Ultrasound in Organic Synthesis. 7.[1] Preparation of Organozinc Reagents and Their Nickel-Catalyzed Reactions with α,β-Unsaturated Carbonyl Compounds

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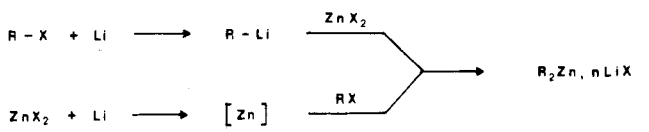
Diorganozinc compounds can be prepared with great ease and efficiency in a one-pot process, by sonication of lithium, an organic halide, and a zinc halide in THF or toluene THF mixtures. The reagents thus obtained give rise to clean and selective conjugate additions to α,β-unsaturated aldehydes and ketones in the presence of catalytic amounts of nickel acetylacetonate.

Introduction

The synthetic potential of organic derivatives of zinc has been recognized for a long time. In a number of cases, they can be obtained directly from the activated metal.[3] Recently, ultrasonic irradiation has been shown to improve the formation of allylic,[4] benzylic,[5] and perfluoroalkyl[6] organozincs and the Simmons–Smith[7] and Reformatsky[8] reactions. But in general direct attack of the metal is difficult, and the zinc reagents are obtained by a two-step process from organolithium or magnesium precursors and a zinc halide.[9] The reagents prepared by this method have received numerous applications in synthesis.[10] Organozinc derivatives exhibit a tendency to add in a conjugate fashion to α,β-unsaturated carbonyl compounds[11] in contrast to their relative inertness towards saturated ketones.[12] However, organocopper derivatives are generally preferred for effecting this transformation.[13] New selective organometallics such as high-order cuprates,[14,15] boron,[16] aluminum,[17] and zirconium[18] derivatives have also been proposed.

Scheme I



Although excellent results can be obtained with these reagents, we thought of interest to investigate the properties of organozinc derivatives, due to their accessibility under sonochemical conditions, the scarcity of studies of their conjugated additions, and their low cost, a potential advantage for large-scale preparative reactions.

Sonochemical Preparation of Organozinc Reagents

Due to their important mechanical effects, ultrasonic waves are able to initiate the erosion of metallic surfaces.[19] However, until now with several types of commercial ultrasound generators, it has not been possible to utilize this physical activation in reactions starting from metallic zinc (with the exceptions listed above[4-8]).

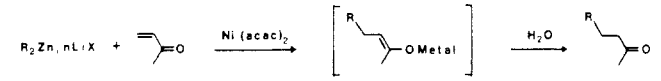
We thus focused our efforts on the classical transmetallation preparation of organozinc reagents. The effects of sonication were expected to make it possible in a one-step procedure, with increased yields in shorter times. The first experiments run in a common laboratory ultrasonic cleaner confirmed these predictions. Aryl halides, lithium wire, and zinc bromide when sonicated in diethyl ether or tetrahydrofuran (THF) yielded the corresponding diarylzinc without any noticeable side reaction.[20]

This method was found to be restricted to aryl derivatives as low or erratic yields were obtained from alkyl halides, with the exception of methyl iodide. The technique of sonication was changed in order to overcome this

(1) Previous paper in this series: Luche, J. L.; Pêtrier, C.; Dupuy, C. *Tetrahedron Lett.* **1984**, *25*, 3463–3466.
(2) Predoctoral fellow of CNPq (Brazil).
(3) Among the numerous procedures, the reduction of zinc halides with alkali metals gives highly reactive zinc slurries. See: Rieke, R. D.; Li, P. T. J.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4323–4324.
(4) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 1475–1478.
(5) Han, B. H.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 751–752.
(6) Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1981**, 1679–1680. Solladie-Cavallo, A.; Farkhani, D.; Fritz, S.; Lazrak, T.; Suffert, J. *Tetrahedron Lett.* **1984**, *25*, 4117–4120.
(7) Yamashita, J.; Inoue, Y.; Kondo, T.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2335–2336. Repic, O.; Vogt, S. *Tetrahedron Lett.* **1982**, *23*, 2729–2732.
(8) Bose, A. K.; Gupta, K.; Manhas, M. S. *J. Chem. Soc., Chem. Commun.* **1984**, 86–87. Han, B. H.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 5030–5032.
(9) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: Oxford, 1974; p 249.
(10) For recent examples see: Negishi, E.; Matsushita, H.; Kobayashi, M.; Rand, C. L. *Tetrahedron Lett.* **1983**, *24*, 3823–3824. Russel, C. E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1983**, *105*, 943–949. Tius, M. A.; Thurkauf, A. *J. Org. Chem.* **1983**, *48*, 3839–3841. Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340–348. Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841–870. Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158–163. Negishi, E.; Miller, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 6761–6763. Hayashi, T.; Hagihara, T.; Katsuro, Y; Kumada, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 363–364. Kozikowski, A. P.; Greco, M. N.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 6873–6874.
(11) Shono, T.; Nishiguchi, I.; Sasaki, M. *J. Am. Chem. Soc.* **1978**, *100*, 4314–4315. Kataoka, K.; Tsuruta, T. *Polym. J. (Tokyo)* **1977**, *9*, 595–604. Gilman, H.; Kirby, R. H. *J. Am. Chem. Soc.* **1941**, *63*, 2046–2048.
(12) Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F. T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181–5184. Ashby, E. C.; Chao, L. C.; Laemmle, J. *J. Org. Chem.* **1974**, *39*, 3258–3263. Jones, P. R.; Goller, S. L.; Kaufmann, W. J. *J. Org. Chem.* **1969**, *34*, 3566–3571. Grey, R. A. *J. Org. Chem.* **1984**, *49*, 2288–2289. See however the reactions of benzaldehyde with R_2Zn reagents: Ogun, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823–2824.
(13) Posner, G. H. "An Introduction to Synthesis Using Organocopper Reagents"; Wiley Intersciences: New York, 1980 and references cited therein.
(14) Still, W. C.; Macdonald, T. L. *Tetrahedron Lett.* **1976**, 2659–2662. Clive, D. L. J.; Farina, V.; Beaulieu, P. *J. Chem. Soc., Chem. Commun.* **1981**, 643–644. For a recent important improvement, see: Lipschutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. L. *Tetrahedron Lett.* **1984**, *25*, 5859–5862.
(15) Lipschutz, B. H.; Wilhem, R. S.; Kozlowski, J. *J. Org. Chem.* **1984**, *49*, 3938–3942.
(16) Sinclair, J. A.; Molander, G. A.; Brown, H. C. *J. Am. Chem. Soc.* **1977**, *99*, 954–956. Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178–184.
(17) Schwartz, J.; Carr, D. B.; Hansen, R. T.; Dayrit, F. M. *J. Org. Chem.* **1980**, *45*, 3053–3061.
(18) Schwartz, J.; Loots, M. J.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333–1340.
(19) Howkins, S. D. *J. Acoust. Soc. Am.* **1966**, *39*, 55–61.
(20) Luche, J. L.; Pêtrier, C.; Lansard, J. P.; Greene, A. E. *J. Org. Chem.* **1983**, *48*, 3837–3839.

0022-3263/85/1950-5761$01.50/0

Scheme II



limitation. Irradiations were performed in a glass reactor described in a previous paper,[1] with a titanium horn sonicator. The energy level was adjusted at the minimum giving the cavitation noise, and the cell was thermostated in a cooling bath. Under such conditions, i.e., with an efficient control of the reaction temperature and ultrasound energy, excellent reproducibility was obtained and most of the reactions investigated gave rise to nearly quantitative yields of the desired organozinc reagent. The first experiments were conducted in ethereal solvents, but we found of interest to prepare the reagents in other media, especially those enriched in hydrocarbons. Sonication of alkyl halides, metallic lithium, and zinc bromide in toluene–THF mixtures produced the expected organometallic almost quantitatively within ca. 20–40 min. In comparison the same reaction with stirring replacing sonication takes place much more slowly (1–2 h) with a yield lower by ca. 25%.

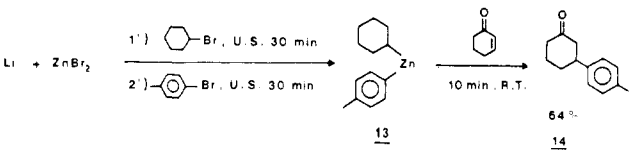
That the reaction effected in THF–toluene mixture is improved by ultrasonic irradiation can be interpreted in connection with the great importance of solvent effects in sonochemistry. In the presence of ultrasonic waves, a solvent is not only a dispersing medium but more importantly the *energy carrier*. As noted before by several authors, its physical properties must meet some specifications for optimal yields.[21,22] Indeed in Barbier reactions we observed that sonication has to be effected, all things being equal, for longer times in diethyl ether than in THF.[23] In the same way, dispersion of sodium metal as a very fine suspension occurs much more readily in xylene than in toluene.[24] Thus, although a toluene–THF mixture would seem less favorable to the formation of organometallic species in comparison to pure ethers, the sonochemical reaction occurs efficiently with all the organic halides tested.

From a mechanistic point of view, the hypothesis of an organolithium intermediate undergoing a metal exchange in a second step seems probable. An alternate reaction path would involve the reduction of the zinc bromide to the highly reactive, finely dispersed metal (Scheme I). Zinc suspensions prepared according to Rieke's method[3] gave only poor results under our sonication conditions.

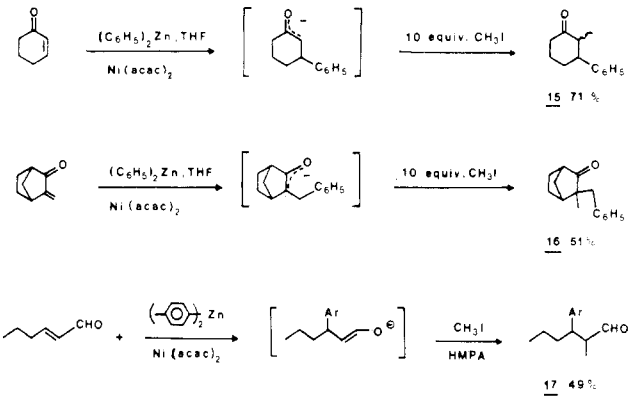
Reactions of Sonically Prepared Organozinc Reagents with Conjugated Carbonyl Compounds

This step is carried out by addition of the substrate and a catalytic amount of nickel acetylacetonate [$Ni(acac)_2$, 1% of the stoichiometry] in THF solution to the stirred solution of the reagent. The thermal stability of the zinc derivatives, in contrast to many of their organocopper equivalents,[25] allows the reaction to be run at room temperature in many instances. Reactions run in toluene–

Scheme III

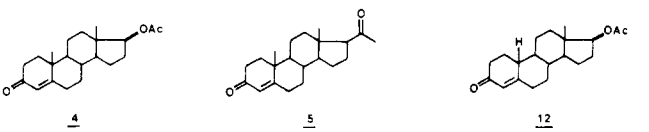


Scheme IV



THF mixtures frequently give cleaner products in comparison to pure ethereal solvents. The reaction time varies from a few minutes for reactive enones, to a few hours for hindered substrates. After completion determined by TLC, the desired product is obtained by the usual quenching and workup followed by purification by standard methods.

Arylation of unsaturated aldehydes gave satisfactory results[26] (see Scheme II). Conjugate addition to α-enones appear to be general. As shown in Table I, even β,β-disubstituted ones undergo a clean and efficient reaction, giving to this process a broader scope than that of the conjugate addition of organozincates.[27] It is interesting to point out the successful methylation of enone **2** while other methods are reported to fail (see Table I, ref *e*). Conjugate addition to Δ^4-3-keto steroids give the 5β-substituted adduct, as established by comparison with reported data (Table I, ref *i* and *j*). Arylation of steroidal enones which has not yet been reported, occurs with a satisfactory 52% yield from compound **12**, but low yields were noted from **4**, probably due to a severe steric hindrance of the addition.



From a stoichiometric point of view, it is important to note that the reagents that we use in this method are diorganometallic species which transfer only one organic residue. Experiments run with R–ZnX compounds, obtained by sonicating lithium and $ZnBr_2$ with only one equivalent of R–X, show that the organic group is transferred in very low yield. A possible method to overcome this drawback is offered by mixed diorganozinc reagents. As an example, the preparation of cyclohexyl(4-tolyl)zinc was effected in analogy to the method of Krause[28] and

(21) Suslick, K. S.; Schubert, P. R.; Goodale, J. W. *J. Am. Chem. Soc.* **1981**, *103*, 7342–7344. Sehgal, C.; Yu, T. J.; Sutherland, R. G.; Verrall, R. E. *J. Phys. Chem.* **1982**, *86*, 2982–2986. Suslick, K. S.; Gawienowski, J. J.; Schubert, P. R.; Wang, H. H. *Ultrasonics* **1984**, *22*, 33–36.

(22) Inter alia: Boucher, R. M. G. *Brit. Chem. Eng.* **1970**, *15*, 363–367. Jennings, B. H.; Townsend, S. N. *J. Phys. Chem.* **1961**, *65*, 1574–1579.

(23) Luche, J. L.; Damiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 7926–7927. Luche, J. L.; Pêtrier, C., unpublished observations.

(24) Luche, J. L.; Pêtrier, C.; Dupuy, C. *Tetrahedron Lett.* **1984**, *25*, 753–756.

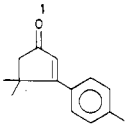
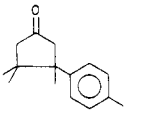
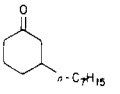
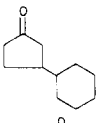
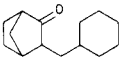
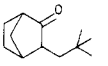
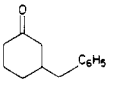
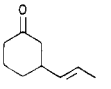
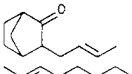
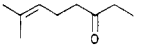
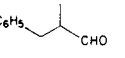
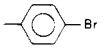
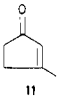
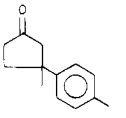
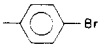
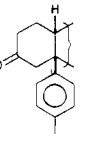
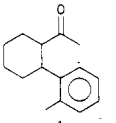
(25) Thermally stable heterocuprates reagents have recently been described: Bertz, S. H.; Dabbagh, G. *J. Org. Chem.* **1984**, *49*, 1119–1122.

(26) Conjugate additions of aryl group to α-enals are briefly described in a recent paper. See: De Souza Barboza, J. C.; Pêtrier, C.; Luche, J. L. *Tetrahedron Lett.* **1985**, *26*, 829–830.

(27) Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Tetrahedron Lett.* **1977**, 679–682.

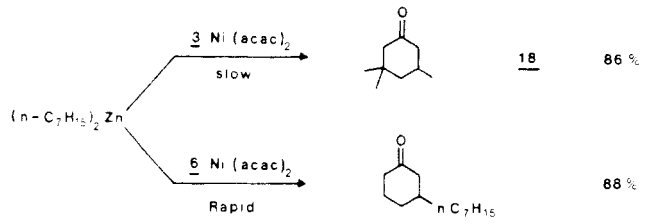
(28) Krause, E.; Fromm, W.; *Ber. Dtsch. Chem. Ges.* **1926**, *59B*, 931–934. See also; Kotchechkov, N. I.; Cheverdina, N. I.; Paleeva, I. E. *Bull. Soc. Chim. Fr.* **1963**, 1472–1474.

Table I

halide	solvent[a]	enone	reaction conditions[b]	adduct	yield, %[c] (lit. yield)
CH_3I	A	 1	4 to 20 °C, 1.5 h		73 (93[d])
	ether	 2	20 °C, 20 h		84[e] (0[f])
	B ether	 3	20 °C, 15 min		90 (88[g]) 75[h]
CH_3Br	ether	4	20 °C 24 h		73[i] (83[j])
	ether	5	20 °C 6 h		30[i,k] (30[l])
n-$C_7H_{15}Br$	A	 6	5 °C 5 min		88
	THF	 7	−28 to 20 °C, 1.5 h		29 (—[m])
	A	 8	20 °C 10 min		66
t-C_4H_9Br	A	8	0 °C 5 min		78
$C_6H_5CH_2Br$	A	6	24 °C 15 min		64[h]
	A	6	−78 to 20 °C, 1 h		83 (—[n])
	A	8	−78 to 20 °C, 1 h		74
	A	 9	−78 to 20 °C, 1 h		42
C_6H_5Br	THF	 10	−40 °C, 55 min		46
	A	 11	0 to 20 °C, 16 h		87 (82[p])
	ether	12	20 °C, 14 h		52[i]
	A	1	0 to 20 °C, 1 h		71

[a] Solvent A; toluene-tetrahydrofuran (5:1); solvent B, toluene-tetrahydrofuran (10:1). [b] See Experimental Section. [c] Isolated yield of purified material. [d] Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishikara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119-126. [e] Greene, A. E.; Lansard, J. P.; Luche, J. L.; Petrier, C. *J. Org. Chem.* **1984**, *49*, 931-932. [f] Casares, A.; Maldonado, L. A. *Synth. Comm.* **1976**, *6* 11-16. [g] Bagnell, L.; Jeffery, E. A.; Meisters, A.; Mole, T. *Aust. J. Chem.* **1975**, *28*, 801-815. [h] Magnesium used instead of lithium. [i] 13 equiv of reagent with respect to the substrate. [j] As the 17β-hydroxy compound. Fetizon, M.; Gramain, J. C. *Bull. Soc. Chim. Fr.* **1968**, 3301-3306. [k] 20% of unreacted 5 recovered. [l] Bagnell, L.; Meisters, A.; Mole, T. *Aust. J. Chem.* **1975**, *28*, 817-820. [m] No yield given. Wolff, S.; Schreiber, W. L.; Smith, A. B.; Agosta, W. C. *J. Am. Chem. Soc.* **1972**, *94*, 7797-7806. [n] No yield given. Casey, C. P.; Boggs, R. A. *Tetrahedron Lett.* **1971**, 2455-2458. [p] Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934-946.

Scheme V



shown in Scheme III. Its addition to cyclohexenone gives the arylated adduct **14**, with a high selectivity. Examples of such preferential transfer of unsaturated over saturated groups have been described in the case of mixed homocuprates (ref 15 and references cited therein). Our observations which agree with these findings will be developed in a future work.

The role of the catalytic amount of $Ni(acac)_2$ appears to be quite important. For example in its absence the reaction of di-4-tolylzinc to 2-cyclohexenone proceeds in a much reduced rate and methylation of enone **2**, does not occur. It can thus be assumed that the reaction mechanism has some analogies to the one proposed by Schwartz et al. for organozirconium addition reactions.[29] The final product before hydrolysis should therefore be a zinc or lithium enolate[30] of the saturated aldehyde or ketone. Trapping experiments of these enolates[31] indeed gave positive results. Thus, adding excess methyl iodide to the reaction mixture results in the formation of α-methyl, β-alkyl, or aryl ketones as exemplified in Scheme IV. The preparation of compound **15** illustrates the efficiency of the procedure. The 71% yield compares favorably to the 33% yield observed in the copper catalyzed addition of phenylmagnesium bromide to 2-methyl-2-cyclohexenone.[32] Trapping experiments were also successful with aldehyde enolates, a reaction which has not frequently been described.

The conjugate addition of organozinc reagents to α-enones depicted above appears to be of general synthetic utility. Side reactions can occur in some cases and should be mentioned.

Coupling of the reagent has been observed for diaryl derivatives. This reaction, which does not occur in the absence of the nickel catalyst,[33] is usually slow under our experimental conditions and does not interfere seriously with the addition. However, because of its possibility, the use of a slight excess of the zinc reagent is recommended.

Another undesired reaction can be observed when "reducing" reagents, i.e., those possessing hydrogen atoms β to the metal are used. This reaction is much slower than the alkyl addition and becomes a major process only when the steric crowding of the enone reduces the rate of the latter process.[34] An example is given in Scheme V.

In conclusion, a variety of organozinc derivatives can be efficiently and rapidly prepared by the technique of sonochemistry. Their addition in the presence of $Ni(acac)_2$ to α-enones leads to β-alkylated ketones in preparative yields, under very simple experimental conditions. Some side reactions can occur with reducing reagents and sterically hindered substrates. Nevertheless, the method can be a valuable alternative to the popular organocopper methods and should be of wide applicability in organic synthesis.

Experimental Section

Lithium, magnesium, and nickel acetylacetonate were obtained from Fluka; zinc bromide and chloride, from Alfa. If necessary $ZnCl_2$ and $ZnBr_2$ are dried by heating overnight at 150 °C in a vacuum oven. Toluene was distilled over $CaCl_2$, THF and diethylether from benzophenone–Na. Sonications were run in a glass vessel[1] with a Ultrason-Annemasse system (Sonimasse®) emitting a 30-KHz wave. Infrared spectra were recorded on a Perkin-Elmer 297 spectrometer. A Bruker WP 80 spectrometer was used for the NMR spectra in $CDCl_3$ solution. Mass spectra were recorded on a VG Micromass 7070 F spectrometer. Microanalyses were effected by the Service Central de Microanalyses (CNRS, Lyon). Aldehydes and some ketones giving unsatisfactory results were submitted to combustion analyses as crystalline derivatives, semicarbazones, or (2,4-dinitrophenyl)hydrazones (2,4-DNP).

General Procedure. Solvents used were pure diethyl ether, pure tetrahydrofuran, or a mixture of toluene–tetrahydrofuran (5:1 or 10:1). The organic halide (10 mmol) and 1.13 g (5.0 mmol) of zinc bromide in 23 mL of the required solvent are placed in the reaction flask under an argon atmosphere. The lithium wire (150 mg, 21 mmol) is placed in the holder under the ultrasonic probe. The flask is cooled in an ice bath and stirring with a magnetic bar ensures an homogeneous temperature. The energy level of the sonication is adjusted to the minimum giving the cavitation noise, and a black color is immediately developed.

After 30 min irradiation is discontinued and the resulting black solution (colorless from methyl iodide or bromide) is transferred via a syringe into a round-bottom flask with a magnetic bar, under argon. When necessary, the flask is cooled in an ice or dry-ice–acetone bath. A solution of the substrate (2.5–4.8 mmol) and 20 mg of $Ni(acac)_2$ in 2 mL of the required solvent is then added dropwise over a few minutes period. When necessary, this addition was made at a lower temperature, which then was allowed to rise spontaneously. The reaction was continued at room temperature for the time indicated in Table I. After disappearance of the starting material (TLC), the mixture is poured into saturated aqueous NH_4Cl and the product worked up and isolated in the usual manner. Purification is effected by column chromatography (SiO_2) and the material identified by the usual physical methods.

3-*n*-Heptylcyclohexanone: oil; IR (neat) 1705, 1450, 1220 cm^{-1}; NMR 2.6–1.4 (m, 8 H), 1.3 (br s, 13 H), 0.9 (t, 3 H) ppm; MS, *m/e* 196 (M^+), 97, 69, 55. Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.52. Found: C, 79.31; H, 12.20.

3-(Cyclohexylmethyl)bicyclo[2.2.1]heptan-2-one: oil; IR (neat) 1740, 1440 cm^{-1}; NMR 2.6 (m, 2 H), 2.2–0.8 (m, 20 H) ppm; MS, *m/e* 206 (M^+), 110, 82, 67, 55. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.21; H, 10.47.

3-(2,2-Dimethylpropyl)bicyclo[2.2.1]heptan-2-one: oil; IR (neat) 1740, 1470, 1360, 1080, 940 cm^{-1}; NMR 2.7 (m, 2 H), 2.1–1.0 (m, 9 H), 0.9 (s, 9 H) ppm; MS, *m/e* 181 $(M + 1)^+$, 180, 165, 152, 124, 123, 112, 95, 81. 2,4-DNP derivative: mp 155–157 (ethanol). Anal. Calcd for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.72; H, 6.42; N, 15.61.

3-(Phenylmethyl)cyclohexanone: oil; IR (neat) 1705, 1600, 1490, 1450, 1220, 720, 700 cm^{-1}; NMR 7.4–7.0 (m, 5 H), 3.0–1.2 (br m, 11 H) ppm; MS, *m/e* 188 (M^+), 130, 97, 91, 69, 55. Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.66; H, 8.63.

3-(2-Butenyl)bicyclo[2.2.1]heptan-2-one: oil (mixture of stereoisomers); IR (neat) 3000, 2950, 1740, 1450, 1160, 1070, 965, 940 cm^{-1}; NMR 5.7–5.1 (m, 2 H), 2.7–1.2 (m, 11 H), 1.65 (2 d, 3 H) ppm; MS, *m/e* 165 $(M + 1)^+$, 164, 123, 95, 79, 67. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.41; H, 9.90.

2-Methyl-3-phenylpropanal: oil; IR (neat) 3020, 2950, 2700, 1715, 1600, 1490, 1445, 920, 740, 700 cm^{-1}; NMR 9.68 (d, 1 H), 7.20 (m, 5 H), 3.10 (m, 1 H), 2.55 (m, 2 H), 1.05 (d, 3 H) ppm;

(29) Dayrit, F. M.; Gladkowski, D. E.; Schwartz, J. *J. Am. Chem. Soc.* **1980**, *102*, 3976–3978.

(30) Four equivalents of lithium halide per mole of organozinc are present in the reaction medium. Possible cation exchanges have not yet been studied.

(31) Conjugate addition followed by α-alkylation ("tandem reaction") has been achieved in many instances in organocopper chemistry—see ref 13, p 47.

(32) Sharma, M. *J. Am. Chem. Soc.* **1975**, *97*, 1153–1160.

(33) Organolithium and magnesium reagents are oxidatively coupled by transition metal catalysts. March, J. "Advanced Organic Chemistry, Reactions, Mechanisms and Structure", 2nd ed.; McGraw-Hill Kogakusha: Tokyo, 1977; pp 664–665.

(34) Caporusso, A. M.; Giacomelli, G.; Lardicci, L. *J. Org. Chem.* **1982**, *47*, 4640–4644.

MS, m/e 148, 91, 78, 71. 2,4-DNP derivative: mp 121–2 °C (methanol). Anal. Calcd for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.71; H, 4.96; N, 16.75.

17β-Acetoxy-5β-(4-methylphenyl)estran-3-one: mp 186–187 °C (methanol); $[\alpha]^{21}_D$ −21.8° (c 1.0, $CHCl_3$); IR (KBr) 1730, 1700, 810 cm^{-1}; NMR 7.4–7.0 (m, 4 H), 4.65 (t, 1 H), 2.8 (q AB system, 2 H), 2.3 (s, 3 H), 2.3–1.1 (m, 20 H), 2.05 (s, 3 H), 0.85 (s, 3 H) ppm; MS, m/e 409 $(M + 1)^+$, 408 (M^+), 351, 350, 290. Anal. Calcd for $C_{27}H_{36}O_3$: C, 79.37; H, 8.88. Found: C, 79.31; H, 8.73.

1-[2-(2-Methylphenyl)cyclohexyl]ethan-1-one: oil; IR (neat) 3020, 1700, 1600, 1440, 1340, 1160, 780, 700 cm^{-1}; NMR 7.4–6.9 (m, 4 H), 3.2–2.4 (m, 3 H), 2.3 (s, 3 H), 2.2–1.1 (m, 7 H), 1.7 (s, 3 H) ppm; MS, m/e 216 (M^+), 173, 131, 111, 105, 91. 2,4-DNP derivative: mp 122–3 (ethanol). Anal. Calcd for $C_{21}H_{24}N_4O_4$: C, 63.62; H, 6.10; N, 14.13. Found: C, 63.74; H, 5.94; N, 14.13.

Preparation and Reaction of the Mixed Reagent, (4-Tolyl)cyclohexylzinc. In 20 mL of dry toluene and 2 mL of dry THF 652 mg (4 mmol) of cyclohexyl bromide, 910 mg (4 mmol) of zinc bromide, and 150 mg (21 mmol) of lithium wire were sonicated as described above. After consumption of the organic halide (TLC check), 684 mg (4 mmol) of 4-bromotoluene in 1 mL of THF was added and sonication was effected for another 30-min period.

Following the standard procedure, 288 mg (3 mmol) of cyclohexenone and 15 mg of $Ni(acac)_2$ in 1 mL of THF were added to the reagent at room temprature and the reaction was allowed to proceed for 10 min. After quenching and workup as usual and purification on a silica gel column, 3-(4-methylphenyl)cyclohexanone **14** was obtained in 64% yield.

3-(4-Methylphenyl)cyclohexanone: oil; IR (neat) 1705, 1500, 1220, 810, 800 cm^{-1}; NMR 7.1 (s, 4 H), 3.2–1.5 (m, 9 H), 2.3 (s, 3 H) MS, m/e 189 $(M + 1)^+$, 188 (M^+), 145, 131, 118, 91. Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.65; H, 8.67.

Conjugate Addition–Alkylation of 2-Hexenal. Bis(2-methylphenyl)zinc (5 mmol) in 23 mL of dry THF were prepared as described above and transferred under argon into a round-bottom flask with magnetic stirrer. $Ni(acac)_2$ (20 mg) in 1 mL of THF was added and the mixture was cooled to −40 °C. 2-Hexenal (0.442 g, 4.5 mmol) was added in 2 mL of THF and stirring was continued for 30 min; 2 mL of dry HMPA were then introduced followed 3 min later by 2.8 mL of methyl iodide (ca. 10 equiv). After 55 min of stirring, the mixture was quenched with saturated aqueous NH_4Cl at 0 °C, then extracted with diethyl ether. The organic phase was washed with aqueous sodium thiosulfate, then worked up as usual to give an oil which was purified by column chromatography. Compound **17** (oil, 0.449 g, 49% yield) was obtained as a 3:1 mixture of diastereomers which could not be resolved by silica-gel or vapor-phase chromatography: IR (neat) 3050, 3010, 2850, 2700, 1720, 1485, 1460, 1380, 920, 895, 760, 730 cm^{-1}; NMR 9.7 (d, 1 H, major isomer), 9.5 (d, 1 H, minor isomer), 7.3 (s, 4 H), 3.2 (m, 1 H), 2.6 (m, 1 H), 2.3 (s, 3 H), 1.8–1.4 (m, 3 H), 1.3–0.7 (m, 4 H), 1.16 (d, 3 H of minor isomer), 0.87 (d, 3 H of major isomer) ppm; MS, m/e 204 (M^+), 147, 105, 91. 2,4-DNP derivative: mp 169–170 (methanol). Anal. Calcd for $C_{20}H_{24}N_4O_4$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.63; H, 6.28; N, 14.49.

Enolate Trapping Experiments. Diphenylzinc (4 mmol) was prepared in THF as described in the general procedure. Cyclohexenone **7** (3 mmol) and $Ni(acac)_2$ catalyst were added in 1 mL of THF to the reagent, and the mixture was stirred for 2 h at room temperature. After the mixture was cooled to 0 °C (ice bath), 30 mmol (10 equiv) of methyl iodide were added over a 5-min period. The mixture was allowed to warm up and stirred at room temperature for 12 h. After the usual quenching and workup the crude mixture was purified by column chromatography to give 2-methyl-3-phenylcyclohexanone (**15**) in 71% yield: oil; IR (neat) 3050, 3020, 1700, 1600, 1450, 1220, 1020, 920, 780, 750, 700 cm^{-1}; NMR 7.2 (m, 5 H), 2.8–2.3 (m, 4 H), 2.2–1.5 (m, 4 H), 0.8 (d, 3 H) ppm; MS, m/e 188 (M^+), 117, 97, 91. Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.81; H, 8.66. 2,4-DNP derivative: mp 220–221 °C (ethanol) lit.[32] 220–221 °C. Following the same procedure, compound **16** was obtained in 51% yield.

3-Methyl-3-(phenylmethyl)bicyclo[2.2.1]heptan-2-one (16): mp 54 °C (hexane–trace of ethyl acetate); IR (film) 3050, 3010, 1735, 1600, 1480, 1460, 1440, 1360, 1050, 740, 700 cm^{-1}; NMR 7.2 (s, 5 H), 2.7 (s, 2 H), 2.6 (m, 1 H), 2.3–1.3 (m, 7 H), 0.8 (s, 3 H) ppm; MS, m/e (215 $(M + 1)^+$, 214 (M^+), 186, 146, 145, 117, 95, 91. Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.11; H, 8.61.

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3,3′-Disubstituted 2,2′-Biphenols: Synthesis of Nonplanar, Tetradentate Chelating Ligands

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The Claisen rearrangement of 2,2′-bis(allyloxy)biphenyl provides an appropriate starting material for the preparation of free and benzyl-protected 3,3′-bis(2-hydroxyethyl)- and 3,3′-bis(3-hydroxy-1-propyl)-2,2′-biphenol. The alcohols are converted via their mesylates to several new metal chelating agents, 3,3′-bis(2-X-ethyl)- and 3,3′-bis(3-Y-propyl)-2,2′-biphenol (X = methylthio or 1-pyrazolyl and Y = methylthio or dimethylamino).

Our interest in preparing models for the active site of the molybdenum oxidases[1] led us to consider the synthesis of new ligands that would bind to a metal ion, leaving two vacant cis-coordination sites. For Mo(VI) complexes, a flexible ligand would have been sufficient since most Mo(VI) systems have two cis Mo=O groups in their coordination spheres that dictate the overall geometry.[2] However, we desired a rigid ligand framework because catalytically active Mo complexes cycle through the +4, +5, and +6 valences and we wanted to be able to minimize reorganization of the coordination environment during catalysis. At the same time, we recognized that the creation of vacant cis sites by ligand design should have wide

(1) Spence, J. T. *Coord. Chem. Rev.* **1983**, *48*, 59.

(2) (a) Tatsumi, K.; Hoffmann, R. *Inorg. Chem.* **1980**, *19*, 2656. (b) Stiefel, E. I. *Prog. Inorg. Chem.* **1973**, *22*, 1.

0022-3263/85/1950-5765$01.50/0