M I in toluene (cyclopentane) yielded the rate constants k and the activation parameters ($\Delta H^{\ddagger}$ = 17 (16) ± 2 kcal/mol, $\Delta S^{\ddagger}$ = 13 (10) ± 3 cal/(mol deg) for the isomerization II $\rightarrow$ IV.

Isomerization could occur by intramolecular nitrogen lithium exchange and/or intramolecular carbon lithium exchange.[16] Degenerate rearrangement of IV (IV $\rightleftharpoons$ II $\rightleftharpoons$ IV′) interchanges the diastereotopic protons of this species. The temperature-dependent line shape of the CH_2Li protons of I in pentane-d_{12} could be simulated on this basis. Apparently, exchange of the methylene protons by inversion at C-α[17] is much slower and need not be taken into account.

Supplementary Material Available: Tables of X-ray crystallographic data for I (6 pages). Ordering information is given on any current masthead page.

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[16] Cf.: Fraenkel, G.; Henrichs, M.; Hewitt, M.; Su, B. M. *J. Am. Chem. Soc.* **1984**, *106*, 255.

[17] Fraenkel, G.; Beckenbaugh, W. E., Yang, P. P. *J. Am. Chem. Soc.* **1976**, *98*, 6878.

Highly Stereoselective Reduction of α-Substituted β-Keto Amides by Means of Hydrosilane/F^- and Hydrosilane/H^+ Reagent. A Practical Approach to Aldols of Both Threo and Erythro Configurations

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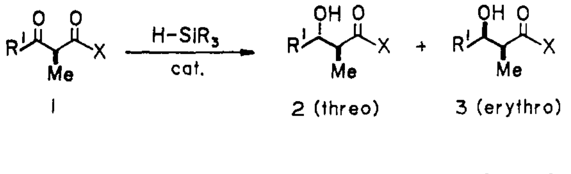
Although the aldol reaction has been well established as a reliable method for the construction of acyclic systems having adjacent chiral centers,[1] difficulties[2] frequently encountered in this process have stimulated search for more practical alternative approaches to the aldols. Stereoselective reduction of α-substituted β-keto acid derivatives has been recognized to be the solution.[3,4] However, it still seems to be problematic in synthetic viewpoints. For example, erythro-selective reduction of high selectivity[4] requires the use of commercially nonavailable pyrophoric zinc borohydride,[5] and threo selective reduction[6] of the same substrates remains unsolved yet. We report that hydrosilane-based reduction[7] of α-substituted β-keto amides proceeds under high stereocontrol. Our disclosure offers a practical approach to aldols of both threo and erythro configurations.[8,9]

The β-keto amide **1a** (1 mmol) was treated with dimethylphenylsilane (1.2 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone (DMPU) (2 mL) in the presence of tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF)[10] (10 mol %) at 0 °C for 12 h. After acid treatment (1 M HCl–MeOH, room temperature, 0.25 h)[11] followed by usual workup, an analysis of the crude mixture[12] by 400-MHz ^1H NMR showed exclusive formation of the threo isomers **2a** (>99% selectivity). Isolation of the pure material (98% yield) was carried out by preparative TLC (silica gel, AcOEt–hexane 1:1). Other examples are shown in Table I. High threo selectivities (>98%) were also recognized for **1b–d** (R^1 = aryl) in sharp contrast to the conventional hydride reduction.[6] The threo selectivity is explained in terms of the Felkin-type model.[13] An ester derivative, methyl 2-benzoylpropionate (**1g**), failed to be reduced due possibly to the abstraction of an active methine proton by the fluoride ion catalyst.[14] In the reduction of **1e** and **1f** (R^1 = alkyl), the erythro isomers were formed predominantly.[15]



Highly erythro-selective reduction of **1** was also achieved by means of hydrosilane/H^+ reagent[16] (Table II). When **1a** (1 mmol) was allowed to react with dimethylphenylsilane (1.2 mmol) in trifluoroacetic acid (2 mL) at 0 °C for 6 h, the erythro alcohol **3a** was afforded exclusively in 98% isolated yield. The erythro selectivity is ascribed to the proton-bridged Cram's cyclic model.[17] The amide derivatives having alkyl, alkenyl, and aryl groups for R^1 underwent the erythro-selective reduction (selectivity >98%). The ester derivatives **1g** also gave erythro isomer **3g** predominantly, but no selectivity was observed in the case of **1l** (R^1 = Me) which probably failed to be reduced through a rigid cyclic transition state.

Noteworthy is that no epimerization at the chiral center takes place during the reaction under these acidic conditions: an optically active substrate **1k**[18] was succesfully transformed to methyl *erythro*-2-methyl-3-phenyl-3-hydroxypropanoate[19] by $PhMe_2SiH/H^+$ reduction followed by methanolysis (0.1 M MeONa in MeOH, 0 °C, 15 min, 93%) without loss of the enantiomeric purity.[21]

The stereocontrolled reduction of α-methyl-β-keto amide opens a way to each diastereomer of α-aryl-β-methyl-γ-aminopropyl alcohols of pharmacological interest.[22] For example, $PhMe_2SiH/F^-$ or H^+ reduction of **1m** followed by $LiAlH_4$ reduction gave *threo* or *erythro*-γ-amino alcohol **4**,[23] respectively.

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[1] (a) Heathcock, C. H. "Asymmetric Synthesis"; by Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 111–212. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Topics Stereochem.* **1984**, *13*, 1–116.

[2] Careful experiments at low temperatures are required for high selectivities. Strongly basic conditions of lithium enolate reactions or oxidative workup involved in boron enolate reactions are not applicable to the substrates which are sensitive to these conditions.

[3] Canceill, J.; Jacques, J. *Bull. Soc. Chem. Fr.* **1970**, 2180.

[4] (a) Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641. (b) Nakata, T.; Kuwabara, T.; Tani, Y.; Oishi, T. *Ibid.* **1982**, *23*, 1015. (c) Ito, Y.; Yamaguchi, M. *Ibid.* **1983**, *24*, 5385. (d) Dipardo, R. M.; Bock, M. G. *Ibid.* **1983**, *24*, 4805. (e) Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc.* **1984**, *106*, 1154.

[5] Gensler, W. J.; Johnson, F.; Sloan, A. D. B. *J. Am. Chem. Soc.* **1960**, *82*, 6074.

[6] Although it is reported that KBH_4[3] or Me_4NBH_4[4a] reduction of methyl 2-benzoylpropionate gave the threo alcohol predominantly, the selectivity is moderate (threo:erythro = ca. 7:3). **Note Added in Proof**: Quite recently, Yamaguchi et al. found threo-selective reduction of β-keto amides with $KBEt_3H$. Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 4643.

[7] (a) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 4629. (b) Hiyama, T.; Kobayashi, K.; Fujita, M. *Tetrahedron Lett.* **1984**, *25*, 4959.

[8] Although racemic **1** was employed unless noted, one enantiomer is shown for the sake of simplicity.

[9] The relative stereochemical nomenclature: Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598, ref. 32.

[10] For the fluoride ion source, TASF was used throughout this work instead of tetrabutylammonium fluoride (TBAF) employed in the previous work.[7] Preparation of TASF: *U.S. Patent* 3 940 402; *Chem. Abstr.* **1976**, *85*, 6388*j*.

[11] In a parallel experiment without acid treatment, the *O*-silyl derivative was isolated in >90% yield.

[12] Rapidly filtered through silica gel short-path column to remove the solvent.

[13] (a) Chêrest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61.

[14] Fluoride ion has a weak basicity in aprotic polar solvents: Parker, A. J. *Adv. Org. Chem.* **1965**, *5*, 1. Yakobson, G. G.; Akhmetova, N. E. *Synthesis* **1983**, 169.

[15] Enantioface selectivity in the hydrosilylation of prochiral ketones catalyzed by fluoride ion is discussed; Fry, J. L.; McAdam, M. A. *Tetrahedron Lett.* **1984**, *25*, 5859.

[16] Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633.

[17] Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245.

[18] Prepared according to the method reported by Evans et al.: $[\alpha]^{20}_D$ +153° (c 0.5, CH_2Cl_2) (lit.[4e] $[\alpha]_D$ +154.5° (c 0.5, CH_2Cl_2)).

[19] $[\alpha]^{25}_D$ −24.7° (c 1, $CHCl_3$); lit.[20] $[\alpha]^{25}_D$ −23.1° (c 3.2, $CHCl_3$).

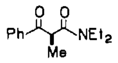
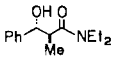
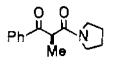
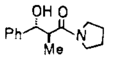
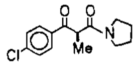
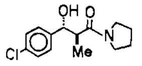
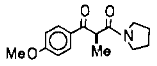
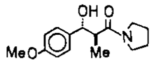
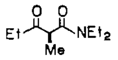
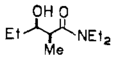
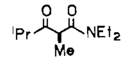
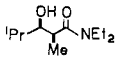
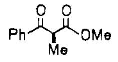
[20] Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

[21] The enantiomeric purity of the product was shown to be >98% by 400-MHz ^1H NMR analysis using $Eu(tfc)_3$ as the chiral shift reagent.

[22] (a) Ilarionov, I.; Avramova, P.; Palamareva, M.; Dryanovska, L. *Probl. Farm.* **1982**, *10*, 9. (b) Ilarionov, I.; Avramova, P.; Dryanovska, L. *Farmatsiya* (*Sofia*) **1983**, *33*, 9. (c) Yoshida, A.; Morita, M.; Ogawa, S. *Yakugaku Zasshi* **1973**, *93*, 1138.

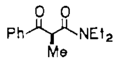
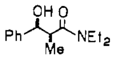
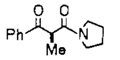
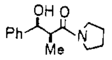
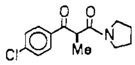
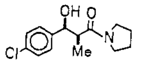
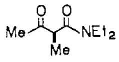
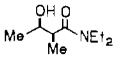
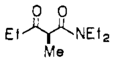
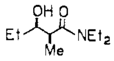
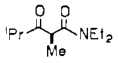
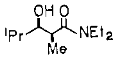
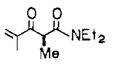
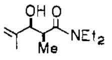
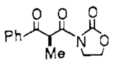
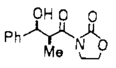
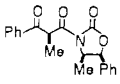
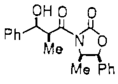
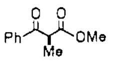
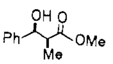
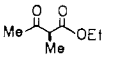
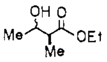
0002-7863/85/1507-8294$01.50/0

Table I. Stereoselective Reduction of 1 with PhMe$_2$SiH/F$^-$ Reagent[a]

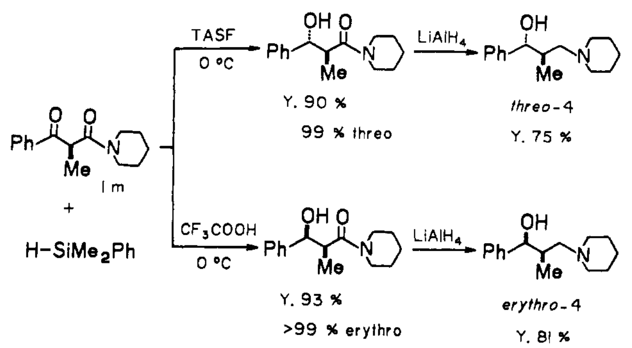
substrate[b]	conditions	product[d]	% yield[e]	threo:erythro[f,g]
 1a	0 °C, 12 h	 2a	98	>99:1
 1b	0 °C, 22 h	 2b	91	98:2
 1c	0 °C, 16 h	 2c	86	99:1
 1d	0 °C, 16 h	 2d	92	99:1
 1e	0 °C, 22 h	 3e	93	23:77[h]
 1f	0 °C, 24 h → rt,[c] 72 h	 3f	27 (84)[i]	25:75
 1g	rt,[c] 12 h	no reaction		

[a] PhMe$_2$SiH (1.2 mol equiv), TASF (10 mol %), and DMPU (1–2 mL) were employed. [b] See ref 8. [c] Room temperature. [d] Major stereoisomers are shown. [e] Total yields of 2 and 3 are given. [f] Relative stereochemistry of the products was determined by ^{1}H and ^{13}C NMR spectroscopies.[24] [g] Analysis with 90- or 400-MHz ^{1}H NMR machine unless noted. [h] GLC analysis. [i] A yield based on the consumed 1f.

Table II. Erythro-Selective Reduction of 1 with PhMe$_2$SiH/H$^+$ Reagent[a]

substrate[b]	compd no.	time, h	product[c]	compd. no.	% yield[d]	threo:erythro[e,f]
	**1a**	4		**3a**	98	1:>99
	**1b**	3		**3b**	99	1:99
	**1c**	6		**3c**	98	1:>99
	**1h**	3		**3h**	94	2:98
	**1e**	6		**3e**	91	2:98[g]
	**1f**	20		**3f**	89	1:99
	**1i**	16		**3i**	65[h,i]	1:>99
	**1j**	5		**3j**	98	1:>99
	**1k**	4		**3k**	98	1:>99
	**1g**	3		**3g**	87	1:>99
	**1l**	10		**2l + 3l**	90	1:1

[a] Reactions at 0 °C employing PhMe$_2$SiH (1.2 mol equiv) and CF$_3$COOH (1–2 mL/mmol). [b] See ref 8. [c] Major isomers are shown. [d] Total yields of **2** and **3** are given. [e] Relative stereochemistry of the product was determined by ^{1}H and ^{13}C NMR spectroscopies.[24] [f] The ratio threo:erythro was assigned by 90- or 400-MHz ^{1}H NMR analysis unless noted. [g] GLC analysis. [h] An NMR yield. [i] The saturated alcohol (**3f**) (24%) was also formed. [j] Optically pure **1k** was employed (see ref 17). [k] No epimerization at the α-carbon to the carbonyl group was confirmed by 400-MHz ^{1}H NMR analysis. [l] Compound **3k**: $[\alpha]^{20}_{D}$ +48.5° (c 0.9, CHCl$_3$), mp 177 °C.



The hydrosilane-based reductions are remarkable in light of practicability [extremely mild conditions (0 °C to room temperature) and easy handling of commercially readily available hydrosilanes] and provide an alternative efficient approach to aldols of both threo and erythro configurations.

Registry No. 1a, 99114-14-4; **1b**, 99114-15-5; **1c**, 99114-16-6; **1d**, 99114-17-7; **1e**, 99114-18-8; **1f**, 99114-19-9; **1g**, 32742-19-1; **1h**, 99114-20-2; **1i**, 99114-21-3; **1j**, 99114-22-4; **1k**, 88635-97-6; **1l**, 64854-05-3; **1m**, 99114-34-8; **2a**, 99114-37-1; **2b**, 99114-39-3; **2c**, 99114-24-6; **2d**, 99114-26-8; **2l**, 92282-67-2; **3a**, 99114-38-2; **3b**, 99114-23-5; **2e**, 99114-27-9; **2f**, 99114-29-1; **2g**, 99210-93-2; **3c**, 99114-25-7; **3e**, 99114-28-0; **3f**, 99114-30-4; **3g**, 99210-95-4; **3h**, 99114-31-5; **3i**, 99114-32-6; **3i** (silyl ether), 99114-40-6; **3j**, 99114-33-7; **3k**, 99210-94-3; **3l**, 63647-69-8; *threo*-**4**, 84412-89-5; *threo*-**4** (amide), 99114-35-9; *erythro*-**4**, 84412-87-3; *erythro*-**4** (amide), 99114-36-0.

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(23) The reduction of α-substituted β-amino ketones with $NaBH_4$ or $LiAlH_4$ gives poor stereoselectivities in general: Tramontini, M. *Synthesis* **1982**, 605.

(24) Stereochemical assignment of α-methyl-β-hydroxycarbonyl compounds by ^{1}H or ^{13}C NMR spectroscopy: Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Porrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *Ibid.* **1979**, *44*, 4294.

New Carbon–Carbon Bond-Forming Reaction of Carbon Monoxide: Remarkable Trialkylation of a Carbonyl Ligand in a Molybdenum Pentadienyl Complex

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Carbon monoxide may be converted to a wide range of chemically more useful materials by means of a variety of very important processes. Among these can be included the water–gas shift reaction, hydroformylation, methanol synthesis, methanation, and the Fischer–Tropsch reaction, as well as the large number of applications for metal carbonyls in organic synthesis.[1c,2] Crucial to these processes is the ability of the carbonyl or carbonyl-containing ligands (e.g., acyl) to undergo facile insertion and coupling reactions. We now wish to report a spontaneous and novel coupling reaction which occurs on the attempted preparation of $(2,4\text{-}C_7H_{11})Mo(CO)_3CH_3$ (C_7H_{11} = dimethylpentadienyl). This reaction is unusual with regard to its facility, as well as the fact that three coupling steps are involved, which lead to trialkylation of a carbonyl group, thereby converting it to an O-bound alkoxide ligand, during which conversion of the pentadienyl group to an η^3-cyclohexenyl ligand takes place. Besides revealing the nature of the coupling reaction, this report suggests that pentadienyl ligands may impart quite unique and potentially useful reaction chemistry to their metal complexes.

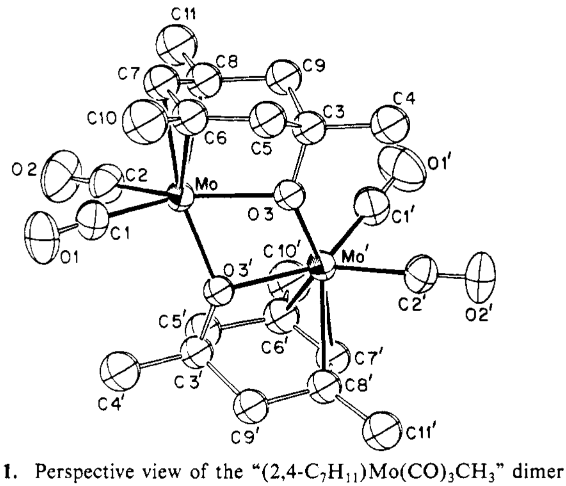
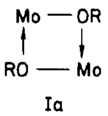
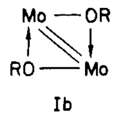


Figure 1. Perspective view of the "$(2,4\text{-}C_7H_{11})Mo(CO)_3CH_3$" dimer. While no crystallographic symmetry is present, the primed atoms are approximately related to the unprimed atoms by an inversion operation.

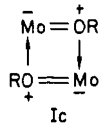
Treatment of $(diglyme)Mo(CO)_3$[3] in THF with 1 equiv of $K(2,4\text{-}C_7H_{11})$ apparently leads to the formation of the $(2,4\text{-}C_7H_{11})Mo(CO)_3$ anion.[4] Addition of 1 equiv of CH_3I at -78 °C leads to a further reaction, producing a dark solution. Subsequent extraction with hexane, followed by low-temperature crystallization, leads to pure, crystalline material in reasonable isolated yield (48%). The product has been characterized by NMR spectroscopy, IR and mass spectroscopy, elemental analysis, and single-crystal X-ray diffraction.[5] The ^{1}H NMR spectrum of this compound is similar to that which would be expected for a compound such as $(2,4\text{-}C_7H_{11})Mo(CO)_3CH_3$ (**1**), in that four resonances were present for the pentadienyl fragment (CH_3, CH, endo and exo CH_2) and a fifth resonance was observed for the additional methyl group. This pattern excluded the possibility of coupling of an alkyl or acyl group to a single end of the pentadienyl fragment as has been found for butadiene ligands.[6] However, the endo and exo CH_2 resonances were unusually close together, appearing as an AA′ pair at ca. 1.64 ppm. In addition, the ^{13}C NMR spectrum contained one extra quaternary carbon atom resonance. The actual nature of the product was elucidated by single-crystal X-ray diffraction (Figure 1).[5c] A dimeric complex has resulted, in which, besides being coordinated by two carbonyl ligands, each molybdenum atom is coordinated by two oxygen atoms and an allyl fragment, which have been constructed from the pentadienyl ligand, the third carbonyl group, and the methyl group. Since a partial resonance hybrid such as Ia would only



Ia



Ib



Ic

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(1) (a) Collman, J. P.; Hegedus, L. S. "Principles and Applications of Organotransition Metal Chemistry"; University Science Books: Mill Valley, CA, **1980**; pp 259–288. (b) Anderson, R. B. "The Fischer–Tropsch Synthesis"; Academic Press: Orlando, 1984. (c) Sneeden, R. P. A. In "Comprehensive Organometallic Chemistry"; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, p 19.

(2) Wender, I.; Pino, P. "Organic Synthesis with Metal Carbonyls"; Wiley: New York, 1968, 1977; Vol. 1, 2.

(3) Werner, R. P. M.; Coffield, T. H. *Chem. Ind.* (*London*) **1960**, 936.

(4) (a) The complex may be isolated following toluene extraction. Good NMR data have been obtained and IR data are similar to those in related anions.[4b–d] (b) Behrens, U.; Edelmann, F. *J. Organomet. Chem.* **1984**, *263*, 179. (c) Ceccon, A.; Gambaro, A.; Venzo, A. *J. Chem. Soc., Chem. Commun.* **1985**, 540. (d) Semmelhack, M. F.; Hall, H. T., Jr.; Farina, R.; Yoshifuji, M.; Clark, G.; Bargar, T.; Hirotsu, K.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 3535.

(5) (a) Anal. Calcd for $C_{11}H_{14}O_3Mo$: C, 45.53; H, 4.86. Found: C, 45.37; H, 5.09. (b) ^{1}H NMR: δ 2.43 (s, 1 H) 1.91 (s, 6 H), 1.64 (AA′ multiplet, 4 H), 1.18 (s, 3 H). (c) The crystals are monoclinic (space group $P2_1/n$) with $Z = 4$ dimeric units and $a = 16.782$ (5) Å, $b = 8.461$ (2) Å, $c = 17.523$ (2) Å, $\beta = 110.99$ (2)°. Data were collected out to 50° in 2θ leading to 2942 unique, observed ($I > 2.5\sigma(I)$) reflections. Anisotropic refinement led to agreement indices of $R = 0.038$ and $R_w = 0.046$.

(6) Bannister, W. D.; Green, M.; Haszeldine, R. N. *Proc. Chem. Soc., London* **1964**, 370.

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