; Herrmann, J. L.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1971**, 1244. Ester **8**, however, was inert to the heterocuprate, BuCu(CN)Li, at 20 °C.

(28) Apparently, as the R^1 group of the acid becomes more electron-rich (**11d** versus **11c**), the intermediate Mg-chelate eliminates to ketone slower relative to the rate of Grignard reagent addition to the THF ester.

(29) Cf. ref 4a.

(30) Further work is necessary to fully understand the nature and degree of the ester's participation. Nevertheless, aqueous washes easily remove most of the 2-hydroxytetrahydrofuran and other byproducts. For byproducts of 2-hydroxytetrahydrofuran, see ref 15a.

(31) Normally the 1,10-phenanthroline method was used: Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

25.4, 25.7, 29.0, 44.1, 49.8, 105.5, 174.5. Anal. Calcd for $C_{11}H_{20}O_3$: C, 66.0; H, 10.1. Found: C, 65.9; H, 9.9.

2-Tetrahydropyranyl Cyclohexanecarboxylate (4). The above procedure employing 2,3-dihydropyran (21.0 mmol) was modified by stirring the reaction for 4 h at −25 °C and then following the same isolation to yield 4.34 g (100%) of **4** as a colorless oil: ^{1}H NMR δ 1.11−1.98 (m, 16H), 2.30 (m, 1H), 3.63 (m, 1H), 3.85 (m, 1H), 5.91 (s, 1H); ^{13}C NMR δ 18.6, 25.1, 25.5, 28.8, 28.9, 29.1, 43.3, 63.0, 92.0, 174.4. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.9; H, 9.2. Found: C, 67.8; H, 9.5.

2-Tetrahydrofuranyl Cyclohexanecarboxylate (5). The above procedure employing 2,3-dihydrofuran (21.0 mmol) was modified by stirring the reaction for 2 h at −25 °C and then following the same isolation to yield 4.01 g (100%) of **5** as a colorless oil: ^{1}H NMR δ 1.10−2.08 (m, 14H), 2.20 (m, 1H), 3.86 (m, 1H), 3.99 (m, 1H), 6.24 (s, 1H); ^{13}C NMR δ 22.8, 25.3, 25.7, 28.8, 32.0, 43.2, 68.6, 98.5, 175.2. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.6; H, 9.2. Found: C, 66.5; H, 9.3.

2-Tetrahydrofuranyl 3-Phenylpropionate (8). To a stirred solution[32] of 3-phenylpropionic acid (200 mmol) and 2,3-dihydrofuran (210 mmol) in dichloromethane (200 mL) at −40 °C was added a solution of methanesulfonic acid (195 μL, 10% v/v in CH_2Cl_2, 0.15 mol %, 0.30 mmol). The stirred reaction mixture was warmed over 30 min to 0 °C, stirred for 4 h, and then recooled to −40 °C. A solution of dry 1,2-ethylenediamine[33] (800 μL, 10% v/v in CH_2Cl_2, 0.60 mol %, 1.2 mmol) was added, and the reaction mixture was warmed to 10 °C and placed in a separatory funnel containing dichloromethane (450 mL). The dichloromethane solution was washed with chilled bicarbonate solution (2 × 200 mL, 1/1/1 H_2O/brine/saturated $NaHCO_3$, 5 °C) and brine (2 × 100 mL), dried (Na_2SO_4), evaporated in vacuo (40 °C bath), and chased by dilution and evaporation with hexanes (2 × 60 mL) to yield **8** as a clear oil (43.54 g, 99% yield): ^{1}H NMR δ 1.85−2.07 (m, 4H), 2.62 (t, J = 7, 2H), 2.95 (t, J = 7, 2H), 3.93 (m, 1H), 4.02 (m, 1H), 6.30 (d, J = 4, 1H), 7.20 (m, 3H), 7.29 (m, 2H); ^{13}C NMR δ 22.7, 30.6, 31.9, 35.9, 68.7, 98.8, 126.0, 128.0, 128.2, 140.2, 172.0. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3. Found: C, 70.9; H, 7.4.

2-Tetrahydrofuranyl Cinnamate. The above procedure was used to yield 15.3 g (100%) of the cinnamate as a white solid: mp 73−75 °C (Et_2O); ^{1}H NMR δ 1.89−2.10 (m, 4H), 3.96 (m, 1H), 4.1 (m, 1H), 6.4 (d, J = 16, 1H), 6.43 (m, 1H), 7.38 (m, 3H), 7.51 (m, 2H), 7.68 (d J = 16, 1H); ^{13}C NMR δ 23.0, 32.3, 69.0, 99.2, 118.2, 128.0, 128.8, 130.2, 134.3, 145.0, 166.0. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.5; H, 6.5. Found: C, 71.6; H, 6.6.

Reaction of THF Esters with Grignard Reagents. General Procedure. To a stirred solution of the THF ester (10.0 mmol) in dichloromethane (30 mL) at −20 °C under nitrogen was added dropwise over 5 min the organomagnesium reagent (in Et_2O or THF, 1−3 M, 10.0 mmol) to yield a clear lightly colored solution. After 30 min at −20 °C, the reaction mixture was slowly warmed to 18 °C over 18 h and then recooled to 0 °C during dropwise addition with stirring into 1.0 M H_3PO_4 (14 mL) at 0 °C.[34] The mixture was warmed to 20 °C, diluted with water (10 mL), and added to a separatory funnel using dichloromethane (50 mL). The organic layer was separated, and the aqueous phase was extracted (CH_2Cl_2, 3 × 10 mL). The combined organic phases were shaken with 0.25 M H_3PO_4 (12 mL) for 5 min, separated,[35] washed with aqueous $NaHCO_3$ (3 × 20 mL, 1/1, H_2O/saturated $NaHCO_3$) and brine (25 mL), and then dried (Na_2SO_4) and evaporated (up to 40 °C). Dilution and evaporation with hexanes (2 × 60 mL) yielded the crude ketone as an oil. Chromatography on silica gel using pentane/Et_2O, when necessary, provided the pure ketone.

1-Phenyl-3-pentanone (9a).[36] The above procedure was employed using ethylmagnesium bromide to yield 289 mg (88%) of a clear oil: ^{1}H NMR δ 1.05 (t, J = 7, 3H), 2.42 (q, J = 7, 2H), 2.73 (m, 2H), 2.93 (m, 2H), 7.15−7.35 (m, 5H); ^{13}C NMR δ 7.7, 22.7, 30.6, 31.9, 35.9, 126.7, 128.4, 129.3, 134.3, 208.0.

4-Methyl-1-phenyl-3-pentanone (9b).[37] The above procedure was employed using THF as solvent and isopropylmagnesium bromide to yield 202 mg (82%) of a clear oil: ^{1}H NMR δ 1.07 (d, J = 7, 3H), 2.57 (sept, J = 7, 2H), 2.76 (m, 2H), 2.89 (m, 2H), 7.13−7.32 (m, 5H); ^{13}C NMR δ 18.0, 29.8, 40.9, 41.9, 125.9, 128.2, 128.3, 141.2, 213.5.

4,4-Dimethyl-1-phenyl-3-pentanone (9c).[38] The above procedure was employed using *tert*-butylmagnesium bromide into yield 91 mg (50%) of a clear oil: ^{1}H NMR δ 1.05 (s, 9H), 2.75 (m, 2H), 2.82 (m, 2H), 7.08−7.33 (m, 5H); ^{13}C NMR δ 26.2, 30.0, 38.3, 43.9, 125.8, 128.19, 128.22, 141.4, 214.5.

1,3-Diphenyl-1-propanone (9f).[39] The above procedure was employed using phenylmagnesium bromide to yield 497 mg (70%) of a clear oil: ^{1}H NMR δ 3.05 (m, 2H), 3.28 (m, 2H), 7.11−7.56 (m, 8H), 7.93 (d, J = 8, 2H); ^{13}C NMR δ 30.0, 40.3, 125.9, 126.6, 127.8, 129.0, 128.2, 128.3, 128.4, 132.9, 199.0.

1-Phenyl-4-heptyn-3-one (9g). The above procedure was employed using 1-hexynylmagnesium bromide to yield 198 mg (75%) of a clear oil: ^{1}H NMR δ 0.91 (t, J = 7, 3H), 1.35−1.62 (m, 4H), 2.35 (t, 2H), 2.86 (m, 2H), 2.95 (m, 2H), 7.15−7.35 (m, 5H); ^{13}C NMR δ 13.5, 18.6, 21.9, 29.7, 46.9, 80.8, 94.8, 126.1, 128.2, 128.4, 140.2, 187.0; HRMS calcd for $C_{15}H_{18}O$ (M^+) 214.1357, found 214.1358.

Single Flask Acylation Reaction. General Procedure. To a stirred solution[32] of the carboxylic acid (10.0 mmol) in dichloromethane (40 mL) at −20 °C under nitrogen was added 2,3-dihydrofuran (10.5 mmol) and then a solution of methanesulfonic acid (1.0% v/v in CH_2Cl_2, 0.20 mol %, 0.020 mmol). The stirred reaction mixture was warmed to 0 °C over 4 h and then recooled to −20 °C. The organomagnesium reagent (in ether or THF, 1−3 M, 10.0 mmol) was added dropwise over 5 min to yield a clear colored solution. After 30 min at −20 °C, the reaction mixture was very slowly warmed to 18 °C over 18 h, then recooled to 0 °C. Quenching and isolation as described in the above reaction with Grignard reagents yielded the pure ketone.

1-Phenyl-2-butanone (12a).[40] The above procedure was employed using phenylacetic acid and ethylmagnesium bromide to yield 1.36 g (90%) of a clear oil: ^{1}H NMR δ 1.07 (t, J = 7, 3H), 2.52 (q, J = 7, 2H), 3.73 (s, 2H), 7.23−7.46 (m, 5H); ^{13}C NMR δ 7.8, 35.2, 49.8, 126.8, 128.6, 129.3, 134.4, 208.8.

1-Phenyl-4-methyl-3-pentanone (9b). The above procedure was employed using 3-phenylpropionic acid and isopropylmagnesium bromide to yield 2.7 g (86%) of a clear oil whose physical properties were the same as above.

1-Phenyl-3-methyl-2-butanone (12b).[41] The above procedure was employed using phenylacetic acid and isopropylmagnesium bromide to yield 1.31 g (81%) of a clear oil: ^{1}H NMR δ 1.11 (d, J = 7, 6H), 2.75 (sept, J = 7, 1H), 3.76 (s, 2H), 7.16−7.42 (m, 5H); ^{13}C NMR δ 18.2, 40.0, 47.6, 126.7, 128.4, 129.3, 134.3, 215.4.

Isobutyrophenone (12c).[42] The above procedure was employed using benzoic acid and isopropylmagnesium bromide to yield 1.27 g (86%) of **12a** as a clear oil.

3,4-Dimethoxyphenyl Isopropyl Ketone (12d).[43] The above procedure was employed using 3,4-dimethoxybenzoic acid and isopropylmagnesium bromide to yield 1.92 g (72%) of a clear oil: ^{1}H NMR δ 1.24 (d, J = 7, 6H), 3.56 (sept, J = 7, 1H), 3.96 (s, 3H), 3.97 (s, 3H), 6.91 (d, J = 8, 1H), 7.57 (d, J = 2, 1H), 7.62 (dd, J = 8, 2, 1H); ^{13}C NMR δ 19.4, 34.7, 55.87, 55.94, 109.9, 110.5, 122.5, 129.2, 149.0, 152.9, 203.0.

JO9607471

(32) When the carboxylic acid was not completely soluble at −40 or −20 °C, addition of the methanesulfonic acid to the suspension catalyzed a slow clarification to form a solution of the more soluble THF ester.

(33) Dry amine quenches (dilute ammonia, triethylamine, or 1,2-ethylenediamine in CH_2Cl_2) at low temperature gave better results than an aqueous alkaline quench ($NaHCO_3$).

(34) Quenching by bolus addition of the quench into the vigorously stirred reaction mixture gave similar results. The ketone **9g** was quenched with pH 7, 0.1 M phosphate buffer.

(35) If the THF ester is still present (TLC), the CH_2Cl_2 solution is stirred with methanesulfonic acid and methanol (e.g., 5 μL and 1 mL, respectively), at 20 °C until hydrolyzed (1 h).

(36) Schultz, E. M.; Bicking, J. B. *J. Am. Chem. Soc.* **1953**, *75*, 1128.

(37) Jacquier, R.; Mousseron, M.; Boyer, S. *Bull. Soc. Chim. Fr.* **1956**, 1653.

(38) Berliner, E.; Berliner, F. *J. Am. Chem. Soc.* **1950**, *72*, 222.

(39) Russell, G. A.; Mikol, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 5498.

(40) Castelli, F.; Canonne, P. *Bull. Soc. Chim. Fr.* **1974**, 317.

(41) Bordwell, F. G.; Almy, J. *J. Org. Chem.* **1973**, *38*, 575.

(42) Inukai, T.; Yoshizawa, R. *J. Org. Chem.* **1967**, *32*, 404.

(43) Horton, W. J.; Paul, E. G. *J. Am. Chem. Soc.* **1957**, *79*, 2264.