Table I. Iron-Catalyzed Oxidation of *N,N*-Dimethylanilines with Oxygen[a]

aniline (subst)	cat.[b]	product,[c] mM 2	3	4	5	6	concn of 1 after rctn,[c] mM
1a (H)	A	28			69		793
1b (3-Me)	A	77			109		595
1c (3-Cl)	A	53			52		811
1d (4-Me)	A	203	266			46	293
1d (4-Me)[d]	A	22				20	885
1e (4-MeO)	A	169	18				696
1f (4-Cl)	A	357	124				331
1a (H)	B	208	231	12	5		197
1b (3-Me)	B	222	262	6	10		106
1c (3-Cl)	B	90	100	18	5		647
1d (4-Me)	B	364	275				75
1e (4-MeO)	B	407	254				351
1f (4-Cl)	B	223	168				495

[a] The reaction was carried out in acetonitrile under oxygen at 60 °C for 20 h; 1, 1.0 M; catalyst, 3.0 mM. [b] A, $FeCl_3$; B, [Fe(salen)]OAc. [c] Determined by GC analysis. [d] The reaction in the presence of BHT (50 mM).

Table II. Reaction of *N,N*-Dimethylanilines with Butyl Vinyl Ethers[a]

aniline (subst)	vinyl ether	product,[b] mM tetrahydroquinoline	2	3	concn of 1 after rctn,[b] mM
1a (H)	7[c]	105	10		855
1a (H)	8	136	8	18	827
1d (4-Me)	7	108	12	14	861
1d (4-Me)	8	99	10	13	848
1e (4-MeO)	7	86	14		900
1e (4-MeO)	8	78	10		902

[a] The reaction was carried out in acetonitrile under oxygen at 60 °C for 20 h; 1, 1.0 M; vinyl ether, 2.0 M; $FeCl_3$, 3.0 mM. [b] Determined by GC analysis. [c] Reaction for 10 h. Taken from the data in ref 4.

also isolated by column chromatography on silica gel using hexane–ethyl acetate as eluant.

Oxidative Coupling of *N,N*-Dimethylanilines 1 with Vinyl Ethers 7 and 8. A mixture of 1 (10 mmol) and a vinyl ether 7 or 8 (20 mmol) was stirred in the presence of $FeCl_3$ (0.03 mmol) under oxygen at 60 °C for 20 h. Then the mixture was poured into water, and the products were extracted with ether. After removal of the solvent and excess of 1 and the vinyl ether in vacuo, the coupling product was isolated by column chromatography on silica gel using hexane–ethyl acetate as eluant.

Products. The purity of the following products isolated was judged to be ≥90% by GC and/or ^1H and ^{13}C NMR analyses. The dimerized products **4a**,[12a,b] **4b**,[12d] **5a**,[12b,c] **5b**,[12d] and **6**[12d] are known and compared with authentic specimens. The dimer **4c** was an oil; MS *m/e* 308, 310, and 312 (M^+); ^1H NMR (100 MHz) δ 2.87 (s, 6 H), 2.98 (s, 3 H), 4.46 (s, 2 H), 6.40–7.20 (m, 7 H). The dimer **5c** was a solid: mp 106–109 °C (from benzene–hexane); MS *m/e* 322, 324, and 326 (M^+); ^1H NMR (100 MHz) δ 2.90 (s, 12 H), 4.00 (s, 2 H), 6.44–6.96 (m, 6 H). Anal. Calcd for $C_{17}H_{20}N_2Cl_2$: C, 63.2; H, 6.2; N, 8.7; Cl, 21.9. Found: C, 63.0; H, 6.2; N, 8.7; Cl 21.9. The tetrahydroquinoline **9** was an oil: MS *m/e* 219 (M^+); ^1H NMR (400 MHz) δ 0.91 (t, *J* = 7.6 Hz, 3 H), 1.29–1.43 (m, 2 H), 1.52–1.62 (m, 2 H), 1.87–1.95 (m, 1 H), 2.08–2.14 (m, 1 H), 2.91 (s, 3 H), 3.08–3.13 (m, 1 H), 3.36–3.43 (m, 1 H), 3.45–3.65 (m, 2 H), 4.31 (t, *J* = 3.7 Hz, 1 H), 6.61–6.65 (m, 2 H), 7.14–7.26 (m, 2 H); ^{13}C NMR δ 13.94, 19.50, 27.32, 32.17, 38.95, 46.36, 67.60, 73.10, 111.36, 115.60, 121.63, 129.21, 130.34, 146.34. The tetrahydroquinoline **10** was an oil: MS *m/e* 219 (M^+); ^1H NMR (400 MHz) δ 0.905 (d, *J* = 6.8 Hz, 3 H), 0.915 (d, *J* = 6.8 Hz, 3 H), 1.83–1.95 (m, 2 H), 2.07–2.14 (m, 1 H), 2.91 (s, 3 H), 3.08–3.13 (m, 1 H), 3.23–3.35 (m, 2 H), 3.35–3.42 (m, 1 H), 4.29 (t, *J* = 3.7 Hz, 1 H), 6.62–6.65 (m, 2 H) 7.14–7.26 (m, 2 H); ^{13}C NMR δ 19.51, 19.62, 27.29, 28.70, 38.95, 46.42, 73.24, 74.89, 111.34, 115.62, 121.78, 129.13, 130.28, 146.34. The tetrahydroquinoline **11** was an oil: MS *m/e* 233 (M^+); ^1H NMR (400 MHz) δ 0.91 (t, *J* = 7.3 Hz, 3 H), 1.35–1.44 (m, 2 H), 1.55–1.62 (m, 2 H), 1.87–1.95 (m, 1 H), 2.07–2.13 (m, 1 H), 2.23 (s, 3 H), 2.88 (s, 3 H), 3.04–3.09 (m, 1 H), 3.28–3.35 (m, 1 H), 3.46–3.60 (m, 2 H), 4.28 (t, *J* = 3.7 Hz, 1 H), 6.55–6.57 (m, 1 H), 6.96–6.97 (m, 2 H); ^{13}C NMR δ 13.95, 19.51, 20.28, 27.49, 32.21, 39.25, 46.60, 67.67, 73.15, 111.74, 121.93, 124.93, 129.74, 130.81, 144.38. The tetrahydroquinoline **12** was an oil: MS *m/e* 233 (M^+); ^1H NMR (400 MHz) δ 0.918 (d, *J* = 6.8 Hz, 3 H), 0.923 (d, *J* = 6.4 Hz, 3 H), 1.84–1.95 (m, 2 H), 2.06–2.27 (m, 1 H), 2.23 (s, 3 H), 2.88 (s, 3 H), 3.04–3.09 (m, 1 H), 3.25–3.35 (m, 3 H), 4.26 (t, *J* = 4.3 Hz, 1 H), 6.55–6.57 (m, 1 H), 6.95–6.98 (m, 2 H); ^{13}C NMR δ 19.55, 19.66, 20.28, 27.43, 28.71, 39.26, 46.65, 73.30, 75.00, 111.74, 122.07, 124.93, 129.68, 130.78, 144.40. The tetrahydroquinoline **13** was an oil: MS *m/e* 249 (M^+); ^1H NMR (400 MHz) δ 0.92 (t, *J* = 7.3 Hz, 3 H), 1.32–1.45 (m, 2 H), 1.56–1.63 (m, 2 H), 1.92–1.99 (m, 1 H), 2.07–2.17 (m, 1 H), 2.86 (s, 3 H), 3.03–3.08 (m, 1 H), 3.22–3.29 (m, 1 H), 3.48–3.65 (m, 2 H), 3.75 (s, 3 H), 4.30 (t, *J* = 4.2 Hz, 1 H), 6.59–6.62 (m, 1 H), 6.77–6.81 (m, 2 H); ^{13}C δ 13.94, 19.51, 27.67, 32.19, 39.69, 47.02, 55.89, 67.83, 73.30, 112.87, 115.05, 115.76, 123.39, 141.31, 150.95. The tetrahydroquinoline **14** was an oil: MS *m/e* 249 (M^+); ^1H NMR (400 MHz) δ 0.849 (d, *J* = 6.8 Hz, 3 H), 0.857 (d, *J* = 6.7 Hz, 3 H), 1.70–1.92 (m, 2 H), 2.1 (m, 1 H), 2.79 (s, 3 H), 2.97–3.00 (m, 1 H), 3.15–3.34 (m, 3 H), 3.68 (s, 3 H), 4.22 (t, *J* = 4.2 Hz, 1 H), 6.52–6.55 (m, 1 H), 6.69–6.75 (m, 2 H); ^{13}C NMR δ 19.55, 19.62, 27.63, 28.73, 39.70, 47.09, 55.87, 73.46, 75.13, 112.87, 115.00, 115.69, 123.54, 141.33, 150.95.

Supplementary Material Available: NMR and mass spectra for **9**–**14** and mass spectrum for **4c** (13 pages). Ordering information is given on any current masthead page.

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A New Entry into C7-Oxygenated Tetrahydro-1*H*-3-benzazepines: Efficient Labeling with Carbon-14 in the Benzo Ring

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Derivatives of 2,3,4,5-tetrahydro-1*H*-3-benzazepine ("3-benzazepine") constitute a large class of pharmacologically important compounds. A number of compounds in this group have agonist activity at peripheral and/or central nervous system dopamine receptor systems[1] and have

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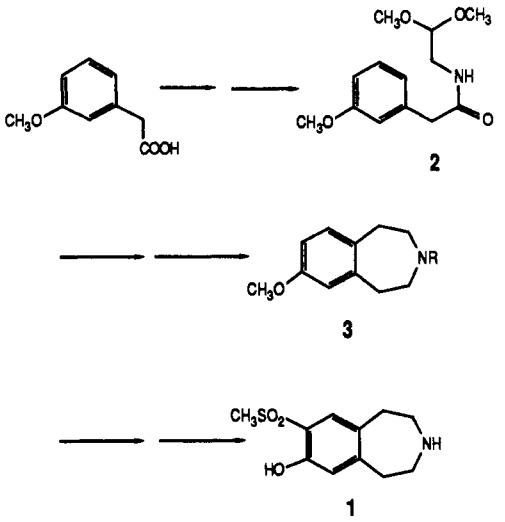
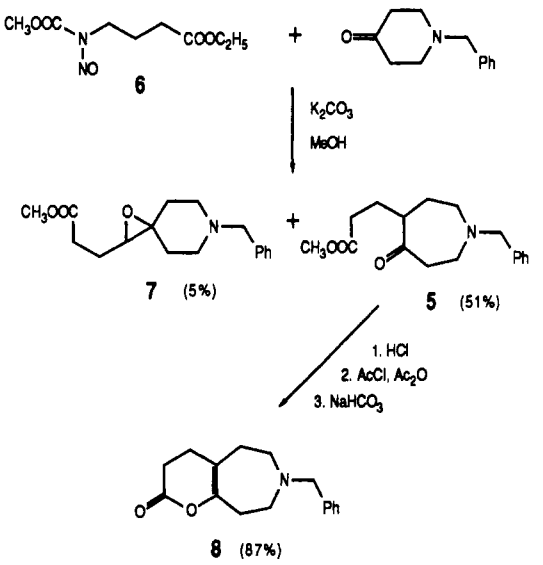
0022-3263/89/1954-4702$01.50/0

Scheme I



Scheme II



potential therapeutic utility in a number of disease states. Certain 3-benzazepines which are centrally acting dopamine antagonists show neuroleptic properties.[2] Other members of this class are antagonists at α-adrenergic receptor sites[3] and are of potential interest in the treatment of hypertension, glaucoma, and congestive heart failure. More recently, certain compounds in this class have been found to have selective activity at serotonin receptors,[4] opening the way for investigations of new pharmacological activity profiles. A compound of particular interest to us was 7-hydroxy-8-(methylsulfonyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SK&F 103829, 1), a selective partial 5-HT_2 agonist with potential therapeutic use in gastrointestinal disorders.[5] We desired to prepare this compound labeled with carbon-14 in the benzo ring for use in a number of studies.

Previous syntheses of the 3-benzazepine skeleton have usually been accomplished via electrophilic cyclization of a 3-aza-6-phenylpentane derivative,[3] in which the chain terminus is a halo, hydroxy, or acetal function. The cyclization substrate is usually constructed beginning with a commercially available multisubstituted benzene derivative. For example, the recently reported synthesis[6] of unlabeled 1 (Scheme I) proceeds from 3-methoxyphenylacetic acid via acetal 2. Cyclization followed by two reduction steps gave 3-benzazepine 3 (R = H), which was converted to the methanesulfonate salt of 1 in several more steps. Such a synthetic route is unattractive for the preparation of [*benzo*-^{14}C]-1 because of its length. The required steps would include not only those illustrated in Scheme I, but also those required to prepare 3-methoxy-[^{14}C]phenylacetic acid from a commercially available precursor, such as [^{14}C]benzene. Therefore we sought a different route to 1, which would provide for efficient incorporation of carbon-14 into the benzo ring from a readily available carbon-14-labeled starting material.

The Fujimoto–Belleau reaction[7] has often been used to prepare 5- and 6-membered bicyclic enones by addition of a Grignard reagent to a δ-enol lactone followed by aldol ring closure. Labeled methyl iodide has been used efficiently in this reaction to prepare steroidal 4-en-3-ones labeled at C4.[8] To our knowledge, however, this reaction has not been used for the preparation of nitrogen heterocyclic or 6,7-bicyclic ring systems. We now report the application of the Fujimoto–Belleau reaction to such a system which provides a new entry into 7-oxygenated 2,3,4,5-tetrahydro-1*H*-3-benzazepines. In addition, the present synthesis is efficient, providing *N*-benzylmethoxybenzazepine 3, labeled with carbon-14 at C6, in three steps and 28% overall yield from the inexpensive and readily available [^{14}C]methyl iodide.

Hydrazepinone ester 5 (Scheme II) was prepared in 51% yield by base-induced decomposition of nitrosocarbamate 6 in the presence of *N*-benzyl-4-piperidone according to the procedure of Hauptmann and Hirschberg.[9] The only significant byproduct of this reaction, occurring in a yield of about 5%, was identified as the epoxide 7; it was easily separated from 5 by silica gel chromatography. Acid hydrolysis of 5 followed by treatment of the resulting crude amino acid hydrochloride with acetyl chloride–acetic anhydride at 80 °C provided the hydrochloride salt of enol lactone 8 in quantitative yield. The free base of 8 was isolated by extraaction from aqueous sodium bicarbonate and recrystallized to purity in 87% yield. None of the enol lactone having the isomeric exo oriented double bond was detected. Cursory attempts to prepare the latter isomer by kinetic deprotonation of 5 were unsuccessful, possibly because its instability prevented ready detection and isolation.

Reaction of enol lactone 8 (Scheme III) with methylmagnesium iodide or methylmagnesium bromide in ether or THF at 0 °C or above led to complex mixtures. However, addition of 1.5 equiv of the Grignard reagent to a solution of 8 in ether at −20 °C to −30 °C, followed by

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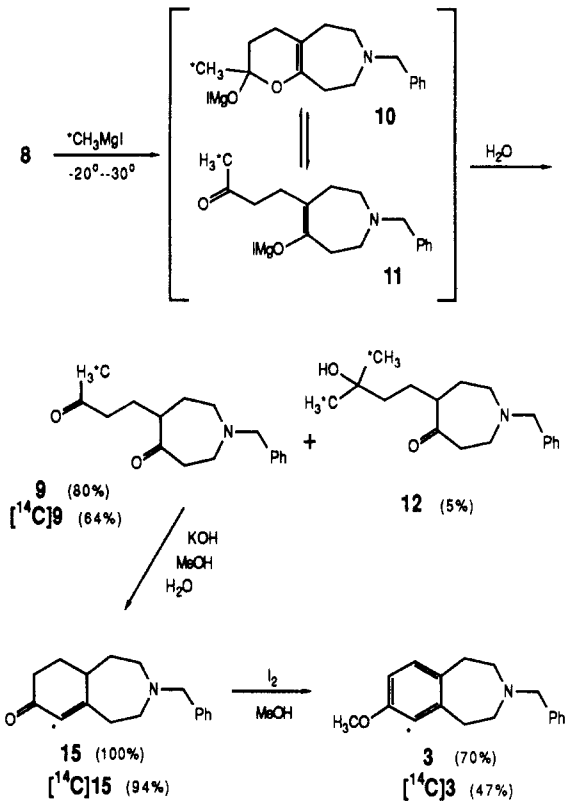
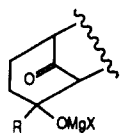
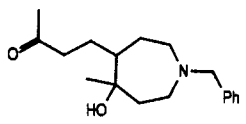
Scheme III



quenching with water and workup of the ether layer, provided the 1,5-diketone **9** (* = ^{12}C) in up to 80% yield after flash chromatography. Under these reaction conditions, the Grignard adduct (**10** or **11**) precipitates from solution instantly upon addition of methylmagnesium iodide. This precipitation may retard reaction of the adduct with a second Grignard equivalent. Nevertheless, under these reaction conditions, keto alcohol **12** is formed as a byproduct in about 5% yield. It becomes the major product if 2 equiv of methylmagnesium bromide are used and the reaction mixture is warmed above 0 °C before quenching. In neither case is a detectable quantity of the isomeric **14** observed. The structure of **12** was established by spectrometric characterization of the unlabeled compound, and by ^1H and ^{13}C NMR spectra of [$^{13}C_2$]-**12** isolated from a Grignard reaction run with $^{13}CH_3MgI$. The spectra showed ^1H–^{13}C three-bond coupling (3.6 Hz) and ^{13}C–^{13}C coupling (2.5 Hz) between the enriched methyl carbon signals. The results of this reaction are consistent with a reaction course (**8–10–11–9**), which is more like that of dihydropyrones than that of the more usual Fujimoto–Belleau substrates, whose double bond is oriented exo to the lactone ring. In the latter case the keto enolate, analogous to **11** above but having the isomeric double bond position, is thought to aldolize to a bicyclic keto alcoholate (e.g., **13**).[7] This species usually reverts to the 1,5-diketone during acidic workup, but the bicyclic keto alcohol can sometimes be isolated via a mild basic workup. A second Grignard addition to an intermediate analogous to **13** would give **14** and not **12**.



13



14

In two repetitions of this reaction beginning with a stoichiometric quantity of [^{14}C]methyl iodide (250 mCi at a specific activity of 56 mCi/mmol), [^{14}C]-**9** (* = ^{14}C) was obtained in an average yield (radiochemical basis) of 64%. This and subsequent steps were first carried out with unlabeled materials, and the products were purified and characterized by standard spectroscopic methods. In radioactive reactions, intermediate products were identified by chromatographic comparison with authentic unlabeled standards.

Aldol cyclization of crude [^{14}C]-**9** with potassium hydroxide in aqueous methanol at room temperature gave the enone [^{14}C]-**15** in 94–95% yield and 93–94% radiochemical purity without purification. In the corresponding reaction with pure unlabeled **9**, yields of 90–100% were achieved. [^{14}C]-**15** was treated with iodine in methanol according to the procedure of Tamura and Yoshimoto,[10] to provide 3-benzyl-7-methoxy-2,3,4,5-tetrahydro-[6-^{14}C]-1*H*-3-benzazepine ([^{14}C]-**3**, R = benzyl). The yield of this labeled benzazepine after chromatographic purification was 47%, for an overall yield of 28% from [^{14}C]methyl iodide. Yields up to 70% were obtained in the aromatization reaction beginning with pure unlabeled enone. Aromatization of the enone with NBS,[11] bromine,[12] or cupric bromide[13] was less satisfactory, as was the two-step sequence via the dienol methyl ether. In the latter case, a mixture of all three possible double bond isomers was formed on treatment of the enone with toluenesulfonic acid in trimethyl orthoformate.

In subsequent steps, [^{14}C]-**3** (R = benzyl) was debenzylated by catalytic hydrogenolysis, and the resulting [^{14}C]-**3** (R = H) was converted into [^{14}C]-**1** methanesulfonate salt by methods similar to those previously reported.[6]

The results described above demonstrate the utility of the Fujimoto–Belleau reaction in the synthesis of 3-benzazepines, and it also allows the imbedding of isotopic carbon in the benzo ring, in good overall yield from labeled methyl iodide. Based on the well-known scope of diazo insertion reactions of carbocyclic and heterocyclic ketones,[14] we anticipate that this route may be useful for the preparation of other benzo-fused structures analogous to **3**.

Experimental Section

General Procedures. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM400 spectrometer at 400 and 100.6 MHz, respectively. Peak assignments in ^1H and ^{13}C NMR spectra were assisted by use of COSY and DEPT experiments, respectively. Infrared spectra were measured on a Nicolet 20 DXB fourier transform spectrophotometer. Low-resolution mass spectra were obtained in electron impact mode (70 eV) on a Finnegan 1020 instrument, and high resolution mass spectra were recorded on a MAT CH-5 instrument. TLC analyses were carried out on Merck silica gel 60 F254 plates, and radiochromatograms were recorded either on a Berthold LB 2722 radioactivity scanner or a Berthold LB 2832L Linear Analyzer. [^{14}C]Methyl iodide was purchased from Chemsyn Science Laboratories, Lenexa, KS.

1-Benzyl-5-(2-carbomethoxyethyl)-1,2,3,5,6,7-hexahydro-4*H*-azepin-4-one (5). The reaction of *N*-benzyl-4-piperidone (5.0

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g, 26.3 mmol) with ethyl 4-[(methoxycarbonyl)nitrosoamino]-butyrate[9] (6.5 g, 29.8 mmol) in the presence of potassium carbonate (6.47 g, 46.9 mmol) was carried out by the method of Hauptmann and Hirschberg.[9] Flash chromatography (4:96 methanol/chloroform) provided 3.9 g (51%) of **5** as a clear oil. ^{1}H NMR ($CDCl_3$): δ 1.65 (m, 2 H, CH_2), 1.76 (m, 2 H, CH_2), 2.04 (m, 1 H, CH), 2.32 (m, 2 H, CH_2), 2.45 (m, 2 H, CH_2), 2.66 (m, 2 H, CH_2), 2.91 (m, 2 H, CH_2), 3.62 (AB q, J = 11.0, 13.4, 2 H, benzylic CH_2), 3.66 (s, 3 H, CH_3), 7.30 (m, 5 H, arom). ^{13}C NMR ($CDCl_3$): δ 26.6 (CH_2), 31.1 (CH_2), 31.6 (CH_2), 43.6 (CH_2), 50.1 (OCH_3 or C5), 50.4 (CH_2), 51.6 (OCH_3 or C5), 56.3 (CH_2), 62.5 (benzylic C), 127.1 (phenyl C4), 128.3 (phenyl *o*- or *m*-CH), 128.7 (phenyl *o*- or *m*-CH), 138.8 (phenyl C1), 173.8 (ester C=O), 213.2 (ketone C=O). IR (neat): 3100–3000, 3000–2750, 1737 (ester C=O), 1704 (ketone C=O), 1200–1150, 736, 700 cm^{-1}. Mass spectrum: m/z 289 (M^+, 11), 258 (9), 216 (30), 198 (5), 175 (3), 146 (35), 132 (5), 112 (4), 91 (100), 77 (1), 65 (10), 55 (6). High-resolution mass spectrum calcd for $C_{17}H_{23}O_3N$ 289.1677, found 289.1685. Also isolated from later column fractions was 389 mg (5%) of 6-benzyl-2-(2-(methoxycarbonyl)ethyl)-1-oxa-6-azaspiro[2.5]octane (**7**) as a clear oil. ^{1}H NMR ($CDCl_3$): δ 1.54 (m, 2 H, C1′-H_2), 1.70–1.98 (m, 4 H, C3-H_2 + C7-H_2), 2.43–2.64 (m, 4 H, C4-H_2 + C6-H_2), 2.75 (t, J = 6.1, 2H, C2′-H_2), 2.82 (dd, J = 5.0, 7.6, 1 H, C2-H), 3.55 (s, 2 H, benzyl CH_2), 3.69 (s, 3 H, $COOCH_3$), 7.26–7.33 (m, 5 H, ArH). ^{13}C NMR ($CDCl_3$): δ 23.6 (CH_2), 28.9 (CH_2), 30.9 (CH_2), 34.6 (CH_2), 51.7 (CH_2), 51.8 (OCH_3), 51.8 (CH_2), 61.5 (C3), 62.8 (benzylic C), 62.9 (C2), 127.1 (phenyl C4), 128.2 (phenyl C), 129.1 (phenyl C), 138.3 (phenyl C1), 173.3 (C=O). IR (neat): 3100–2950, 2920–2670, 1740 (ester C=O), 1201 (C—O), 1174 (C—O), 741, 700 cm^{-1}. Mass spectrum: m/z 289 (M^+, 7), 258 (7), 203 (11), 202 (81), 172 (8), 91 (100), 83 (12). High-resolution mass spectrum calcd for $C_{17}H_{23}NO_3$ 290.1746, found 290.1751.

7-Benzyl-4,5,6,7,8,9-hexahydropyrano[2,3-*d*]azepin-2-(3*H*)-one (8). A solution of **5** (7.4 g, 24.8 mmol) in 20 mL of 2 N aqueous HCl was heated to 90 °C for 2 h and then cooled. The solvent was removed in vacuo, assisted by addition and evaporation of toluene. The resulting off-white solid was dissolved in a mixture of 5 mL of acetyl chloride and 3 mL of acetic anhydride and heated at 65 °C for 4.5 h. The mixture was cooled, and the volatiles were removed in vacuo. The off-white solid residue was partitioned between saturated aqueous sodium bicarbonate and ether. The ether solution was dried ($MgSO_4$), filtered, and evaporated in vacuo. The resulting solid was recrystallized from hexane to give 5.54 g (87%) of **8** as white spades, mp 74.5–5 °C. ^{1}H NMR ($CDCl_3$): δ 2.26 (dd, J = 4.8, 5.6, 2 H), 2.31 (t, J = 7.6, 2 H), 2.47 (dd, J = 4.8, 5.6, 2 H), 2.57 (t, J = 7.7, 2 H), 2.62–2.67 (m, 4 H), 3.63 (s, 2 H, benzylic CH_2), 7.26–7.33 (m 5 H, Ar H). ^{13}C NMR ($CDCl_3$): δ 26.3 (CH_2), 28.5 (CH_2), 31.0 (CH_2), 31.6 (CH_2), 52.4 (CH_2), 54.0 (CH_2), 62.6 (benzylic C), 113.3 (C4a), 127.0 (phenyl C4), 128.2 (phenyl C), 128.9 (phenyl C), 138.7 (phenyl C1), 149.3 (C9a), 169.2 (C2). IR (KBr): 3100–3000, 3000–2750, 1756 (C=O), 1701 (C=C), 1139, 745, 737, 702 cm^{-1}. Mass spectrum: m/z 257 (M^+, 29), 229 (10), 185 (9), 138 (16), 133 (58), 132 (39), 91 (100). High-resolution mass spectrum calcd for $C_{16}H_{19}NO_2$ 257.1424, found 257.1420.

1-Benzyl-1,2,3,5,6,7-hexahydro-5-(3-oxo[4-^{14}C]butyl)-4*H*-azepin-4-one ([^{14}C]-9). [^{14}C]Methyl iodide (250 mCi, 56 mCi/mmol, 4.46 mmol) was added by static vacuum transfer to 153 mg of magnesium turnings in 6 mL of ether, and the mixture was stirred during formation of the Grignard reagent (30 min). The ethereal solution was added dropwise by cannula over 5 min to a vigorously stirred solution of 1.15 g (4.47 mmol) of **8** in 100 mL of ether maintained at between −20 °C and −30 °C, resulting in formation of a voluminous white precipitate. The mixture was allowed to warm to near 0 °C over 30 min, then 15 mL of water was added. Volatile radioactivity was removed by static vacuum transfer. The organic phase was separated from the aqueous phase, and the latter was extracted twice with ether. The combined organics were dried over magnesium sulfate and evaporated in vacuo to provide 1.15 g of a clear oil, containing 164 mCi of radioactivity (66% yield). TLC analysis (SiO_2, 4:96 (v/v) ethanol/dichloromethane) showed that 94.5% of the radioactivity comigrated with authentic unlabeled **9**. A second run, carried out identically, resulted in 1.14 g (159 mCi, 64%) of [^{14}C]-**9** with a radiochemical purity of 93.0%. Analytical characterization of unlabeled **9** prepared the same way and purified by flash chromatography (EtOH/CH_2Cl_2) gave the following. ^{1}H NMR ($CDCl_3$): δ 1.60–1.70 (m, 2 H), 1.74 (m, 1 H), 1.93 (m, 1 H), 2.10 (s, 3 H, C4′-H3), 2.36–2.53 (m, 5 H), 2.66 (m, 2 H), 2.90 (m, 2 H), 3.62 (AB q, J = 8.4, 21.9, 2 H, benzylic CH_2), 7.24–7.35 (m, 5 H, ArH). ^{13}C NMR ($CDCl_3$): δ 25.5 (CH_2), 29.9 (C4′), 31.3 (CH_2), 41.0 (CH_2), 43.4 (CH_2), 50.1 (C5), 50.4 (CH_2), 56.1 (CH_2), 62.4 (benzylic C), 127.0 (phenyl C4), 128.3 (phenyl C), 128.6 (phenyl C), 138.8 (phenyl C1), 208.5 (C3′), 213.5 (C4). IR (neat): 3100–3000, 3000–2750, 1718 (C3′ carbonyl), 1697 (C4 carbonyl), 737, 700 cm^{-1}. Mass spectrum: m/z 273 (M^+, 8), 230 (7), 217 (9), 216 (58), 202 (8), 146 (34), 91 (100). High-resolution mass spectrum calcd for $C_{17}H_{23}NO_2$ 273.1746, found 273.1737. Also isolated from later chromatographic fractions was 1-benzyl-5-(4-hydroxy-4-methylpentyl)-1,2,3,5,6,7-hexahydro-4*H*-azepin-4-one (**12**). ^{1}H NMR ($CDCl_3$): δ 1.22 (s, 6 H, 2 CH_3), 1.42–1.48 (m, 3 H), 1.70 (m, 1 H), 1.81 (m, 2 H), 2.38–2.53 (m, 3 H), 2.68 (m, 2 H), 2.90 (m, 2 H), 3.12 (AB q, J = 13.5, 22.2, 2 H, benzylic CH_2), 7.21–7.32 (m, 5 H, ArH). ^{13}C NMR ($CDCl_3$): δ 29.1 (CH_3), 29.4 (CH_3), 31.2, 32.6, 41.0, 43.6, 50.5, 51.4, 56.3, 62.5, 127.1 (phenyl C4), 128.2 (phenyl C), 128.3 (phenyl C), 138.9 (phenyl C1), 214.2 (C=O). Mass spectrum (CI, CH_4): m/z 290 ($(M + H)^+$, 60), 272 (100), 244 (5), 212 (4). High-resolution mass spectrum: calcd for $C_{18}H_{27}NO_2$ 290.2108, found 290.2114.

3-Benzyl-1,2,3,4,5,8,9,9a-octahydro-[6-^{14}C]-7*H*-3-benzazepin-7-one ([^{14}C]-15). The sample of [^{14}C]-**9** (1.15 g, 164 mCi, 2.93 mmol by radioactivity) was dissolved in a solution of 517 mg (10.8 mmol) of potassium hydroxide in 4 mL of water and 10 mL of methanol under an argon atmosphere, and the solution was allowed to stand at room temperature for 3 h. Water (25 mL) was then added, and the mixture was extracted four times with ether. The combined extracts were washed twice with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated in vacuo to give 760 mg (156 mCi, 95%) of [^{14}C]-**15** as a pale yellow oil. Analysis by TLC (SiO_2, 4:96 (v/v) ethanol/dichloromethane) showed a radiochemical purity of 94.4%. A second run from 159 mCi of [^{14}C]-**9** gave 740 mg (150 mCi, 94%) of [^{14}C]-**15** with a radiochemical purity of 94.6%. Analytical characterization of unlabeled **14** prepared in the same way and purified by flash chromatography (EtOH/CH_2Cl_2) gave the following. ^{1}H NMR ($CDCl_3$): δ 1.76–2.02 (m, 4 H, C1-H_2 + C9-H_2), 2.29–2.81 (m, 9 H, 4CH_2 + CH), 3.61 (AB q, J = 13.4, 24.6, 2 H, benzylic CH_2), 5.84 (s, 1 H, C6-H), 7.29–7.33 (m, 5 H, ArH). ^{13}C NMR ($CDCl_3$): δ 31.4 (CH_2), 33.1 (CH_2), 36.9 (CH_2), 37.7 (CH_2), 39.8 (C9a) 54.4 (CH_2), 55.3 (CH_2), 62.6 (benzylic CH_2), 126.7 (C6), 127.2 (phenyl C4), 128.4 (phenyl C), 129.0 (phenyl C), 139.0 (phenyl C1), 170.3 (C5a), 199.8 (C7). IR (KBr): 3100–3000, 3000–2750, 1666 (C=O), 1614 (C=C), 741, 733, 700 cm^{-1}. Mass spectrum: m/z 255 (M^+, 55), 164 (24), 146 (14), 132 (8), 91 (100). High-resolution mass spectrum calcd for $C_{17}H_{21}NO$ 255.1639, found 255.1631.

3-Benzyl-2,3,4,5-tetrahydro-7-methoxy-[6-^{14}C]-1*H*-3-benzazepine ([^{14}C]-3, R = Benzyl). Crude [^{14}C]-**15** (740 mg, 150 mCi, 2.68 mmol by radioactivity) was dissolved in 25 mL of absolute methanol. A 1.67-g (6.57-mmol) portion of iodine was added, and the reaction was stirred under an argon atmosphere at 65–70 °C for 130 min. Twenty-five-milliliter portions of water and ether were added to the cooled reaction, and small portions of solid sodium bisulfite were added with stirring until the color of iodine was discharged. Solid sodium bicarbonate was added cautiously to basify the aqueous phase. The organic layer was separated, and the aqueous phase was extracted three times with ether. The combined organic solutions were washed with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated in vacuo to give 650 mg of an amber oil containing 129 mCi of radioactivity. This product was combined with another (660 mg, 132 mCi) made in the same way and purified by silica gel chromatography (35:65 (v/v) ethyl acetate/hexane). A total of 650 mg (143 mCi) of [^{14}C]-**3** (R = benzyl) was isolated as a clear oil (47% from [^{14}C]-**15**). TLC analysis (SiO_2, 4:6 (v/v) ethyl acetate/hexane) showed that 99.9% of the radioactivity comigrated with authentic unlabeled **3** (R = benzyl) prepared in the same way and characterized. ^{1}H NMR ($CDCl_3$): δ 2.60–2.64 (m, 4 H, C2-H_2 + C4-H_2), 2.85–2.89 (m, 4 H, C1-H_2 + C5-H_2), 3.63 (s, 2 H, benzylic CH_2), 6.65 (m, 2 H, C6H + C8H), 6.98 (d, J = 7.9, 1 H, C9H), 7.25–7.36 (m, 5 H, ArH). ^{13}C NMR ($CDCl_3$): δ 35.7 (CH_2), 36.9 (CH_2), 55.2 (OCH_3), 55.3 (CH_2), 55.7 (CH_2), 63.5 (benzylic CH_2), 110.5 (C8), 114.9 (C6), 126.9 (phenyl C4), 128.2 (phenyl C), 129.1 (phenyl C), 138.7 (phenyl

C1), 143.5 (C5a), 157.9 (C7). IR (KBr): 3100–3000, 3000–2750, 1610, 1583, 1506, 1267, 738, 699 cm^{-1}. Mass spectrum: m/z 267 (M^+, 60), 266 (24), 252 (20), 190 (12), 176 (36), 148 (20), 135 (68), 134 (35), 132 (21), 91 (100). High-resolution mass spectrum calcd for $C_{18}H_{21}NO$ 267.1617, found 267.1620.

Electron Transfer in the Additions of Organolithium Reagents to Benzophenone and Benzaldehyde

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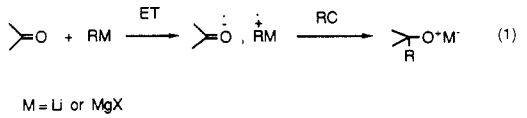
The mechanism of addition reactions of organolithium and organomagnesium reagents to ketones has recently been shown to differ in spite of the fact that the two types of reagents react in a similar manner to give 1,2-addition products.[1,2] For example in the reaction with benzophenone, MeLi exhibited no carbon kinetic isotope effect (KIE, $^{12}k/^{14}k$ = 1.000) for the carbonyl ^{14}C-labeled compound and only very small electronic and steric effects of substituents on reactivity,[1a] while MeMgI showed a large KIE (1.056) and considerable substituent effects both electronically and sterically.[1b] These results were interpreted by assuming a rate-determining electron transfer (ET) mechanism for MeLi and a fast ET process followed by a slow rate-determining C–C bond formation (RC) for MeMgI (eq 1). The interpretation for the MeMgI reaction



M = Li or MgX

is consistent with the current view that the Grignard reaction proceeds via an ET mechanism with aromatic ketones.[3] However, the conclusion for MeLi might be controversial because (1) there are no reports indicating an ET mechanism for the addition of MeLi to ketones and (2) there are only a few examples of ET processes which give very small KIE and substituent effects.

We have recently reported that the reaction of benzophenone with allylmagnesium bromide proceeds with a carbonyl carbon KIE of unity as well as with small steric and electronic substituent effect as for the MeLi system.[1c] These results can be interpreted as indicating a rate-determining ET mechanism, and thereby provide indirect support for the earlier conclusion of an ET mechanism for MeLi. Furthermore, the results indicated that the barrier heights of the two steps, ET and RC, are so comparable in the Grignard reaction that the rate-determining step could easily be shifted by the change in the structure of RMgX. In the present study, we measured KIEs and substituent effects for two different lithium reagents and two different substrates in order to see whether the reactions of lithium reagents other than MeLi may also proceed via an ET mechanism (eq 1) and whether the rate-determining step could be varied with a change in the R group of the lithium reagent as in the Grignard reaction. The reactions we examined are (1) benzophenone/PhLi, (2) benzophenone/allyllithium, and (3) benzaldehyde/PhLi. The results are compared with those observed with the benzophenone/MeLi system.

The carbonyl carbon-^{14}C KIEs for the three reactions were determined as described previously[4] and are listed in Table I. In the case of reaction 1, both unreacted benzophenone and product alcohol could be isolated from the reaction mixture and purified by preparative TLC and recrystallization. The standard Tong–Yankwich equations[5]

Table I. Kinetic Isotope Effects in Reactions of Carbonyl Compounds with Organolithium Reagents[a]

substrate	reagent	solvent	$^{12}k/^{14}k$
$(C_6H_5)_2CO$	PhLi	cyclohexane–Et_2O (7:3)	1.003 ± 0.001
$(C_6H_5)_2CO$	allyllithium	Et_2O	0.994 ± 0.003
C_6H_5CHO	PhLi	cyclohexane–Et_2O (7:3)	0.998 ± 0.003

[a] Reactions were carried out at 0.0 °C.

Table II. Relative Reactivities of Substituted Carbonyl Compounds with Various Lithium Reagents at 0.0 ± 0.1 °C[a]

	k_X/k_H		
substituent	$Ph_2C{=}O$/PhLi[b]	$Ph_2C{=}O$/allyllithium[c]	PhCHO/PhLi[b]
2,4,6-Me_3	0.06 ± 0.03	0.39 ± 0.04	*d*
o,*p*-Me_2	*d*	*d*	0.91 ± 0.05
p-MeO	1.03 ± 0.03	0.83 ± 0.02	0.96 ± 0.01
m-MeO	1.03 ± 0.02	*d*	1.17 ± 0.08
p-Me	1.06 ± 0.01	0.91 ± 0.06	0.85 ± 0.03
m-Me	0.94 ± 0.05	0.96 ± 0.01	0.95 ± 0.01
o-Me	0.56 ± 0.03	0.79 ± 0.03	0.91 ± 0.04
p-F	1.18 ± 0.01	1.15 ± 0.12	1.03 ± 0.09
m-F	*d*	*d*	1.03 ± 0.03
p-Cl	1.10 ± 0.05	0.99 ± 0.06	1.21 ± 0.09
m-Cl	1.26 ± 0.04	1.20 ± 0.13	1.09 ± 0.01
o-Cl	0.81 ± 0.03	0.93 ± 0.07	1.13 ± 0.03
m-CF_3	1.48 ± 0.03	*d*	*d*

[a] Listed values are averages of two to four determinations. Error limits are the standard deviations. [b] In cyclohexane–ether (7:3). [c] In ether. [d] Not determined.

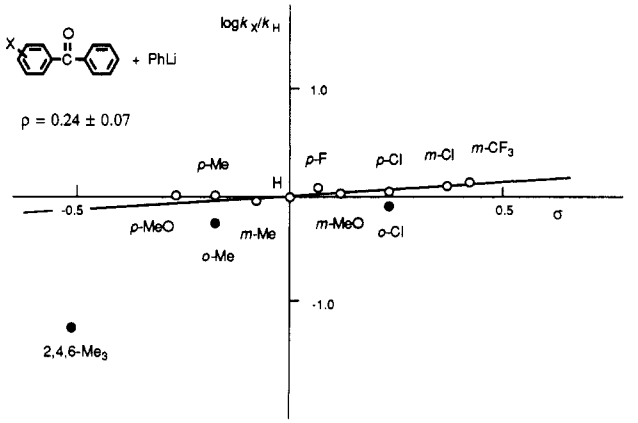


Figure 1. Variations of reactivity with σ values for the reactions of substituted benzophenones with PhLi.

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