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Organolithium Addition to Aldehyde Dimethylhydrazones: A Highly Diastereocontrolled Synthesis of Threo 2-Amino Alcohols and (1*R*,2*R*)-(−)-Norpseudoephedrine

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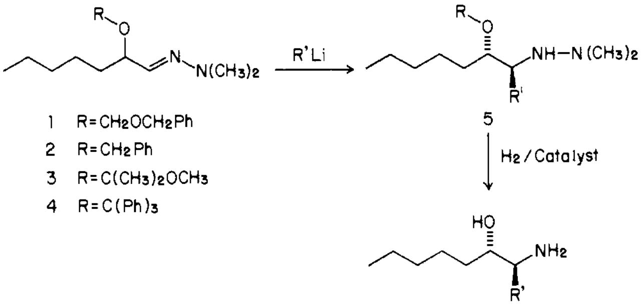
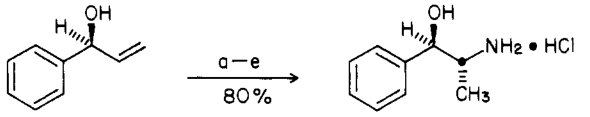
Our investigations of adrenergic agents[1] required a methodology for the enantioselective synthesis of various threo 2-amino alcohols. Recently, stereoselective strategies for construction of 2-amino alcohols have been described.[2-8] One approach,[7,8] organometallic additions to α-alkoxy imines and sulfinimines, appeared attractive, although problematic. Hydrazone derivatives[9] would eliminate the problems associated with imine derivatives; however, only limited[10] or preliminary[11] reports of their electrophilic reactions with organometallic reagents have appeared. The threo diastereoselectivity would presume a chelation controlled (Cram cyclic model) intermediate[12,13] which would provide a suitable route to threo 2-amino alcohols obtained by hydrogenolytic cleavage of the hydrazines **5**.

Various organometallic reagents (Grignard reagents were sluggish or unreactive), additives, and solvents were investigated in the reaction shown in Scheme I. Organolithium reagents in diethyl ether were successful and most suitable for our needs.[16]

Scheme I



Scheme II[a]



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7 (−) Norpseudoephedrine

[a] (a) 2-Methoxypropene/$POCl_3$ (catalytic)/0 → 25 °C/100%. (b) (i) $O_3/CH_2Cl_2/-78$ °C; (ii) $CH_3SCH_3/-78 \rightarrow -30$ °C; (iii) $H_2NN(CH_3)_2/-30 \rightarrow 0$ °C/Na_2SO_4/95%. (c) MeLi (2.5 equiv)/−10 → 25 °C/ether/95%. (d) PtO_2/1% HOAc in MeOH/H_2, 55 psig/90%. (e) HCl(g)/ethanol/ether.

Table I contains examples[17] which demonstrate the high threo diastereoselectivity, organolithium reagent generality, and efficiency obtained under the reaction conditions.[18] The trityl ether in entry 10 eliminates the chelating effect of the oxygen atom such that the erythro diastereomer is produced with good specificity consistent with a Cram open-chain model.[12,19] This reaction is considerably slower (approximately 15 h at 25 °C for completion) than the threo selective examples (approximately 1 h at 0 → 25 °C).

The influence of a β-oxygen was investigated using the dimethyl hydrazone of (*R*)-glyceraldehyde acetonide.[20] Only fair selectivity was obtained with MeLi (entry 11), but it could be improved at the expense of yield (entry 12). The addition of catalytic CuI (entry 13) reversed the diastereoselectivity.[21,23] Reactions of hydrazones **1–4** were uneffected by organocopper reagents.

This methodology provides optically active intermediates limited only by the availability of the starting hydrazones. The hydrazines obtained from entry 11 were converted to β-adrenergic antagonists enantioselectively.[24]

Sharpless' methodology[25] for kinetic resolution provides access to hydrazones of known configuration. This has been exploited

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[1] For an overview, see: *The Pharmacological Basis of Therapeutics*; Gilman, A. G., Goodman, L. S., Gilman, A., Eds.; MacMillan: New York, 1980.

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[11] Takahashi, H.; Tomita, K.; Otomasu, H. *J. Chem. Soc., Chem. Commun.* **1979**, 668–669.

[12] For reviews addressing the chelation- and non-chelation-controlled additions to α-alkoxy compounds, see: (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556–569. (b) Yamamoto, Y.; Muruyama, K. *Heterocycles* **1982**, *18*, 357–386. (c) Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, Part A, 125–155. (d) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice-Hall: Englewood Cliffs, NJ, 1971. (e) For a recent example of non-chelation-controlled addition of alkyllithium reagents to α-hetero ketones, see: Wade, P.; Price, D. T.; McCauley, J. P.; Carrol, P. J. *J. Org. Chem.* **1985**, *50*, 2804–2805.

[13] Five-membered chelation of Li^+ is usually nonexistent[12c] or weak although exceptions have been reported.[12] A six-membered chelate of Li^+ involving the dimethylamino nitrogen with an equilibrium concentration of the anti isomer (hydrogen and nitrogen are trans) is possible. Aldehyde hydrazones exist exclusively as syn isomers in solid and solution.[14] However, an anti isomer of an aldehyde dimethylhydrazone has been characterized and its spontaneous isomerization to the thermodynamically more stabile syn isomer demonstrated.[15]

[14] Kitaev, Y. P.; Buzykin, B. I.; Troepol'skaya, T. V. *Russian Chem. Rev.* (Engl. Transl.) **1970**, *39*, 441–456.

[15] Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1337–1361.

[16] The presence of other solvents, required for the preparation of the organolithium reagents, had no deleterious effects.

[17] **1–4** were prepared in 80–90% yield from protected (±)-3-hydroxy-1-octene by (1) $O_3/-78$ °C/CH_2Cl_2; (2) $(CH_3)_2S/-78 \rightarrow -30$ °C; and (3) $(CH_3)_2NNH_2/Na_2SO_4/-30 \rightarrow 0$ °C.

[18] The crude products were >98% pure by ^1H NMR and were suitable for further chemical transformations. Entry 8 was confirmed by X-ray diffraction analysis[29] of the cyclic carbamate (from hexane, mp 71.5–72.5 °C).

[19] Inspection of Dreiding molecular models suggests a six-membered chelate[13] of Li^+ would be prevented by steric interactions.

[20] Obtained by (1) $Pb(OAc)_4$ cleavage of 1,2:5,6-diisopropylidine-D-mannitol in THF; (2) filtration through Celite; and (3) $(CH_3)_2NNH_2$/0 °C/Na_2SO_4 (anhydrous).

[21] Similar results were obtained with $(CH_3)_3CuLi_2$ and high order cuprate reagents.[22]

[22] (a) MacDonald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280–5281. (b) Lipsutz, B. H.; Wilhelm, R. S. *Tetrahedron* **1984**, *40*, 5005–5038.

[23] Our results may be rationalized by either the competing chelation with the β-oxygen or an acyclic (Felkin-Anh or Cornforth) model. For recent discussions, see: (a) Reetz, K. M. T.; Kesseler, K. *J. Org. Chem.* **1985**, *50*, 5436–5438. (b) Mead, K.; MacDonald, T. L. *J. Org. Chem.* **1985**, *50*, 423–424. (c) Sato, F.; Kobayashi, Y.; Takahashi, O.; Chiba, T.; Takeda, Y.; Kusakabe, M. *J. Chem. Soc., Chem. Comm.* **1985**, 1636–1638.

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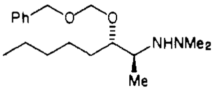
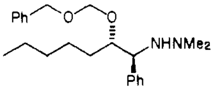
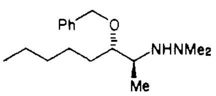
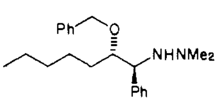
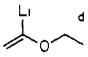
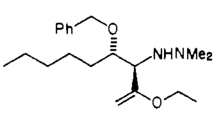
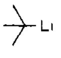
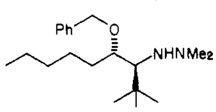
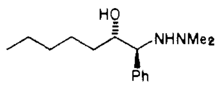
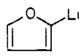
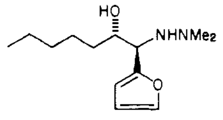
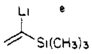
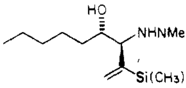
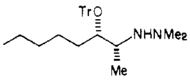
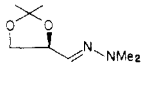
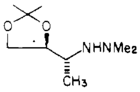
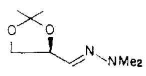
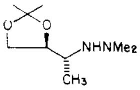
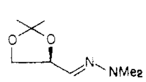
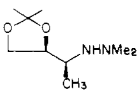
Table I. Reactions of Hydrazones

entry	hydrazone	organometallic reagent[a]	major product[b]	yield, %	threo/erythro[c]
1	1	MeLi		95	97/3
2	1	PhLi		95	>98/2
3	2	MeLi		98	97/3
4	2	PhLi		93	>98/2
5	2	 [d]		94	>98/2
6	2			98	>98/2
7	3	PhLi		93	>98/2
8	3	 [d]		85	>98/2
9	3	 [e]		88	98/2
10	4	MeLi		85	1/10
11		MeLi		95	3/1
12		MeLi[d,f]		75	6/1
13		MeLi[g] (CuI, 0.1 eq)		96	1/3

[a] Reactions were conducted under argon by adding the hydrazone in diethyl ether (0.4 M) to 1.5 equiv of organolithium reagent at -10 °C. The mixture was allowed to warm to 25 °C (over 1 h) and quenched with H_2O. The products were obtained by extractive workup. Entries 7-9 were acidified with 0.1 N HCl and then isolated by extraction after basifying with Na_2CO_3. [b] Entries 1-10 are racemic. [c] Determined by ^1H NMR and/or HPLC. [d] 5 equiv of lithium reagent. [e] 2.5 equiv of lithium reagent. [f] At -55 °C for 5 days, quenched with MeOH at -78 °C. [g] At -20 °C for 3 h, quenched with MeOH at -50 °C, then extracted from saturated aqueous NH_4Cl.

in an enantioselective synthesis of (−)-norpseudoephedine[26] (**7**) (Scheme II). (*S*)-Alcohol **6**[27] was converted to **7** without significant racemization and requiring no chromatography (isolated as the hydrochloride in 92% ee ($[\alpha]_D$ −38.9° (H_2O, *c* 1.0)). The erythro diastereomer was undetectable in the crude ^1H NMR (300 MHz). The conditions (PtO_2, 0.8 equiv/1% HOAc in MeOH (20 mL/mmol)/55 psig of H_2/3.5 h) for clean reductive cleavage of the hydrazine were critical.[28]

Supplementary Material Available: Reaction scheme and optical rotation data for β-adrenergic blocker intermediates; NMR, NOE, IR, and TLC data for compounds **1**–**7** and the products, intermediates, and oxazolidinone derivatives contained in Table I; and X-ray data containing tables of atomic positional and thermal parameters, bond distances, and bond angles for the oxazolidinone derivative of entry 8 of Table I (13 pages). Ordering information is given on any current masthead page.

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(26) For a recent synthesis, see ref 4b.

(27) The *R* isomer of **6** has been reported $[\alpha]_D$ +8.2° (*c* 5.2, benzene): Duveen, D. I.; Kenyon, J. *J. Chem. Soc.* **1939**, 1697–1701. The *S* isomer was prepared in 31% yield [95% ee, $[\alpha]_D$ −7.8° (*c* 5.0, benzene)] by kinetic resolution,[30] using (+)-DIPT.

(28) Various activities of Raney nickel as an hydrogenolysis catalyst resulted in epimerization giving a mixture of norephedrine and norpseudoephedrine.

(29) X-ray structure determinations were kindly provided by J. P. Springer and J. Hirshfield; see supplementary material for the data of entry 8 of Table I.

(30) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922–1925.

Electrochemistry of Quadruply Bonded Molybdenum Dimers. Evidence for Metal-to-Halide Back-Bonding

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Studies of the spectroscopic and photophysical properties of quadruply bonded metal dimers have provided valuable insights about the nature of the metal–metal bonding in the lowest electronic states.[1-3] Results for the redox-active $Mo_2X_4(PR_3)_4$ (X = Cl, Br, I; R = Me, Et, *n*-Pr, *n*-Bu) series[3,4] have been particularly useful, because they have revealed the effects of ligand variations on these electronic energy levels.

This report is concerned with the electrochemical behavior of the $Mo_2X_4(PR_3)_4$ complexes (Table I). The orbital involved in oxidation is δ, while reduction of the neutral complex places an electron in δ*. Except as noted, all redox couples are quasi-reversible in tetrahydrofuran (THF) and methylene chloride solutions at a scan rate of 500 mV/s.[5] Surprisingly, the $Mo_2X_4(PMe_3)_4$ complexes are more easily oxidized and difficult to reduce in the order Cl > Br > I. This is the inverse of the order expected from simple electronegativity arguments, since Cl is more electron withdrawing than Br or I.

It is not likely that this unusual redox behavior is attributable to differences in solvation, since the "inverse halide order" (IHO) also is found for complexes [e.g., $Mo_2X_4(PEt_3)_4$] where the influence of the halide on solubility is small compared to the phosphine. In addition, the same ordering of oxidation potentials[6]

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(1) (a) Trogler, W. C.; Gray, H. B. *Acc. Chem. Res.* **1978**, *11*, 232. (b) Cotton, F. A.; Walton, R. A. *Multiple Bonds Between Metal Atoms*; Wiley: New York, 1982.

(2) Miskowski, V. M.; Goldbeck, R. A.; Kliger, D. S.; Gray, H. B. *Inorg. Chem.* **1979**, *18*, 86.

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(4) (a) Zietlow, T. C.; Klendworth, D. D.; Nimry, T.; Salmon, D. J.; Walton, R. A. *Inorg. Chem.* **1981**, *20*, 947. (b) Schrock, R. R.; Sturgeoff, L. G.; Sharp, P. R. *Inorg. Chem.* **1983**, *22*, 2801. (c) Ouyang, J.; Zietlow, T. C.; Hopkins, M. D.; Fan, F.-R. F.; Gray, H. B.; Bard, A. J. *J. Phys. Chem.* **1986**, *90*, 3841.

(5) Our criterion for reversibility is that $i_{p,c}/i_{p,a} \simeq 1$. In our experiments the peak-to-peak splittings were greater than 60 mV due to uncompensated solution resistance.[4c]

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