crop of **6** (1.69 g) was obtained. The total yield of pyrone **6** was 91% and the spectroscopic data of the product were identical with those reported:[14] mp 109–111 °C [lit.[14] mp 109.5–110.5 °C].

6-(Bromomethyl)-5-[(ethoxycarbonyl)(phenylthio)methyl]-4-methoxy-2*H*-pyran-2-one (7). A solution of ethyl diazoacetate (4.183 g, 36.7 mmol) in toluene (5 mL) was added dropwise during 3 h over a magnetically stirred mixture of the bromo lactone **6** (4.00 g, 12.2 mmol), a catalytic amount of rhodium(II) acetate, and toluene (45 mL) kept at 55 °C. Quantitative evolution of nitrogen was observed. The final mixture was washed with 2 N HCl and with aqueous sodium chloride. The organic layer was dried with sodium sulfate and evaporated. The residue was chromatographed through silica gel (230–400 mesh) with mixtures of hexane/ethyl acetate. A total of 1.545 g (4.7 mmol) of the starting material **6** was recovered, eluting with 80% hexane. Finally 1.854 g (37%) of **7** was eluted with 75% hexane: mp 154–156 °C; IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3 H, J = 7 Hz), 3.80 (s, 3 H), 3.70, 3.85, 3.90, 4.05 (AB system, 2 H, J = 11 Hz), 4.20 (q, 2 H, J = 7 Hz), 4.90 (s, 1 H), 5.55 (s, 1 H), 7.20–7.55 (m, 5 H); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ 13.2, 23.5, 47.5, 56.1, 62.1, 89.6, 111.3, 128.6, 128.7, 132.2, 134.2, 156.6, 162.4, 168.2; MS, m/z (relative intensity) 414 (7), 412 (M^+, 7), 305 (64), 303 (44), 277 (23), 275 (26), 259 (21), 247 (32), 245 (25), 239 (49), 233 (29), 225 (43), 179 (37), 169 (20), 167 (23), 151 (20), 125 (54), 124 (20), 123 (43), 111 (24), 110 (29), 109 (100), 95 (27), 83 (21), 77 (25), 69 (68), 66 (32), 65 (40), 59 (42), 53 (23), 51 (27), 43 (40). Anal. Calcd for $C_{17}H_{17}BrO_5S$: C, 49.40; H, 4.15; Br, 19.33; S, 7.76. Found: C, 49.46; H, 3.82; Br, 19.27; S, 7.78.

5-[(Ethoxycarbonyl)(phenylthio)methyl]-6-formyl-4-methoxy-2*H*-pyran-2-one (8). A solution of pyrone **7** (800 mg, 1.94 mmol) in anhydrous pyridine (16 mL) was stirred for 6 h at room temperature. Ether (140 mL) was added and a white precipitate of the corresponding pyridinium bromide (940 mg, 99%) was formed. It was very hygroscopic and was used without further purification. 4-Nitroso-*N*,*N*-dimetylaniline (280 mg, 1.87 mmol) and a suspension of potassium carbonate (1.402 g, 10.3 mmol) in water (4 mL) were added at room temperature in the indicated order to a stirred solution of the above pyridinium salt (840 mg, 1.71 mmol) in ethanol (8 mL). The mixture was stirred at room temperature for 30 min and at 0 °C for 1 h. The formed precipitate (819 mg) was the unstable nitrone *N*-[[5-[(ethoxycarbonyl)(phenylthio)methyl]-4-methoxy-2-oxo-2*H*-pyran-6-yl]-methylene]-4-(dimethylamino)aniline *N*-oxide (99%). A mixture of this nitrone (745 mg, 1.55 mmol), benzene (31 mL) and 2N HCl (53 mL) was strongly stirred at room temperature for 21 h. The organic layer was washed with aqueous sodium chloride, dried with sodium sulfate and evaporated. The residue was chromatographed through a silica gel column (230–400 mesh) using hexane:ethyl acetate (1:1) to afford the aldehyde **8** (457 mg, 85%): mp 103-105 °C; IR (KBr) 2930, 2850, 1720, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3 H, J = 7 Hz), 3.85 (s, 3 H), 4.20 (q, 2 H, J = 7 Hz), 5.75 (s, 1 H), 6.00 (s, 1 H), 7.3 (m, 5 H), 9.30 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 45.5, 56.7, 62.3, 94.6, 117.5, 129.1, 132.5, 134.9, 148.6, 160.4, 167.5, 168.1, 184.5; MS m/z 348 (M^+, 10), 319 (5), 302 (16), 239 (17), 167 (39), 139 (23), 109 (100), 69 (34), 65 (28). Anal. Calcd for $C_{17}H_{16}O_6S$: C, 58.61; H, 4.63; S, 9.20. Found: C, 58.13; H, 4.79; S, 9.24.

5-[Bis(methoxycarbonyl)(phenylthio)methyl]-6-(bromomethyl)-4-methoxy-2*H*-pyran-2-one (9) and 6-[2,2-Bis(methoxycarbonyl)-2-(phenylthio)ethyl]-5-bromo-4-methoxy-2*H*-pyran-2-one (10). A solution of dimethyl diazomalonate (316 mg, 2.0 mmol) in toluene (2 mL) was added during 2 h over a stirred mixture of pyrone **6** (327 mg, 1.0 mmol), a catalytic amount of rhodium(II) acetate, and toluene (8 mL) kept at 70 °C under an argon atmosphere. Quantitative nitrogen evolution was observed. The mixture was washed with 2 N HCl and with aqueous sodium chloride. The organic layer was dried with sodium sulfate and evaporated. The residue was chromatographed through a silica gel column (230–400 mesh) with hexane/ethyl acetate mixtures. The following products were eluted: 6-[2,2-bis(methoxycarbonyl)-2-(phenylthio)ethyl]-5-bromo-4-methoxy-2*H*-pyran-2-one (**10**) with 70% hexane (40 mg, 9%): mp 143–145 °C; IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.40 (s, 2 H), 3.85 (s, 6 H), 3.95 (s, 3 H), 5.50 (s, 1 H), 7.25–7.60 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 38.1, 53.4, 56.9, 62.7, 88.9, 98.8, 128.9, 130.1, 137.0, 157.3, 160.9, 166.3, 167.7; MS, m/z (relative intensity) 458 (1), 456 (M^+, 1), 377 (100), 317 (32), 315 (43), 267 (57), 207 (26), 205 (33), 203 (26), 179 (44), 177 (23), 149 (61), 147 (52), 109 (44), 91 (23), 83 (27), 69 (42), 65 (28), 59 (49), 53 (39). Anal. Calcd for $C_{18}H_{17}BrO_7S$: C, 47.28; H, 3.75; Br, 17.47; S, 7.01. Found: C, 47.41; H, 3.55; Br, 17.34; S, 6.83. Pyrone **9** eluted with 60% hexane: mp 125–126 °C; IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.55 (s, 3 H), 3.85 (apparent s, 8 H), 5.40 (s, 1 H), 7.25–7.40 (m, 3 H), 7.50–7.70 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.7, 54.2, 56.4, 65.9, 89.8, 111.7, 128.6, 129.5, 130.3, 138.0, 158.0, 160.9, 166.6, 167.8; MS, m/z (relative intensity) 458 (0.2),456 (M^+, 0.2), 235 (37), 233 (32), 218 (29), 167 (21), 109 (100), 77 (26), 69 (68), 65 (35), 59 (66), 53 (23), 45 (22). Anal. Calcd for $C_{18}H_{17}BrO_7S$: C, 47.28; H, 3.75; Br, 17.47; S, 7.01. Found: C, 47.45; H, 3.72; Br, 17.19; S, 7.05.

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Registry No. **5**, 105525-73-3; **6**, 93338-98-8; **7**, 116054-34-3; **8**, 116054-35-4; **8** (pyridinium bromide), 116054-36-5; **9**, 116054-37-6; **10**, 116054-38-7; *N*-[[5-[(ethoxycarbonyl)(phenylthio)-methyl]-4-methoxy-2-oxo-2*H*-pyran-6-yl]methylene]-4-(dimethylamino)aniline *N*-oxide, 116054-39-8; dimethyl diazomalonate, 6773-29-1.

Carboxamidation of Organolithium and Organomagnesium Reagents by a Two-Step One-Flask Reaction. Promotion by Magnesium Alkoxides

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An organometallic route to aldehydes that has found some synthetic application is based on the reaction of an organolithium[1] or Grignard[2] reagent with dimethylformamide (eq 1). Reaction 1 involves the formation of a

$$RLi + Me_2NCHO \rightarrow \underset{\mathbf{1}}{RCH(OLi)NMe_2} \xrightarrow{H^+} \underset{\mathbf{2}}{[RCH(OH)NMe_2]} \xrightarrow{H^+} RCHO \quad (1)$$

hemiaminal derivative, **1**, which undergoes facile hydrolysis and results in the corresponding aldehyde. Indeed, hemiaminals **2**, with a few exceptions,[3] are not stable enough to be isolated, and this is perhaps the reason that the synthetic potential of this interesting class of organic compounds has not been fully exploited. The α-(dialkylamino)alkoxide group, however, has been shown to direct orthometalation in aromatic systems as well as functioning as a protected aldehyde or ketone.[4] The

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Table I. Transformation of *n*-BuM (M = Li, MgX, MgBu-*n*) into *n*-BuCONMe$_2$

entry	metal alkyl (mmol)	metal alkoxide (mmol)	solvent[a]	yield, %[b]
1	*n*-BuLi (20)		MCH/CH	0
2	*n*-BuLi (20)	$Mg(OCH_2CH_2OEt)_2$ (10)	MCH/CH	53
3	*n*-BuLi (20)	$LiOCH_2CH_2OEt$ (20)	MCH/CH	0
4	*n*-BuLi (20)	$LiOCEtMe_2$ (60)	MCH/CH	0
5	*n*-BuLi (20)	$Mg(OCH_2CH_2OEt)_2$ (1)	MCH/CH	32
6	*n*-BuMgCl (20)		Et_2O	0
7	*n*-BuMgI (20)		Et_2O	0
8	*n*-BuMgCl (20)	$LiOCH_2CH_2OEt$ (20)	Et_2O/MCH[c]	60
9	*n*-$Bu_2Mg(Et_2O)_2$ (10)		MCH	42
10	*n*-Bu_2Mg (10)	$LiOCH_2CH_2OEt$ (10)	MCH	66

[a] MCH = methylcyclohexane, CH = cyclohexane. [b] By NMR from benzyl alcohol/dimethylvaleramide mixtures (see the Experimental Section). [c] 50/50 v/v.

intermediate 1 is expected to show reactivity typical of an alkoxide and this expectation is realized in that compounds of type 1 take part in an Oppenauer type reaction (eq 2), a process that comprises a new route to tertiary carboxylic acid amides.

$$RCH(OM)NMe_2 \xrightarrow{R'_2CO} RCONMe_2 \qquad (2)$$

In this paper we describe the transformation of a number of organolithium and organomagnesium reagents to mono- and ditertiary amides by the reaction sequence 3.

$$R^1M + HCONR^2_2 \rightarrow \underset{\mathbf{3}}{R^1CH(OM)NR^2_2} \xrightarrow[\text{or } Ph_2CO]{PhCHO} R^1CONR^2_2 \qquad (3)$$

$$M = Li, MgCl(I), MgR^1$$

The reaction is carried out without isolation of the intermediate 3, and therefore eq 3 constitutes a one-flask synthesis of tertiary carboxamides.

In order to determine the factors influencing the yield of amide in the reaction sequence 3, the system *n*-BuM (M = Li, MgX, MgBu-*n*) and $HCONMe_2$, with subsequent oxidation byPhCHO, has been studied in detail. The results are summarized in Table I. Entry 1 indicates that butyllithium alone fails to produce any *N*,*N*-dimethylvaleramide. Addition of 0.5 molar equiv of magnesium 2-ethoxyethoxide, 4, resulted in a 53% yield of amide (entry 2). Changing the alkoxide to lithium 2-ethoxyethoxide, 5, or lithium *tert*-amyl oxide, we see that no amide is formed (entries 3 and 4). Therefore, the presence of magnesium alkoxide in the system is a decisive factor for the successful carboxamidation of butyllithium and, most probably, of organolithium reagents in general. There is an indication (entry 5) that the role of 4 is catalytic since a reduction of the amount of magnesium alkoxide by 1/10 resulted in only 20% reduction of the absolute yield of the amide. Grignard reagents prepared from *n*-butyl chloride or iodide did not give any dimethylvaleramide (entries 6 and 7). However, when the same reaction was attempted in the presence of an equimolar quantity of 5, a fair yield of amide was produced (entry 8). It appears probable that the successful carboxamidation of Grignard reagents in the presence of 5 is due to the transformation of BuMgX to $BuMgOCH_2CH_2OEt$. This, in turn, could either stabilize $BuCH(OMgCH_2CH_2OEt)NMe_2$ with respect to decomposition to the corresponding enamine[5] or facilitate the Oppenauer oxidation. Dibutylmagnesium etherate without any additive was carboxamidated in 42% yield (entry 9). Likewise, unsolvated *n*-Bu_2Mg in the presence of 5 gave better results (entry 10). It should be mentioned that 5 solubilizes unsolvated dibutylmagnesium in methylcyclohexene,[6] and therefore reaction took place under homogeneous conditions.

In general, one may ascribe to the alkoxide at least two roles. The first unequivocally is its catalytic function in the Oppenauer oxidation.[7] The second seems to be related to the stabilization of intermediate 3. Indeed, 3 can eliminate MOH and be transformed into the corresponding enamine.[5] It is very likely that 3 forms a mixed cluster with the added alkoxide,[8] and this cluster formation could affect its stability as well as its reactivity toward the oxidant carbonyl compound.

The scope and limitations of the carboxamidation reaction are illustrated by the preparation of various amides from a number of organometallics. The results are shown in Table II. For practical purposes benzophenone was chosen as oxidant in preference to benzaldehyde. Its reduction product, benzhydrol, can generally be separated more easily than benzyl alcohol, and, more importantly, benzaldehyde also undergoes a Tishchenko reaction under the reaction conditions giving benzyl benzoate, which can then react with amide to give the corresponding benzamide. Of the organometallics employed, only the benzylic type organolithiums (entries 7 and 8) failed to give any amide. This can perhaps be understood on the basis of the increased acidity of the β-hydrogens (with respect to OLi) in the intermediate $ArCH_2CH(OLi)NR^2_2$, which results in facile elimination.[5] In all other cases studied the yield of amide ranged from ca. 30 to 80%. The low yield in entry 14 is probably due to the fact that the reaction mixture became gel-like, thus preventing efficient stirring.

Experimental Section

All reactions were carried out under an atmosphere of pure argon. Solvents were dried, degassed, and argon-saturated before use.

Preparation of *N*,*N*-Dimethylvaleramide (General Procedure, Entries 1–10, Table I). The appropriate quantity of the organometallic alkylating agent plus alkoxide (if any) in 20 mL of solvent were cooled in ice, and 20 mmol dimethylformamide was added such that the reaction mixture temperature did not exceed 5 °C. After the mixture was stirred for 1.5 h at this

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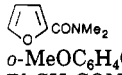
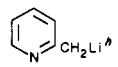
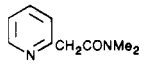
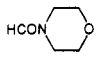
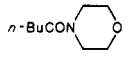
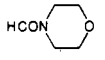
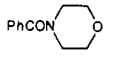
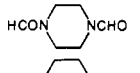
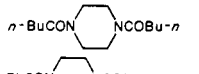
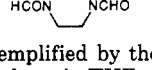
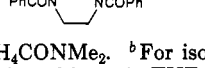
Table II. Magnesium 2-Ethoxyethoxide Promoted Carboxamidation of Various Organometallic Reagents[a]

entry	organometallic reagent	formamide	solvent	product	yield,[b] %	ref[j]
1	*n*-BuLi	$HCONMe_2$	MCH/CH	*n*-$BuCONMe_2$	65	11
2	Ph_2Mg[c]	$HCONMe_2$	toluene	$PhCONMe_2$	80	12
3	*s*-Bu_2Mg	$HCONMe_2$	MCH	*s*-$BuCONMe_2$	65	13
4		$HCONMe_2$	CH/THF		61	14
5		$HCONMe_2$	CH/THF		29	15
6	*o*-$MeOC_6H_4Li$[f]	$HCONMe_2$	CH/THF	*o*-$MeOC_6H_4CONMe_2$	71	16
7	$PhCH_2Li$[g]	$HCONMe_2$	CH/THF	$PhCH_2CONMe_2$	0	
8		$HCONMe_2$	CH/THF		0	
9	$PhCH(Me)CH_2Li$[i]	$HCONMe_2$	THF	$PhCH(Me)CH_2CONMe_2$	34	this work
10	*n*-BuLi	HCON(Ph)Et	MCH/CH	*n*-BuCON(Ph)Et	39	this work
11	*n*-BuLi		MCH/CH		53	17
12	Ph_2Mg		toluene		68	18
13	*n*-BuLi		MCH/CH		71	19
14	Ph_2Mg		toluene		17	20

[a] The experimental procedure is exemplified by the synthesis of *o*-$MeOC_6H_4CONMe_2$. [b] For isolation, spectroscopically pure product. [c] Reference 10. [d] By metalation of thiophene in THF with *n*-BuLi. [e] By metalation of furan in THF with *n*-BuLi. [f] By metalation of anisole in THF with *n*-BuLi. [g] By metalation of toluene in THF with *n*-BuLi. [h] By metalation of 2-picoline in THF with *n*-BuLi. [i] By reaction of $PhCH(Me)CH_2SPh$ with $Li^+C_{10}H_8^{\bullet-}$ in THF (ref 9). [j] The physical constants of the carboxamides as well as their NMR spectra agreed with those reported in the literature.

temperature, benzaldehyde (20 mmol) was added, and stirring was continued for 1 h at bath temperature and for 2 h at room temperature. The reaction mixture was hydrolyzed with cold, dilute H_2SO_4, extracted with CH_2Cl_2, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was vacuum distilled and the $PhCH_2OH$/*n*-$BuCONMe_2$ codistillate (90 °C/4 mm) was collected. The yield of amide was calculated from the integrated ^1H NMR spectrum.

Preparation of *N,N*-Dimethyl-*o*-methoxybenzamide. This is given as a typical preparation of the amides in Table II. (*o*-Methoxyphenyl)lithium, prepared by addition of butyllithium (20 mmol as 1.7 M cyclohexane solution) to anisole (20 mmol) in 4 mL of THF at 5 °C, and after being stirred at room temperature overnight, was treated at 5 °C with 10 mmol of **4**. After being stirred at room temperature for 1 h, the reaction mixture was cooled in ice, and 20 mmol dimethylformamide was added. After the mixture was stirred at the bath temperature for 1 h and at room temperature for 2 h, 5.5 g of benzophenone were added, and stirring was continued overnight. The reaction mixture was hydrolyzed with cold, dilute H_2SO_4, extracted with CH_2Cl_2, and dried over anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was chromatographed on silica gel. Benzophenone and benzhydrol were eluted with toluene and the product with 1:1 CH_2Cl_2/AcOEt. Evaporation of the solvents gave 2.6 g (71%) of the title compound, mp 69–70 °C (lit.[16] mp 71 °C).

***N,N*-Dimethyl-3-phenylbutyramide.** The product was isolated by column chromatography (see previous experiment) as an oil: yield 1.3 g, 34%; ^1H NMR (ppm, $CDCl_3$) 1.33 (d, 3 H), 2.54 (m, 2 H), 2.83 (d, 6 H), 3.31 (m, 1 H), 7.25 (s, 5 H); ^{13}C NMR (ppm, $CDCl_3$) 21.57 (CCH_3), 35.11 (NCH_3), 36.42 (CH_2), 36.97 (NCH_3), 41.51 (CH), 126.61, 126.79, 128.32, 146.44 (aromatic), 171.58 (CO).

***N*-Ethyl-*N*-phenylvaleramide**: Yield 1.6 g, 39%; Bp 120 °C/(2 mmHg); ^1H NMR (ppm, $CDCl_3$) 0.7–0.9 (m, 10 H), 1.95 (m, 2 H), 3.63 (q, 2 H), 7.3 (center of m, 5 H); ^{13}C NMR (ppm, $CDCl_3$) 13.05 (CH), 13.68 (CH_3), 22.27 ($CH_3CH_2CH_2$), 27.59 ($CH_2CH_2CH_2$), 34.03 (CH_2CO), 43.89 (NCH_2), 127.67, 128.37, 129.54, 142.64 (aromatic), 172.41 (CO).

Registry No. **4**, 116005-37-9; **5**, 22065-26-5; $HCONMe_2$, 68-12-2; *n*-$BuCONMe_2$, 6225-06-5; *o*-$MeOC_6H_4CONMe_2$, 7291-34-1; *o*-$MeOC_6H_4Li$, 31600-86-9; $PhCH(Me)CH_2CONMe_2$, 77515-93-6; *n*-BuCON(Ph)Et, 116005-38-0; *n*-BuLi, 109-72-8; $LiOCEtMe_2$, 53535-81-2; *n*-BuMgI, 1889-20-9; *n*-BuMgCl, 693-04-9; *n*-$Bu_2Mg(Et_2O)_2$, 110303-53-2; *n*-Bu_2Mg, 1191-47-5; Ph_2Mg, 555-54-4; $PhCONMe_2$, 611-74-5; *s*-Bu_2Mg, 17589-14-9; *s*-$BuCoNMe_2$, 5592-02-9; $PhCH_2Li$, 766-04-1; $PhCH(Me)CH_2Li$, 64740-49-4; HCON(Ph)Et, 5461-49-4; 2-thienyllithium, 2786-07-4; *N,N*-dimethyl-2-thiophenecarboxamide, 30717-57-8; 2-furyllithium, 2786-02-9; *N,N*-diemthyl-2-furylcarboxamide, 13156-75-7; (2-pyridinylmethyl)lithium, 116005-39-1; 4-morpholinecarboxaldehyde, 4394-85-8; 4-valerylmorpholine, 22342-18-3; 4-benzoylmorpholine, 1468-28-6; 2,3,5,6-tetrahydropyrazine-1,4-dicarboxaldehyde, 4164-39-0; 1,4-bis(1-oxopentyl)-2,3,5,6-tetrahydropyrazine, 18903-08-7; 1,4-dibenzoyl-2,3,5,6-tetrahydropyrazine, 6091-41-4.

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Synthesis of 16α- and 16β-Fluoro-17β-estradiol by Fluorination of Estrone Enols

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Recently the stereospecific synthesis of 16α-fluoro-17β-estradiol (**1**) and 16β-fluoro-17β-estradiol (**2**) were reported by Katzenellenbogen et al. who used a method of displacement of triflate by fluoride to achieve stereospecificity.[1] The importance of **1** and **2** stems from their very high receptor binding affinities with estrogen receptor protein.[2] Thus, the high receptor binding affinities of **1** (RBA = 80) and **2** (RBA = 30) relative to estradiol (RBA

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