75717-51-0; **9f**, 75717-52-1; **9g**, 60965-23-3; **9h**, 75717-53-2; **9i**, 75717-54-3; **15**, 75717-55-4; **15** *O*-acetyl derivative, 75717-56-5; **15**, 75717-57-6; **15** imine *N,O*-diacetyl derivative, 75717-58-7; 2-hydroxyphenol, 120-80-9; 6-methoxy-2-hydroxy-α-chloroacetophenone, 75717-59-8; 4-hydroxyphenol, 123-31-9.

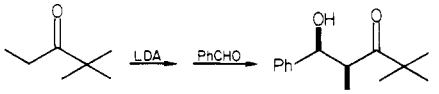
Acyclic Stereoselection. 10. A General Synthesis of *erythro*-α-Alkyl-β-hydroxy Ketones[1]

Charles T. White and Clayton H. Heathcock*

Department of Chemistry, University of California, Berkeley, California 94720

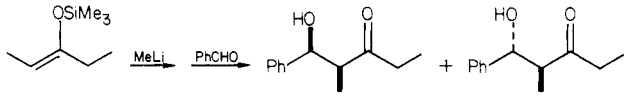
Received June 11, 1980

Ketones having one bulky group attached to the carbonyl usually give rise to homogeneous *Z* enolates, which condense with aldehydes to give erythro aldols.[2] Thus, ethyl *tert*-butyl ketone reacts with benzaldehyde to give aldol **1**.[2,3] However, other ketones give mixtures of *Z* and



1

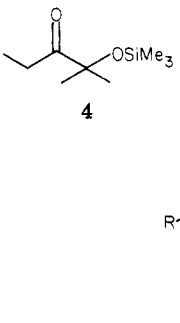
E enolates, which undergo the aldol condensation with various degrees of kinetic stereoselectivity. Even when pure *Z* enolates of such ketones are obtained by indirect means, kinetic stereoselection is not complete. For example, the *Z* enolate of diethyl ketone reacts with benzaldehyde to give the erythro and threo aldols **2** and **3** in

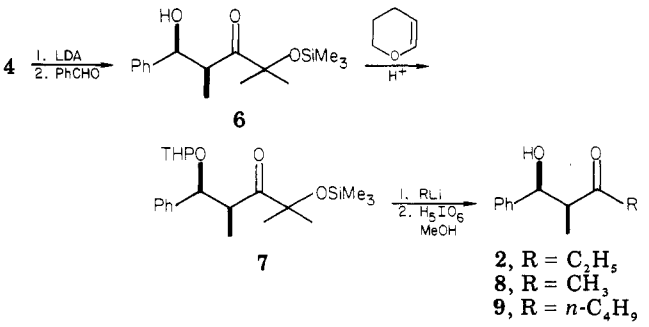


2 **3**

a ratio of only 90:10.[2,4] In this note, we put forth a general method whereby pure erythro aldols such as **2** may be obtained with high stereoselectivity (≥80:1).

Ketone **4** has previously been used to convert a variety of aldehydes into erythro β-hydroxy carboxylic acids[2] and aldehydes. For preparation of an acid, the initial aldol **5** is oxidized by periodic acid.[2] For preparation of an aldehyde, the aldol is reduced with lithium aluminum hydride and then cleaved with sodium periodate.[1] In principle, ketones are obtainable by addition of an organometallic reagent, followed by periodic acid oxidation. In practice, the process is more successful if the initial aldol is protected as its tetrahydropyranyl ether prior to addition of the organometallic reagent. Alkyllithium reagents add to the resulting protected aldols, and the products are then cleaved to obtain the pure erythro β-hydroxy ketones. Grignard reagents are not suitable, as complex mixtures are obtained. The process has been demonstrated with the preparation of aldols **2**, **8**, and **9** in overall yields of





52–70%. A separate deprotection step is not necessary; the tetrahydropyranyl group is conveniently removed in the course of the vicinal diol cleavage. Note that the process not only accomplishes stereospecific synthesis of aldols derived from a wide range of simple ketones but also allows the preparation of *regiospecified* aldols. Thus, **9** is the aldol resulting from condensation of 3-heptanone specifically at C_2.

Experimental Section

For general experimental details, see ref 2.

2,4-Dimethyl-1-phenyl-1-(tetrahydropyranyloxy)-4-(trimethylsiloxy)-3-pentanone (7). To a solution of 0.46 mL (3.3 mmol) of diisopropylamine in 10 mL of dry THF at 0 °C was added 2.2 mL (3.3 mmol) of a 1.5 M solution of *n*-butyllithium in hexane. After 10 min the solution was cooled to −70 °C and 0.56 g (3.0 mmol) of 2-methyl-2-(trimethylsilyloxy)-3-pentanone (**4**)[2] was added over a 3-min period. After the mixture was stirred at −70 °C for 30 min, 0.31 mL (3.0 mmol) of benzaldehyde was added, and the mixture was stirred for 2 min and quenched with 10 mL of saturated $NaHCO_3$. After warming to room temperature, the reaction mixture was extracted two times with ether. The ether layers were combined, dried (Na_2SO_4), and evaporated to give 0.89 g (100%) of **6** as a colorless oil. The crude product was dissolved in 18 mL of methylene chloride and treated with 1.0 mL (10 mmol) of dihydropyran. *p*-Toluenesulfonic acid was added in 1-mg portions every 15 min until TLC indicated some formation of product (TLC: 15% ether in hexanes; **6**, R_f 0.19; **7**, R_f 0.36). The reaction was allowed to stand for 1 h, the solvent was removed in vacuo, and the residue was purified by chromatography on 40 g of silica gel (15% ether/hexanes) to yield 0.88 g (78%) of **7** (colorless oil) as a 1:1 mixture of diastereomers: IR (thin film) 1710, 1450, 1250, 1200, 1040, 1010, 840 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (9 H, s), 0.61 (s) and 0.67 (3 H, s), 1.13 (3 H, s), 1.3 (3 H, 2 d), 4.7 (1 H, 2 d), 7.1 (5 H, br s).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 66.63; H, 9.05. Found: C, 67.01; H, 9.26.

4-Hydroxy-3-methyl-4-phenyl-2-butanone (8). To a solution of 0.27 g (0.71 mmol) of protected ketol **7** in 5 mL of dry THF was added 1.1 mL (1.5 mmol) of 1.4 M methyllithum in ether. After being stirred for 4 h at room temperature the mixture was treated with 5 mL of saturated $NaHCO_3$. The reaction mixture was extracted two times with ether. The ether layers were combined, dried ($MgSO_4$), and evaporated to give 0.25 g of crude product as a pale yellow oil which was used without further purification. This material was dissolved in a mixture of 5 mL of dioxane and 10 mL of 2:1 methanol–water and 1.1 g (4.8 mmol) of H_5IO_6 was added. After being stirred for 16 h at room temperature the reaction mixture was diluted with water and extracted three times with 25 mL of CH_2Cl_2. The CH_2Cl_2 layers were

(1) For part 9, see C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, and D. VanDerveer, *J. Org. Chem.*, **45**, 3846 (1980).
(2) C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.* **45**, 1066 (1980).
(3) J.-F. Dubois and P. Fellman, *C. R. Hebd. Seances Acad. Sci., Ser. C.*, **274**, 1307 (1972).
(4) See also J.-E. Dubois and P. Fellman, *Tetrahedron Lett.*, 1225 (1975).

0022-3263/81/1946-0191$01.00/0

combined, washed one time with saturated $Na_2S_2O_3$, dried ($MgSO_4$), and evaporated to give 0.12 g (87%) of 4-hydroxy-3-methyl-4-phenyl-2-butanone (8) as a nearly colorless oil: IR (thin film) 3450, 1700, 1450, 1360, 1180, 1020, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (3 H, d, J = 6), 2.05 (3 H, s), 2.8 (1 H, dq, J = 6, 4), 3.4 (1 H, br s), 4.93 (1 H, d, J = 4), 7.18 (5 H, s). An analytical sample was prepared by chromatography on silica gel (50% ether/hexanes).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.03; H, 7.89.

1-Hydroxy-2-methyl-1-phenyl-3-pentanone (2). The foregoing procedure was repeated, using ethyllithium instead of methyllithium. Aldol **2** was obtained in 65% yield as a colorless oil after chromatography: IR (thin film) 3450, 1700, 1450, 1010, 980, 770, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (3 H, t, J = 7), 1.05 (3 H, d, J = 7), 2.4 (2 H, dq), 2.9 (1 H, dq, J = 4, 7), 4.93 (1 H, d, J = 4), 7.22 (5 H, s).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.14; H, 8.38.

1-Hydroxy-2-methyl-1-phenyl-3-heptanone (9). The foregoing procedure was employed using n-butyllithium. Aldol **9** was obtained in 88% yield as a colorless oil after chromatography: IR (thin film) 3450, 1700, 1450, 1020, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (3 H, d, J = 7), 2.4 (2 H, m), 2.9 (1 H, dq, J = 4, 7), 4.90 (1 H, d, J = 4), 7.23 (5 H, s).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.55; H, 9.16.

Acknowledgment. This reasearch was supported by a grant from the United States Public Health Service (Grant AI-15027).

Registry No. 2, 71699-15-5; **4**, 72507-50-7; **6**, 71699-17-7; **7** (isomer 1), 75600-08-7; **7** (isomer 2), 75658-53-6; **8**, 75600-09-8; **9**, 75600-10-1; benzaldehyde, 100-52-7; dihydropyran, 110-87-2; *erythro*-2,5-dihydroxy-2,4-dimethyl-1-phenyl-3-pentanone, 72658-44-7.

Preparation of Thermally Stable and Soluble Mesitylcopper(I) and Its Application in Organic Synthesis

Tetsuo Tsuda, Tetsuo Yazawa, Katsuhiko Watanabe, Tomoyuki Fujii, and Takeo Saegusa*

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto 606, Japan

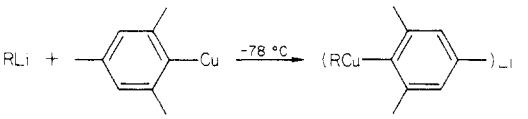
Received June 11, 1980

Copper(I) *tert*-butoxide, *t*-BuOCu,[1] which is the first example of thermally stable copper(I) alkoxide has been frequently used in organic synthesis as a metalation reagent[2] and as a "holding group" in a mixed lithium cuprate reagent (R_TCuOBu-*t*)Li.[3] However, in the metalation reaction, the liberation of *tert*-butyl alcohol from *t*-BuOCu puts a limitation to the variety of active-hydrogen compounds to be metalated. Moreover, the relatively low solubility of *t*-BuOCu in organic solvents is inconvenient for its use. Here we report the preparation of thermally stable and soluble mesitylcopper(I) (1) and its utilization in organic synthesis as an efficient metalation reagent and as a useful "holding group" in the mixed lithium cuprate reagents.

1 was prepared as a pale yellow solid by the reaction of mesitylmagnesium bromide with copper(I) chloride. 1 is thermally stable up to 100 °C. 1 reacted with allyl bromide in hexamethylphosphoric triamide (HMPA) at 90 °C to give allylmesitylene almost quantitatively. At 120 °C, 1 partly decomposed in HMPA to produce bimesityl. Ordinary organocoppers(I) including alkylcoppers(I) are insoluble in common organic solvents due to their associations.[4] 1 is highly soluble in various organic solvents such as benzene, ether, tetrahydrofuran (THF), and HMPA and is partly soluble in *n*-pentane and *n*-hexane. Recently an *o*-methyl-substituted phenylcopper(I) has been shown to have a high thermal stability and a low degree of association.[5]

On metalation of active-hydrogen compounds, 1 releases mesitylene which is inert and easily removable. On the basis of this property together with its high solubility and stability, 1 functions as an efficient metalation reagent to produce various types of copper(I) complexes without the concurrent production of salts. The metalation reactivity of 1 is higher than that of *t*-BuOCu. 1 easily metalates primary and secondary amines whereas *t*-BuOCu cannot metalate these amines. For example, evaporation of a THF solution of 1 and diethylamine in vacuo after an overnight reaction at ambient temperature gave copper(I) diethylamide. To our knowledge, this is the first example of isolation of a copper(I) amide derived from an ordinary amine.[6] 1 also metalated *tert*-amyl mercaptan and *tert*-butyl alcohol to produce copper(I) *tert*-amylmercaptide and *tert*-butoxide, respectively.

Several mixed lithium cuprate reagents (R_TCuR)Li having a nontransferable ligand R (a holding group) have been developed for the purpose of saving a valuable transferring group.[3,7] Recently Corey et al. have reported the use of soluble $MeOC(CH_3)_2C{\equiv}CCu$ as a precursor for mixed cuprates.[8] 1 was found to be effective for the formation of a soluble mixed cuprate reagent (2) in which



1

2a, R = *n*-Bu
b, R = *sec*-Bu
c, R = *t*-Bu

the mesityl group acts as a nontransferable holding group. **2a** and **2b** effected a selective conjugate addition of the R group to cyclohexenone (Table I). In **2c**, however, both mesityl and *tert*-butyl groups were transferred at a comparable ratio. The conjugate addition of organocuprate reagents to α,β-unsaturated aldehydes has not been widely studied.[9] **2a** caused the conjugate addition to *trans*-2-hexenal, transferring its *n*-butyl group selectively (Table I).

Recently several complex copper hydride reagents such as LiCuRH,[10] $LiAl(OCH_3)_3H$–CuI,[11] and Li_2CuH_3[12] have

(1) Tsuda, T.; Hashimoto, T.; Saegusa, T. *J. Am. Chem. Soc.* **1972**, *94*, 658.

(2) Logue, M. W.; Moore, G. L. *J. Org. Chem.* **1975**, *40*, 131. Cohen, T.; Berninger, R. W.; Wood, J. T. *Ibid.* **1978**, *43*, 837. Rogic, M. M.; Demmin, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 5472. Sir Cornforth, J.; Sierakowski, A. F.; Wallace, T. W. *J. Chem. Soc., Chem. Commun.* **1979**, 294.

(3) Posner, G. H.; Whitten, C. E. *Tetrahedron Lett.* **1973**, 1815. Posner, G. H.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 3076. Posner, G. H.; Whitten, C. E.; Sterling, J. J. *Ibid.* **1973**, *95*, 7788.

(4) Jukes, A. E. *Adv. Organomet. Chem.* **1974**, *12*, 251–322.

(5) Hofstee, H. K.; Boersma, J.; van der Kerk, G. J. M. *J. Organomet. Chem.* **1978**, *144*, 255.

(6) Various copper(I) amides derived from ordinary amines including ammonia and aniline have been prepared by the metalation using 1, which will be published elsewhere together with their characterizations.

(7) Corey, E. J.; Beams, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210. House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 3893.

(8) Corey, E. J.; Floyd, D.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418.

(9) Posner, G. H. *Org. React.* **1972**, *10*, 24.

(10) Boeckman, R. K., Jr.; Michalak, R. *J. Am. Chem. Soc.* **1974**, *96*, 1624. Masamune, S.; Bates, G. S.; Georghiou, P. E. *Ibid.* **1974**, *96*, 3686.

(11) Semmelhack, M. F.; Stauffer, R. D. *J. Org. Chem.* **1975**, *40*, 3619.

(12) Ashby, E. C.; Lin, J. J.; Goel, A. B. *J. Org. Chem.* **1978**, *43*, 183.

0022-3263/81/1946-0192$01.00/0