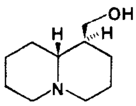
example of a chiral synthesis of (+)-epilupinine.



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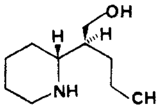

11

We succeeded in developing an extremely short chiral synthesis of the bicyclic alkaloids involving pyrrolizidine, indolizidine, and quinolizidine skeletons. This new method should be applicable to large-scale synthesess of various man-designed anticancer agents.

Selective Hydride-Mediated Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds Using $[(Ph_3P)CuH]_6$

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Hydride-mediated conjugate reduction of α,β-unsaturated carbonyl compounds remains an active area of organic research. By analogy of dialkyl cuprate conjugate addition reactions, in situ generation of unstable copper(I) hydride "ate" complexes have figured prominently in these efforts.[2] In addition, other hydride sources have been used,[3] including several anionic transition-metal hydrido complexes.[4] Despite some success as selective alternatives to catalytic hydrogenation, hydrosilation,[5] and dissolving metal reduction, these methods suffer from, inter alia, significant problems in scope, functional group compatibility, and/or reproducibility.

We wish to report that the stable, well-characterized copper(I) hydride cluster $[(Ph_3P)CuH]_6$[6-9] (**1**) is generally effective for the selective conjugate hydride addition to α,β-unsaturated carbonyl compounds. This mild hydride donor is chemically compatible with added chlorotrimethylsilane, affording an efficient procedure for reductive silylation. Additionally, due to the unusual ability of copper(I) alkoxide complexes to promote heterolytic activation of molecular hydrogen,[7,10,11] this conjugate reduction can potentially be made *catalytic* in the hydride reagent.[12]

For the stoichiometric conjugate reduction, the reaction is best conducted in benzene or toluene under inert atmosphere at room temperature. All 6 hydride equiv per cluster are delivered to the organic substrate.[13] No 1,2-reduction of the carbonyl moiety has been observed, even under prolonged reaction time in the presence of excess hydride reagent. The hydridic character of the conjugate reduction is strongly suggested both by substrate selectivity and deuterium labeling studies. The copper hydride hexamer is completely inert toward a variety of alkenes unactivated toward hydride attack, including, significantly, 1,1-diphenylethylene.[14] Conjugate reduction of 2-cyclohexenone by the deuteriated complex $[(Ph_3P)CuD]_6$[7] yielded cyclohexanone specifically labeled in the 3-position as determined by ^2H NMR.

Although it is presumed that the reaction proceeds via a copper(I) enolate intermediate, direct formation of the product ketone is observed spectroscopically in reactions run at room temperature under inert atmosphere in sealed NMR tubes.[15] We have as yet been unable to unambiguously determine the source of the quenching hydrogen atom in these reactions. Independent synthesis and characterization of copper enolate complexes is currently under investigation.

For substrates sensitive to base-catalyzed aldol condensations, decomposition of the unstable intermediate leads to significant byproduct formation. These undesirable side reactions are completely suppressed by conducting the reaction in the presence of added water.[16] While the copper hydride hexamer is indefinitely

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(4) (a) $NaHFe_2(CO)_8$: Collman, J. P.; Finke, R. G.; Matlock, P. L.; Wahren, R.; Komoto, R. G.; Brauman, J. I. *J. Am. Chem. Soc.* **1978**, *100*, 1119. (b) $Fe(CO)_5$ and aqueous base: Noyori, R.; Umeda, I.; Ishigami, T. *J. Org. Chem.* **1972**, *37*, 1542; (c) $NaHFe(CO)_4$: Yamashita, M.; Miyoshi, K.; Okada, Y.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1329. (d) $KHCr_2(CO)_{10}$: Boldrini, G. P.; Umani-Ronchi, A. *Synthesis* **1976**, 596. (e) H_2, catalytic $K_3[Co(CN)_5H]$: Reger, D. L; Habib, M. M.; Fauth, D. J. *Tetrahedron Lett.* **1979**, 115. Reger, D. L.; Habib, M. M.; Fauth, D. J. *J. Org. Chem.* **1980**, *45*, 3860, and references therein. In stoichiometric form, see: Halpern, J.; Wong, L. Y. *J. Am. Chem. Soc.* **1968**, *90*, 6665, and references therein.

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(12) A transition-metal hydride system which reduces saturated carbonyl functionality catalytically, and may involve heterolytic activation of molecular hydrogen, has been reported recently. The chemoselectivity and regioselectivity of this process has not been reported: Tooley, P. A.; Ovalles, C.; Kao, S. C.; Darensbourg, D. J.; Darensbourg, M. Y. *J. Am. Chem. Soc.* **1986**, *108*, 5465.

(13) The observed stoichiometry of the reduction reaction suggests the existence of multiple complexes containing active hydride ligands. While the intact cluster may be responsible for the hydride transfer that initiates the reaction, hydride deficient hexamers or hydride-containing fragments must also be active toward conjugate reduction.

(14) Geerts, R. L.; Caulton, K. G., unpublished results.

(15) Copper(I) alkoxide complexes have been reported to decompose by both β-elimination and free radical processes: Whitesides, G. M.; Sadowski, J. S.; Lilburn, J. *J. Am. Chem. Soc.* **1974**, *96*, 2829.

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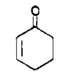
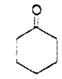
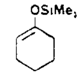
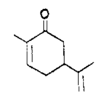
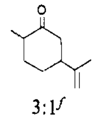
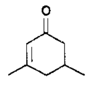
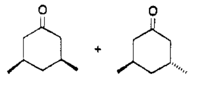
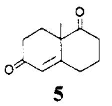
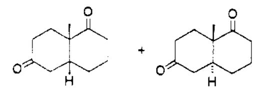
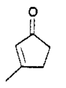
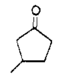
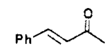
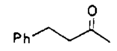
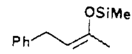
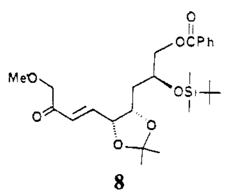
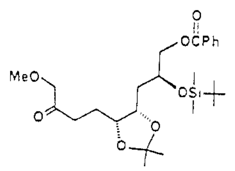
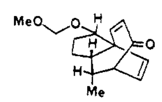
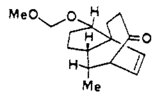
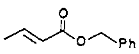
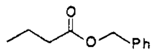
Table I. Conjugate Reduction/Reductive Silation of α,β-Unsaturated Carbonyl Compounds

entry	substrate	method[a]	$[(Ph_3P)CuH]_6$ equiv	time (h)	product(s)[b]	yield[c]
1	 **2**	B	0.16	0.25		94[d]
2	**2**	C	0.18	<0.25		95[d]
3	 **3**	B[e]	0.40	1	 3:1[f]	86 (88[d])
4	 **4**	B	0.24	1	 >100[g] : 1	92[d] 88[g]
5	 **5**	A	0.16	28	 16 : 1	85[h]
6	**5**	B	0.32	8	17 : 1	82
7	 **6**	B	0.32	24		96[d]
8	 **7**	B	0.24	0.33		89 (93[d])
9	**7**	C	0.32	<0.10	 18:1[f]	95[d,i]
10	 **8**	A	0.24	2		83
11	 **9**	B	0.32	15		82
12	 **10**	B	0.24	0.5		95 (97[d])

[a] Method A: room temperature, C_6D_6; method B: H_2O (at least 1 equiv per hydride equiv), room temperature, C_6D_6; method C: Me_3SiCl (1.5 equiv per hydride equiv), room temperature, C_6D_6. [b] Product assignments and stereochemical ratios, except as noted, determined by ^1H NMR compared to authentic materials or literature assignments, see: Supplementary Material [c] Except for volatile compounds as noted, yields are of isolated, purified products. [d] Yield determined by ^1H NMR integrations at long pulse delay against internal standard (dioxane or hexamethyldisiloxane). [e] Excess 0.05 M pH 7 buffer solution used in place of H_2O. [f] Stereochemical assignment not unambiguously determined. [g] Yield and product ratio determined by gas chromatography against authentic mixture. [h] Starting enone (3–4%) was recovered. [i] Reduced, untrapped product ($\leq$5%) was also obtained.

stable to water under inert atmosphere, some of the active copper hydride fragments present in the reaction mixture[13] are apparently less so; under aqueous conditions, more than $^1/_6$ of an equivalent of the hexamer is required to completely consume starting material.

Conjugate reduction by copper(I) hydride complexes shows considerable promise as practical synthetic methodology.[17] The reaction proceeds regiospecifically and in high yield with a variety of cyclic and acyclic unsaturated carbonyl compounds. Repre-

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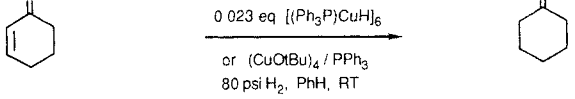
(16) While stoichiometric water is normally sufficient to inhibit byproduct formation, reactions can be run in benzene saturated with degassed water. Qualitative experiments varying water concentration in the reduction of 3-methylcyclohexenone with the hydride reagent show no change in product yield or distribution with use of from 2 to 20 equiv.

(17) The hydride hexamer can be stored indefinitely at room temperature under inert atmosphere and can be handled briefly in the atmosphere without appreciable decomposition,[6] although the material is typically weighed and handled under inert atmosphere. In solution, the complex is sensitive to oxygen.

sentative examples and experimental conditions are given in Table I.[18] Notably, the reaction is quite stereoselective (entries 4–6), affording major products deriving from hydride delivery to the least hindered face of the substrate. The observed selectivities are superior to hydrosilation, catalytic hydrogenation, and reductions with the previously reported hydrido "ate" complexes on closely related substrates.[20] Isolated double bonds, carbonyl groups, and a variety of typical oxygenated functionality are not reduced under the reaction conditions.

Reactions run in the presence of chlorotrimethylsilane afford the corresponding silyl enol ether products in high yield (entries 2 and 9), although some 1,4-reduced untrapped material can be detected spectroscopically for substrates other than cyclohexenone itself.[21] Improved procedures for this reaction and extension to other common electrophiles are under investigation.[22]

The reported high yield synthesis of $[(Ph_3P)CuH]_6$ from $(CuOtBu)_4$ and Ph_3P under hydrogen[7] led us to propose that an intermediate copper(I) enolate in the conjugate hydride reduction would react with hydrogen in an analogous fashion. Slow (<1 turnover/hour) conversion of cyclohexenone to cyclohexanone is observed under 80 psi of H_2 by using a catalytic amount either of complex **1** or $(CuOtBu)_4/PPh_3$ (eq 1). Faster conversion is obtained at higher H_2 pressures (≥200 psi), but surprisingly the reaction proceeds exclusively to cyclohexanol. The nature of the active species and full definition of the reaction parameters and scope of this catalytic process are currently under investigation.



(1)

Extension of both the stoichiometric and catalytic reactions to other unsaturated functionality and to alkyne hydrometalation is in progress. Investigation into the preparation of other hydridic copper(I) complexes is also underway, in an effort to develop a general solution to the problem of effecting hydride reductions catalytically.

Acknowledgment. We thank Professors David R. Williams and Raymond L. Funk for generously providing samples of substrates **8** and **9**, respectively, and Professor William R. Roush for helpful discussion. Financial support (to J.M.S.) from a PPG Industries Foundation Grant of Research Corporation, BRSG Grant S07 RR07031 from the Biomedical Research Support Grant Program of the National Institutes of Health, and National Institutes of Health no. GM38068-01 is gratefully acknowledged.

Supplementary Material Available: Listing of references for product characterization for entries 5, 6, and 9–11 (products of entries 1–4, 7, 8, and 12 are commercial materials) (1 page). Ordering information is given on any current masthead page.

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(18) Representative experimental procedure, for Wieland–Miescher ketone **5** (entry 6): $[(Ph_3P)CuH]_6$ (1.61 g, 0.82 mmol), weighed under inert atmosphere, and **5** (0.400 g, 2.24 mmol) were added to a 100-mL, two-necked flask under positive N_2 pressure. Deoxygenated benzene (60 mL) containing 100 μL of H_2O (deoxygenated by nitrogen purge for 10 min) was added via cannula, and the resultant red solution was allowed to stir at room temperature until starting material had been consumed by TLC analysis (8 h). The cloudy red-brown reaction mixture was opened to air, and stirring was continued for 1 h, during which time copper-containing decomposition products precipitated. Filtration through Celite and removal of the solvent in vacuo gave crude product which was purified by flash chromatography.[19]

(19) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(20) Reaction of 3,5-dimethylcyclohexenone with Boeckman's hydrido cuprate (sixfold excess, 10% HMPA in THF) gave a 9:1 ratio favoring the cis product,[2a] and catalytic hydrogenation (H_2, 5% Pd/C, C_6H_6) gave in our hands ~15:1 ratio favoring cis. With Δ^4-9-methyloctalone, both Boeckman's[2a] and Masamune's[2b] "ate" complexes gave a 7:3 ratio favoring the cis product. Surprisingly, Keinan's hydrosilation on 4-cholesten-3-one favored the trans product in a 60:40 ratio.[5]

(21) With 4-phenyl-3-buten-2-one and several other substrates, reaction in the presence of chlorotrimethylsilane gives varying amounts (2–10%) of reduced untrapped products. As with added H_2O, complete suppression of undesired side reactions is observed in these experiments.

(22) Reductive alkylation experiments on cyclohexenone using MeI as the electrophile give 2-methylcyclohexanone; however, the copper(I) hydride reacts competitively, requiring an excess of reagent.

Condensed Phase Facilitated Transport of Olefins through an Ion Exchange Membrane

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Received September 18, 1987

While numerous biological processes utilize membranes that contain transporting agents (carriers) to separate molecular and ionic permeates,[1] the potential of synthetic membranes for separations in commercial processes has not been fully realized.[2] In principal, the phenomenon of facilitated transport (FT) in membranes, which relies on the reversible formation of a permeate: carrier complex, can provide selective and efficient separations. However, development of useful membrane separation technologies requires the discovery of systems wherein selective complexation reactions can be used to achieve enhanced transport rates for specific permeates through stable membrane structures. Recently, membranes and thin films derived from ion exchange materials, such as Nafion,[3] have received considerable attention with respect to their structural, physical, and chemical properties.[4-10] In particular, ion and electron transport have been studied extensively. Far less is known about transport processes involving neutrals, even though it is the rates of these processes which ultimately will be important for many applications.

Herein we report the facilitated transport of 1-hexene and 1,5-hexadiene between two decane phases separated by thin, hydrated Nafion membranes (ca. 25 μm). The flux of olefin across the membranes is enhanced by factors of several hundred when silver ions are exchanged for sodium ions. The fact that olefin transport is caused by Ag^+ incorporation is demonstrated by monitoring the ion-exchange process with transmission Fourier transform infrared spectroscopy (FTIR). While FT of gaseous permeates such as ethylene and carbon dioxide by ions has been reported,[11] this work describes stable membrane transport for molecules with low volatility from a condensed matrix.

The Nafion membranes used in this study are an experimental material, NE111, and were provided by Dr. Louis L. Burton.[12]

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(2) (a) Noble, R. D.; Way, J. D. ACS Symp. Ser. **1987**, *347*, 1, 110. (b) National Research Council *Separation and Purification: Critical Needs and Opportunities*; National Academy Press: Washington, 1987.

(3) Nafion is the registered trademark of E.I. du Pont de Nemours & Co.

(4) (a) Naegeli, R.; Redepenning, J.; Anson, F. C. *J. Phys. Chem.* **1986**, *90*, 6227. (b) Anson, F. C.; Ni, C. L.; Saveant, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 3442. (c) Buttry, D. A.; Anson, F. C. *J. Am. Chem. Soc.* **1983**, *105*, 685. (d) Buttry, D. A.; Anson, F. C. *J. Electroanal. Chem.* **1981**, *130*, 333.

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