J. Org. Chem. **1981**, *46*, 217-219

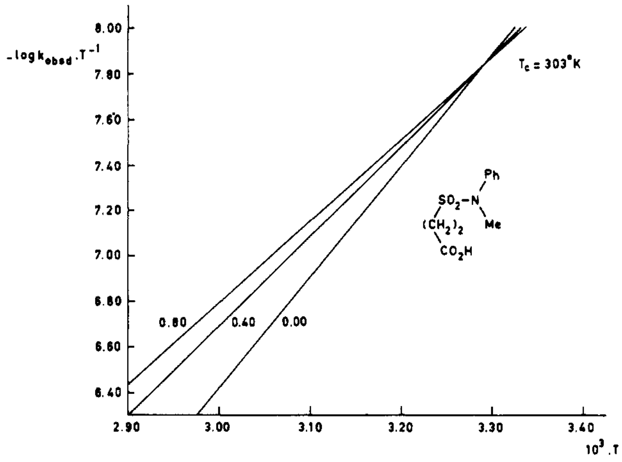

Figure 3. Plots of $-\log k_{\text{obsd}}T^{-1}$ vs. T^{-1} for the intramolecular carboxyl-catalyzed hydrolysis of 1 in water and in the presence of 0.40 and 0.80 M n-Bu_4NBr.

more than compensates for the decrease in $\Delta S^{\ddagger}$).

As noted above, n-Bu_4NBr is the only electrolyte used in this study which exerts a negative salt effect. Thermodynamic activation parameters for the hydrolysis of 1 and 2 are plotted as a function of the molality of n-Bu_4NBr in Figures 1 and 2, respectively. Small changes in $\Delta G^{\ddagger}$ are found to conceal large, compensatory changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. The most pronounced effects are observed for 1: $\Delta H^{\ddagger}$ decreases by more than 5.5 kcal mol^{-1} upon addition of 0.8 M of n-Bu_4NBr whereas $\Delta S^{\ddagger}$ becomes more negative by 18 eu. These changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are at least an order of magnitude larger than the experimental error in these quantities of activation.[16] Applying Petersen's criterion[17] for the existence of an isokinetic temperature (T_c), $-\log k_{\text{obsd}}T^{-1}$ has been plotted vs. T^{-1} for hydrolysis of 1 in water and the two salt solutions (Figure 3). The three straight lines intersect at a single point, which corresponds with T_c = 303 K. The smaller changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for hydrolysis of 2 do not satisfy the Petersen criterion, despite the linear plot of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$. Although a detailed analysis of the variation of these activation parameters would require a dissection into initial-state and transition-state solvation effects,[18] the data strongly suggest the operation of dominant hydrophobic interaction between the substrate and the hydrophobic[12,19] tetra-n-butylammonium cation. This hydrophobic effect, which originates from mutually destructive overlap of the respective hydrophobic hydration spheres, will increase both the enthalpy and the entropy of the initial state,[18,20] leading to the observed trends in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. In the transition state for hydrolysis hydrophobic interaction will be attenuated as a result of the dipolar character of this species. It is noteworthy that in typically aqueous solutions like highly aqueous t-BuOH–H_2O, similar $\Delta H^{\ddagger}$–$\Delta S^{\ddagger}$ mirror image behavior has been observed as a function of solvent composition.[1,5] However, in that case the initial state is more strongly stabilized, leading to a more manifest decrease of the rate of hydrolysis upon increasing concentration of the additive.

Experimental Section

Materials. The synthesis of sulfonamide 1 (pK_A = 3.44; H_2O, 50 °C) has been described previously.[1] Sulfonamide 2 ($pK_A \approx$ 2.8; H_2O, 50 °C) was prepared according to the standard procedure outlined in part IV[1] and gave the expected amine and diacid upon hydrolysis.

3-Carboxy-*N*-methyl-*N*-phenyl-3-pentanesulfonamide (2): mp 91.3–92.3 °C; NMR ($CDCl_3$) δ 0.95 (t, 6 H), 2.15 (q, 4 H), 3.35 (s, 3 H), 7.1–7.5 (m, 5 H), 10.9 (s, 1 H). Anal. Calcd for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; N, 4.91; S, 11.24. Found: C, 54.6; H, 6.8; N, 4.8; S, 11.1.

The salts used in all experiments were of analytical quality and were obtained either from Merck AG or from Aldrich. They were used as received, except n-Bu_4NBr which was crystallized twice from ethyl acetate–ether. Salt concentrations are expressed in the aquamolality scale (M; moles of salt per 55.5 mol of water). The water used in the kinetic measurements was demineralized and distilled twice in an all-quartz distillation unit.

Kinetic Measurements. Rates of hydrolysis of 1 and 2 were determined by following the decrease in absorbance at a suitable wavelength in the UV (usually at 235 nm). The k_{obsd} values were reproducible to within 2%. Thermodynamic activation parameters were calculated from rate constants measured at four different temperatures in the range of ca. 50–65 °C. Estimated errors in $\Delta H^{\ddagger}$ are ±0.2 kcal mol^{-1} and in $\Delta S^{\ddagger}$ are ±1 eu. The rate constants were determined at pH values in the middle of the horizontal part of the log k_{obsd}–pH profile, i.e., at 3.10^{-2} M HCl for 1 and at 0.5 M HCl for 2.

Registry No. 1, 62416-04-0; 2, 75599-75-6.

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[16] For a thorough statistical analysis of enthalpy–entropy compensation, see: Krugg, R. R.; Hunter, W. G.; Grieger, R. A. *J. Phys. Chem.* **1976**, *80*, 2335, 2341.

[17] Petersen, R. C. *J. Org. Chem.* **1964**, *29*, 3133.

[18] Engberts, J. B. F. N. In "Water, a Comprehensive Treatise"; Franks, F. Ed.; Plenum: New York, 1979; Vol. 6, Chapter 4. Although **2** has more hydrophobic surface area than 1, it may be argued that the *change* in hydrophobic interaction during the activation process is less than in the case of **1** in view of the closer proximity of the reacting groups in **2**. This might explain the more pronounced $\Delta H^{\ddagger} - \Delta S^{\ddagger}$ compensation for 1.

[19] (a) Wen, W.-Y. *J. Solution Chem.* **1973**, *2*, 253. (b) Perron, C.; Desrosiers, N.; Desnoyers, J. E. *Can. J. Chem.* **1976**, *54*, 2163. (c) Wen, W.-Y.; Hung, J. H. *J. Phys. Chem.* **1970**, *74*, 170. (d) Tenne, R.; Ben-Naim, A. *Ibid.* **1976**, *80*, 1120.

[20] Compare: (a) Engbersen, J. F. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1975**, *97*, 1563. (b) Engbersen, J. F. J. Ph.D. Thesis, University of Groningen, 1976.

Synthesis and Wittig Reaction of 1-(Triphenylphosphoranylidene)-3-methoxy-2-propanone[1]

Thomas Wayne Bell[2] and Franz Sondheimer*

Chemistry Department, University College London,
London WClH OAJ, England

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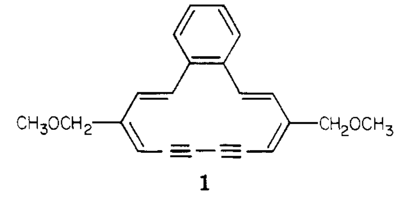
In order to synthesize dehydroannulenes containing methoxymethyl substituents [e.g., 4,11-bis(methoxymethyl)-6,8-didehydrobenz[14]annulene (1)][1] by the method of Darby et al.,[3] we required a simple method to transform an aldehyde (2) to the corresponding 1-methoxy-3-buten-2-one derivative (4). We now describe the



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[1] Taken in part from the Ph.D. thesis of T. W. Bell, University of London, 1980.

[2] Present address: Department of Chemistry, Cornell University, Ithaca, NY 14853.

[3] Darby, N; Cresp, T. M.; Sondheimer, F. *J. Org. Chem.* **1977**, *42*, 1960.

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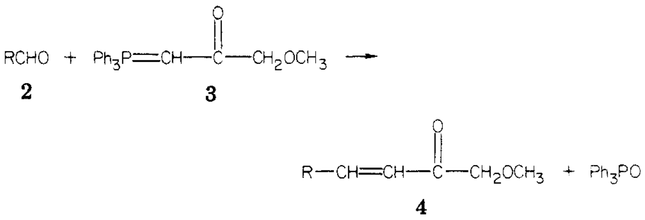
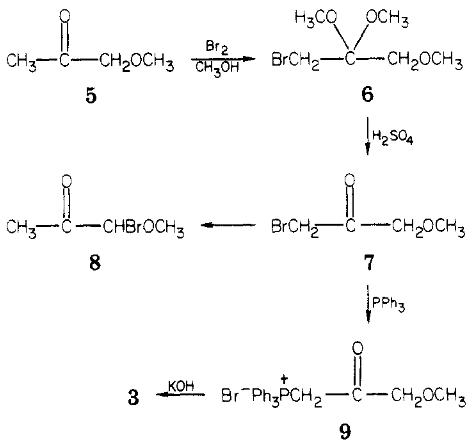
realization of this objective, through the synthesis and Wittig reaction with an aldehyde of 1-(triphenylphosphoranylidene)-3-methoxy-2-propanone (**3**).



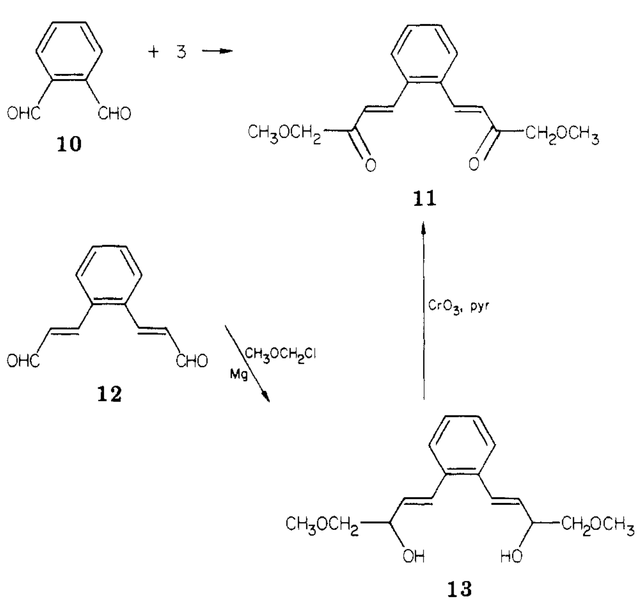
An obvious precursor of the ylide **3** was the previously unknown 1-bromo-3-methoxy-2-propanone (**7**). This compound was readily prepared by bromination of methoxyacetone (**5**) with bromine in methanol, followed by hydrolysis of the resulting bromo ketal **6** with aqueous sulfuric acid.[4] It was found that the bromo ketone **7** readily underwent rearrangement to 1-bromo-1-methoxy-2-propanone (**8**) on standing or distillation. The crude bromo ketone **7** was therefore treated directly with ~1 molar equiv of triphenylphosphine in benzene at 0–18 °C. Dehydrobromination of the resulting triphenylphosphonium bromide **9** with aqueous potassium hydroxide then gave the required ylide **3** in 28% yield (based on **5**) as a stable crystalline compound, mp 187.5–188 °C.



An example of the Wittig reaction of the ylide **3** with an aldehyde was provided by treatment of *o*-phthalaldehyde (**10**) with 2.5 molar equiv of **3** in boiling dichloromethane. This reaction led in essentially quantitative yield to the dimethoxy diketone **11**. The latter compound proved to be identical with a sample obtained by a much less convenient route,[1] involving the conversion of *o*-phthalaldehyde (**10**) to the bisvinylogue **12** (in 40–50% yield),[3] followed by Grignard reaction with an excess of chloromethyl methyl ether and magnesium,[5] and subsequent oxidation of the resulting diol **13** with chromium trioxide and pyridine.[6] The dimethyloxy diketone **11** has been converted to the dehydroannulene derivative **1** in 27% overall yield by a three-step sequence.[1]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 177 or 297 or a Unicam SP200 spectrophotometer. Electronic (UV) spectra were determined on a Unicam SP800 or a Cary 14 spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were recorded with deuteriochloroform solutions on a Varian T-60 spectrometer; all chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectra were determined on an AEI MS-9 or MS-12 mass spectrometer at 70 eV.



1-(Triphenylphosphoranylidene)-3-methoxy-2-propanone (3). Bromine (88 g, 0.55 mol) was added in a fine continuous stream during 20 min to a stirred solution of methoxyacetone (**5**, 44 g, 0.5 mol, Aldrich Chemical Co. Ltd., 99%) in dry methanol (500 mL) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 6 h and poured into water (1.5 L), and 50% aqueous sulfuric acid (10 mL) was added. The solution was stirred under nitrogen for 15 h at 10–15 °C, 20 h at 20–30 °C, and 16 h at 30–34 °C. During this period, hydrolysis of the intermediate ketal **6** was monitored by working up 1-mL aliquots and TLC examination. The hydrolysis proved to be ~90% complete. The reaction mixture was extracted with benzene (4 × 150 mL), and the organic extracts were washed with brine and dried (Na_2SO_4, 0 °C) after the addition of more benzene (75 mL) and petroleum ether (75 mL, bp 40–60 °C) (these solvents were added in order to break up an emulsion).

Evaporation of the solution at this stage under reduced pressure in a bath kept below 40 °C led to 58.1 g (70%) of crude 1-bromo-3-methoxy-2-propanone (**7**) as a colorless mobile lachrymatory liquid; ^{1}H NMR δ 4.22 (s, 2 H), 4.03 (s, 2 H), 3.45 (s, 3 H). Standing or distillation at 66–76 °C (26 mm) of **7** led to crude 1-bromo-1-methoxy-2-propanone (**8**) as a light yellow mobile liquid; ^{1}H NMR δ 5.97 (s, 1 H), 3.60 (s, 3 H), 2.37 (s, 3 H). The rearrangement of **7** to **8** was exothermic, and the 58.1-g sample of crude **7** was found to boil spontaneously after some time on being allowed to stand(!). Neither **7** nor **8** was purified, due to their instability.

For the preparation of **3**, a solution of triphenylphosphine (105 g, 0.4 mol) in benzene (200 mL) was added dropwise with stirring during 1 h to the above-described solution of crude **7** in benzene–petroleum ether (bp 40–60 °C) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for a further 30 min, allowed to stand at 5 °C for 16 h, stirred at 18 °C for 3 h, and recooled to 0 °C for 2 h. The precipitate was collected, washed with cold benzene–petroleum ether (bp 40–60 °C) (3:1), and dried under reduced pressure to constant weight. This procedure gave the crude triphenylphosphonium salt **9** (82.7 g, 38.5% based on **5**) as a colorless powder; ^{1}H NMR δ 7.75 (m, 15 H), 6.02 (d, 2 H), 4.53 (s, 2 H), 3.40 (s, 3 H).

A solution of potassium hydroxide (10.8 g, 0.19 mol) in water (100 mL) was added in portions to a stirred suspension of the crude triphenylphosphonium salt **9** (82.7 g) in water (800 mL) at 25 °C under nitrogen. The resulting yellow suspension was then stirred vigorously under nitrogen for 3 h at 0 °C. The precipitate was collected, washed with cold water (2 × 100 mL), and dried first in air and then under reduced pressure (0.1 mm)

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[4] See Garbisch, E. W. *J. Org. Chem.* **1965**, *30*, 2109. Gaudry, M; Marquet, A. *Bull. Soc. Chim. Fr.* **1969**, 4169, 4178; *Tetrahedron* **1970**, *26*, 5611.

[5] Normand, H.; Crisan, C. *Bull. Soc. Chim. Fr.* **1959**, 199, 459, 463.

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for 12 h. This resulted in the ylide 3 (48.6 g, 28% based on 5) as light tan crystals. Crystallization from benzene–hexane gave an analytical sample: mp 187.5–188 °C; IR (KBr) ν_{max} 3040 (mw), 2980 (w), 2920 (mw), 2870 (w), 2810 (mw), 1527 (s), 1476 (m), 1431 (ms), 1387 (s), 1178 (mw), 1100 (s), 990 (w), 945 (m), 928 (m), 863 (m), 745 (m), 713 (ms), 691 cm^{-1} (s); UV (ether) λ_{max} 303 nm (ϵ 4300); ^{1}H NMR δ 7.50 (m, 15 H), 4.13 (br d, 1 H, J = 26 Hz), 3.93 (s, 2 H), 3.48 (s, 3 H); mass spectrum, *m/e* 348 (M$^+$, 1), 303 (M$^+$ − CH$_2$OCH$_3$, 100), 277 (Ph$_3$PCH$_3$, 4), 262 (PPh$_3$, 7).

Anal. Calcd. for $C_{22}H_{21}O_2P$: C, 75.85; H, 6.08; P, 8.89. Found: C, 75.86; H, 6.09; P, 8.91.

1,2-Bis(4-methoxy-3-oxo-1-*trans*-butenyl)benzene (11). A. From Ylide 3 and *o*-Phthaladehyde (10). A solution of *o*-phthaldehyde (10; 5.37 g, 0.04 mol) in dry dichloromethane (60 mL) was added dropwise with stirring to the ylide 3 (34.84 g, 0.1 mol) in dichloromethane (100 mL) in a flask protected from light. The reaction mixture was stirred at 15–16 °C for 15 min and was then refluxed for 20 h. Evaporation under reduced pressure led to a light brown semisolid residue, which was extracted thoroughly with boiling hexane. Repeated decantation and evaporation of the combined extracts under reduced pressure gave essentially pure dione 11 (10.91 g, 99.5%) as a viscous amber oil. The analytical sample was obtained by distillation at 0.1 mm: IR (film) ν_{max} 3060 (w), 3000 (w), 2940 (m), 2830 (m), 1705 (sh), 1690 (vs), 1615 (vs), 1595 (s), 1478 (m), 1440 (m), 1310 (ms), 1197 (s), 1120 (s), 980 (s), 933 (m), 756 (ms), 721 (ms), 696 cm^{-1} (m); UV (ether) 225 nm (ϵ 9400), 272 (21 000), 303 (15 000); ^{1}H NMR δ 8.03 (d, 2 H, J = 16 Hz), 7.50 (m, 4 H), 6.82 (d, 2 H, J = 16 Hz), 4.23 (s, 4 H), 3.48 (s, 6 H); mass spectrum, *m/e* 274 (M$^+$, 9), 229 (M$^+$ − CH$_2$OCH$_3$, 57), 201 (M$^+$ − COCH$_2$OCH$_3$, 100).

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.18; H, 6.36.

B. From 1,2-Bis(2-formyl-*trans*-ethenyl)benzene (12).[3] Into a 250-mL five-neck round-bottom flask equipped with a mechanical stirrer, thermometer, nitrogen inlet, and two 50-mL dropping funnels was placed magnesium turnings (2.24 g, 92 mmol). The apparatus was flushed with nitrogen and flame dried. Mercuric chloride (90 mg) and dry tetrahydrofuran (45 mL) were added, and the mixture was stirred for 15 min. A small portion of a solution of freshly distilled chloromethyl methyl ether (6.5 g, 81 mmol) in dry tetrahydrofuran (20 mL) was added, and reaction was initiated by slight warming. A solution of the dialdehyde 12[3] (2.32 g, 12.5 mmol) in dry tetrahydrofuran (20 mL) was then added dropwise with stirring at the same rate as addition of the remaining chloromethyl methyl ether solution (addition time ~20 min). If necessary, the reaction could be reinitiated by addition of a vigorously reacting mixture of magnesium and 1,2-dibromoethane. The reaction temperature was maintained below 35 °C at all times by means of an ice bath. The reaction mixture was stirred at 30 °C for 2.5 h and was then cooled to 0 °C. Saturated aqueous ammonium chloride solution (90 mL) was added in small portions, and the layers were separated. The aqueous phase was extracted with ether (3 × 40 mL) and the combined organic extracts were washed with brine. Drying over magnesium sulfate, evaporation under reduced pressure, and finally exposure to a 0.1-mm vacuum led to a diastereomeric mixture of the crude diol 13 (3.47 g, 100%) as a viscous yellow oil; ^{1}H NMR δ 7.30 (m, 4 H), 7.03 (d, 2 H, J = 16 Hz), 6.10, 6.00 (d, 2 H, J = 16 Hz), 4.53 (m, 2 H), 3.47 (m, 10 H), 2.83 (br s, 2 H).

Chromium trioxide (7.5 g, 75 mmol) was added in small portions to a stirred solution of dry pyridine (11.9 g, 150 mmol) in dry dichloromethane (70 mL) at 0 °C under nitrogen. The resulting suspension was stirred for 5 min at 0–5 °C, allowed to warm to room temperature, and then recooled to 0–5 °C. A solution of the crude diol 13 (3.47 g) in dry methylene chloride (30 mL) was added with stirring at this temperature during 5 min. The mixture was allowed to warm to room temperature and stirred for 1 h, and the supernanant liquid was filtered through a column of alumina (60 g, activity V). The residue was thoroughly extracted with dichloromethane and filtered through the column of alumina. The solvents were removed from the combined filtrates (200 mL) by evaporation under reduced pressure. Prolonged exposure of the residue to a 0.1-mm vacuum gave the diol 11 (2.48 g, 72%) as a viscous amber oil, the IR and ^{1}H NMR spectra of which were identical with those obtained by method A.

Acknowledgment. We are indebted to the Royal Society for financial support.

Registry No. 3, 33513-55-2; 5, 5878-19-3; 7, 75522-04-2; 8, 38568-50-2; 9, 75522-05-3; 10, 643-79-8; 11, 75522-06-4; 12, 61650-42-8; 13 (isomer 1), 75522-07-5; 13 (isomer 2), 75522-08-6.

Analysis of Organomagnesium and Organolithium Reagents Using *N*-Phenyl-1-naphthylamine

David E. Bergbreiter* and Ellen Pendergrass[1]

Texas A&M University, Department of Chemistry,
College Station, Texas 77843

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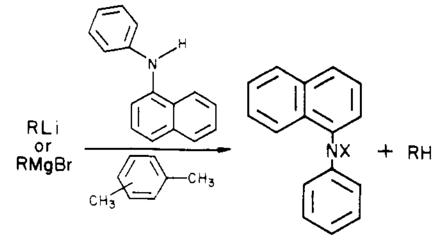
Accurate determination of the concentration of organolithium and organomagnesium reagents can be carried out by a number of procedures with varying degrees of generality.[2-6] The most useful of these procedures permits analysis of the reactive organometallic reagent of interest without interference from any alkoxide or hydroxide base which might be present as a result of adventitious oxidation or hydrolysis. Analytical procedures which directly measure the concentration of an organometallic reagent are thus significantly more useful than a simple total base titration with standard acid which does not distinguish between these possible other bases which might be present. Here we report a general procedure for such titrations in cases where other commonly used procedures have proven to be less effective. The procedure we have developed depends on a rapid acid–base reaction between a diarylamine and a reactive, basic organolithium or organomagnesium reagent (eq 1). Subsequent titration of the resulting yellow-orange diarylamide with a xylene solution of *sec*-butyl alcohol to a cloudy white or colorless end point can then be used to determine the concentration of the organometallic species in question.



(1)

X = Li or MgBr

The principle requirements for successful application of the procedure we describe here are that the organometallic reagent to be titrated has to be substantially more basic than *N*-phenyl-1-naphthylamine and that no highly colored impurities be present in the organometallic solution to be titrated. Thus, all alkyllithium or -magnesium reagents we have tried can be successfully titrated but alkynyllithium or -magnesium reagents do not give reliable

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