# Conjugate reduction of .alpha.,.beta.-unsaturated carbonyl compounds by catecholborane

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tions of salt from 80 to 320 mM show that this extrapolation is not appropriate. Higher order aggregates and even microcrystalline precipitates form long before such high concentrations are reached, and it is not surprising that the nearly linear change of rate with added salt that is observed between 2 and 80 mM salt is not continued at higher concentrations.

The salt effect at low concentrations (≤2 mM, Figure 1) is relevant to our ultimate goal of combining this salt effect with a noncovalent process for assuring salt/substrate proximity (Scheme I). The direct experiments described here show that for this addition reaction, at 2 mM ionic catalyst, we can expect an amine noncovalently attached to a ion pair to react up to 250 times more quickly than unbound amine because unbound amine will be affected only by the general salt effect while bound amine (in the best circumstance) will experience an intracomplex salt effect similar to that measured for the amine 4. At lower concentration than 2 mM catalyst, it may be predicted that bound amine may react up to 430 times faster than unbound amine. These values are at the level of rate acceleration that is required for practical control of organic reactions. They do not approach the accelerations required for control if very small amounts of catalyst/reagent are to be used, but economically acceptable and technically practical control does not always require small amounts of reagent when the reagent is recyclable. Because association constants of $10^3$ $M^{-1}$ are readily obtained for hydrogen bonding systems in nonpolar solvents, we anticipate that this intramolecular salt effect can be applied to the design and synthesis of new selective catalysts and we have begun experiments along those lines.

**Conclusions.** These results reveal the effects that coincide with attachment of an ionic group (a salt pair) in a site adjacent to a nucleophilic reaction center. This paper calls attention to the intramolecular electrostatic effects of ion pairs and suggests that, when coupled with a noncovalent process for solute association, this phenomenon might lead to new selective catalysts. Salt effects on substitution reactions are a classic subject in physical organic chemistry. The experiments discussed above examine for the first time the normal salt effects and the "intramolecular salt effect" for a simple addition reaction. The results are relevant to discussions of enzyme mechanisms because they constitute permissive evidence of the substantial effects that ion pairs within the active sites of enzymes can have on reaction rates. Further data will be required to illuminate the origin and nature of this intramolecular effect on reaction rate. Discussion of hypotheses concerning these matters will be presented in the full paper.[19]

The effects that salts and intramolecular or intramolecular complex electrostatic fields may have on the activity coefficients and free energies of reactants and activated complexes lie at the heart of our ongoing studies.

**Acknowledgment.** This work was supported by funds provided by the Sloan Foundation and by the University of Pittsburgh. We thank Dr. Peter F. M. Koehler, Dean of the Faculty of Arts and Sciences, for his support of this work. Dr. Fu-Tyan Lin of this Department continues to provide essential support and advice in our NMR experiments. Help from Dr. Greg Meisner, Laboratory Instrumentation Manager in the Department, benefits all our projects.

(19) A possibility that the effect of tetrabutylammonium sulfonate in eq 1 is due to hydrogen bond formation is doubtful. Two facts are noted: first, because the product binds to the salt more strongly ($K_a$ = 18 $M^{-1}$) than the starting amine, the product should be an inhibitor of any sulfonate-induced catalysis that is based on hydrogen bond formation. The reaction shows excellent fit to a simple model (second order overall) over 3 half-lives. The buildup of an inhibitory product should cause a detectable deviation of the data from this model and no deviation was observed. Second, we have tested a good H-bond acceptor as a catalyst for this reaction. Triphenylphosphine oxide is not a catalyst of this reaction under the same conditions where tetrabutylammonium tosylate is effective.

# Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds by Catecholborane

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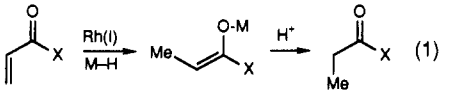
*Received August 2, 1990*

*Summary:* α,β-Unsaturated ketones which can readily adopt an s-cis conformation undergo conjugate reduction by catecholborane at room temperature. α,β-Unsaturated imides, esters, and amides are unreactive under the same conditions. However, catalytic quantities of $Rh(PPh_3)_3Cl$ greatly accelerate the 1,4-addition process, effecting conjugate reduction of these substrates by catecholborane at −20 °C. The resulting boron enolates may be reacted with electrophiles to provide functionalized products.

A number of synthetic methods have been developed which effect the conjugate reduction of α,β-unsaturated carbonyl compounds.[1] For example, it has been demonstrated that rhodium(I) complexes catalyze the 1,4-addition of silicon hydrides to enones and enoates (eq 1, M = $SiR_3$).[2] The purpose of this paper is to report that the analogous rhodium(I)-catalyzed hydroboration[3] with catecholborane may also be realized (eq 1, M = $B(OR)_2$) and to outline the scope and limitations of this complementary reaction, which affords boron enolate intermediates of considerable synthetic utility.




(1)

(1) For other methods of conjugate reduction, see: Larock, Richard C. *Comprehensive Organic Transformations*; VCH: New York, 1989; pp 8-17.

(2) For leading references to the rhodium-catalyzed conjugate reduction of α,β-unsaturated carbonyl compounds by silanes, see: (a) Yoshii, E.; Kobayashi, Y.; Koizumi, T.; Oribe, T. *Chem. Pharm. Bull.* **1974**, *22*, 2767-2769. (b) Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390-1399. (c) Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 6257-6265 and references cited therein.

(3) (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917-6918. (b) Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 2280-2282.

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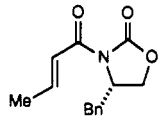
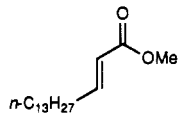
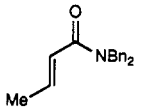
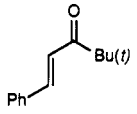
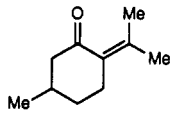
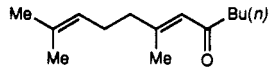
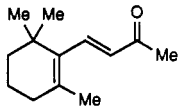
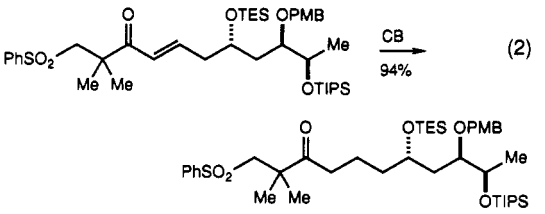
**Table I. Conjugate Reduction with Catecholborane (eq 1)**

| entry | substrate | catalyst | yield,[a] % |
|---|---|---|---|
| A |  | $Rh(PPh_3)_3Cl$ | 70 |
| B |  | $Rh(PPh_3)_3Cl$ | 82 |
| C |  | $Rh(PPh_3)_3Cl$ | 73 (80) |
| D |  | $Rh(PPh_3)_3Cl$ | 55 (95) |
| E |  | none | 94 |
| F |  | none | 95 |
| G |  | | 79 |
| H |  | none | 82[b] |

[a] Reactions were run under standard conditions (see text) and are unoptimized. The yields indicated in parentheses are based on recovered starting material. [b] 1,4-Reduction.

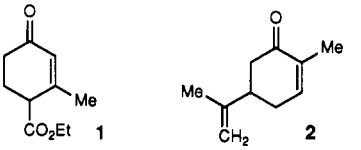
In the absence of a catalyst, $\alpha,\beta$-unsaturated imides, esters, and amides are unreactive at room temperature toward 1,4-addition of catecholborane (CB). However, addition of 2 mol % $Rh(PPh_3)_3Cl$ (Wilkinson's catalyst)[4] results in conjugate reduction of these unsaturated carbonyl compounds under very mild conditions (−20 °C, 12 h) (Table I, entries A–D).[5,6]

In contrast to the corresponding imides, esters, and amides, the analogous conjugate reduction of $\alpha,\beta$-unsaturated ketones does not require rhodium catalysis (Table I, entries E–H).[7-9] The efficient reductions of highly hindered $\beta,\beta$-disubstituted enones (entries F, G), as well as the selective 1,4-reduction of $\beta$-ionone (entry H), are worthy of note. This mild method for conjugate reduction is compatible with a wide variety of functional groups and is amenable to large-scale reactions (eq 2).[10]

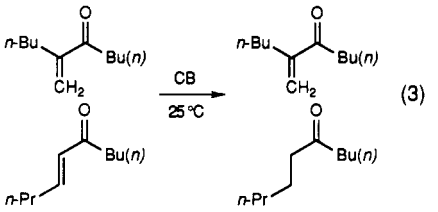


(2)

Cyclic enones bearing an endocyclic olefin (e.g., **1** and **2**) do not undergo 1,4-addition by catecholborane but instead are slowly reduced in a 1,2-fashion. Furthermore,



trans-1,2-disubstituted enones may be reduced selectively in the presence of closely related 1,1-disubstituted systems (eq 3).[11]



(3)

These observations are consistent with the postulate that a readily accessible s-cis conformation is required for the 1,4-reduction of $\alpha,\beta$-unsaturated ketones, which presumably proceeds through a $[4\pi + 2\sigma]$ transition structure (**3**).[12,13] A(1,2) strain raises the energy of the s-cis conformation for $\alpha$-substituted enones (**4**), thereby retarding reduction.[14]

The suggested transition state requires that the *Z* boron enolate be formed upon conjugate addition of catecholborane to an $\alpha,\beta$-unsaturated ketone. We have found that

(4) $[Rh(nbd)(diphos\text{-}4)]BF_4$ also catalyzes the conjugate reduction of $\alpha,\beta$-unsaturated carbonyl compounds by catecholborane, although less effectively than $Rh(PPh_3)_3Cl$.

(5) Typical experimental procedure: Wilkinson's catalyst (9.3 mg, 0.010 mmol) is added to 2.0 mL of anhydrous THF under $N_2$. The reaction vessel is cooled to −20 °C. Benzyl acrylate (81 mg, 0.50 mmol) is added, followed by CB (120 mg, 1.0 mmol). The resulting solution is stirred at −20 °C for 12 h and then quenched by the addition of 1.0 mL of pH 7.00 phosphate buffer. After 30 min at 25 °C, the product is isolated by extraction. Silica gel chromatography (5% EtOAc/hexane) affords benzyl propionate (67 mg, 82%).

(6) We have not pursued detailed mechanistic studies of this reaction. Two possible explanations for the catalysis observed are (1) Rh simply fulfills the role of a Lewis acid, which activates the substrate toward conjugate addition; (2) Catalysis occurs through a mechanism involving oxidative addition of the boron hydride to Rh. Permissive evidence supports the latter process: (1) Conjugate reduction by catecholborane is not catalyzed by $BF_3{\cdot}Et_2O$; (2) $Rh(PPh_3)_3Cl$ catalyzes the conjugate reduction by CB and by 2,2,4-trimethyldioxaborinane, but not by 9-BBN. We and others (Kono, H.; Ito, K. *Chem. Lett.* **1975**, 1095–1096. Mannig, D.; Noth, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 878–879.) have shown that CB and 2,2,4-trimethyldioxaborinane oxidatively add to $Rh(PPh_3)_3Cl$, whereas 9-BBN does not.

(7) In fact, the addition of $Rh(PPh_3)_3Cl$ results in an increased proportion of the 1,2-addition product.

(8) For a report of the reduction of an enamino ketone with catecholborane, see: Melillo, D. G.; Cvetovich, R. J.; Ryan, K. M.; Sletzinger, M. *J. Org. Chem.* **1986**, *51*, 1498–1504.

(9) Typical experimental procedure: Catecholborane (180 mg, 1.50 mmol) is added to a 0 °C solution of $\beta$-ionone (192 mg, 1.00 mmol) in 2.5 mL of THF. The solution is stirred for 0.5 h at 25 °C and then quenched by the addition of 4 mL acetone, followed by 0.5 mL of saturated $NH_4Cl$. The product is purified by silica gel chromatography (8% EtOAc/hexane) to afford the 1,4-reduction product (160 mg, 82%).

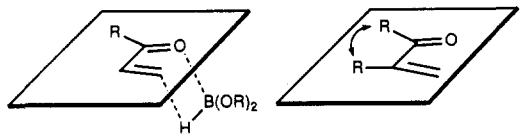
(10) This reaction was carried out on 7.25 g of the enone by Dr. A. Charette in these laboratories. Other methods (e.g., $I_2AlH$) were found to be both less efficient and less convenient for effecting the conjugate reduction of this substrate.

(11) The illustrated 1,1-disubstituted enone is not reduced by catecholborane under the standard reaction conditions (<5% conversion after 12 h at 25 °C).

(12) Use of deuteriocatecholborane results in quantitative incorporation of deuterium at the $\beta$-carbon for both uncatalyzed and Rh-catalyzed conjugate reductions.

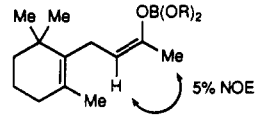
(13) For other examples of conjugate addition reactions that are believed to proceed through a $[4\pi + 2\sigma]$ transition structure, see: (a) Hooz, J.; Layton, R. B. *J. Am. Chem. Soc.* **1971**, *93*, 7320–7322. (b) Jacob, P. III; Brown, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 7832–7833. (c) Ashby, E. C.; Lin, J. J.; Kovar, R. *J. Org. Chem.* **1976**, *41*, 1939–1943. (d) Sinclair, J. A.; Molander, G. A.; Brown, H. C. *J. Am. Chem. Soc.* **1977**, *99*, 954–956. (e) Kawamura, F.; Tayano, T.; Satoh, Y.; Hara, S.; Suzuki, A. *Chem. Lett.* **1989**, 1723–1726.

(14) For example, see: Montaudo, G.; Librando, V.; Caccamese, S.; Maravigna, P. *J. Am. Chem. Soc.* **1973**, *95*, 6365–6370.

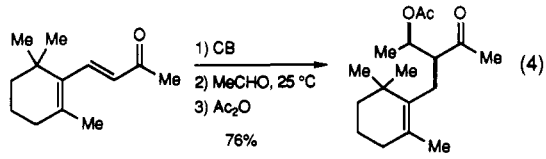



3 4

the reduction of β-ionone generates a single enolate,[15] which NOE experiments establish is indeed the *Z* isomer **5**. This enolate may be functionalized by reaction with electrophiles. For example, its aldol reaction with acetaldehyde affords the syn product with good selectivity (eq 4).



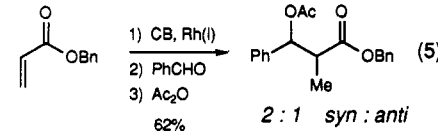

**5**




(4)

*10 : 1 syn : anti*

The boron enolate derived from the rhodium-catalyzed conjugate reduction of benzyl acrylate also appears to be a single isomer by $^1$H NMR analysis, presumably the *Z* isomer.[16] Unexpectedly, the reaction of this species with benzaldehyde affords the syn aldol adduct with low stereoselectivity (syn:anti = 2:1) (eq 5).[17]




(5)

*2 : 1 syn : anti*

The rhodium-catalyzed and the uncatalyzed 1,4-addition reactions of catecholborane described herein comprise a mild and convenient method for effecting the conjugate reduction of α,β-unsaturated carbonyl compounds. Studies further defining the scope and the mechanism of these reactions are in progress.

**Acknowledgment**. Support has been provided by the NIH and Merck. An NSF Predoctoral Fellowship to G. C.F. is gratefully recognized. The NIH BRS Shared Instrumentation Program 1 S10 RR01748-01A1 is acknowledged for providing NMR facilities.

(15) By the limits of detection by $^1$H NMR spectroscopy.

(16) The rhodium-catalyzed hydrosilation of α,β-unsaturated esters has been reported to provide the *Z* ketene acetals with high selectivity (>98:2): Slougui, N.; Rousseau, G. *Synth. Commun.* **1987**, *17*, 1-11. However, the analogous reaction of α,β-unsaturated ketones affords a mixture of isomers: Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390-1399.

(17) For examples of related condensations (α,β-unsaturated esters with ketones) which employ trimethylsilane as the reducing agent and $RhCl_3{\cdot}3H_2O$ as the catalyst, see: Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809-4812. Others have shown that the condensation of silyl enol ethers with aldehydes is catalyzed by Rh(I) complexes: Sato, S.; Matsuda, I.; Izumi, Y. *Tetrahedron Lett.* **1986**, *27*, 5517-5520. Reetz, M. T.; Vougioukas, A. E. *Tetrahedron Lett.* **1987**, *28*, 793-796.

# α-Metalated Tertiary Enol Carbamates. New Acyl Anion Equivalents

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*Received June 1, 1990*

*Summary:* α-Metalated enol carbamate **1g** constitutes a new, conveniently generated (*sec*-BuLi/TMEDA/THF/−78 °C), and well-behaved acyl anion equivalent. The utility and scope of this synthon for the preparation of a variety of useful synthetic building blocks (**4**, **6**, **8**, **11**, **12**) has been demonstrated.

First enunciated by Corey and Seebach in their seminal studies on metalated 1,3-dithianes,[1] the *umpolung* (polarity reversal) principle has become a powerful concept in synthetic design.[2] The subsequent discovery of α-lithiation of alkyl vinyl ethers[3] and alkyl vinyl sulfides[4] has allowed the recent emergence of a distinct group of α-metalated α-heteroatom substituted olefins **1** as valuable *umpolung* synthons.[5-7] Stripped to the simplest form, these constitute readily available acyl anion equivalents **2**, which are generally useful in direct functionalization

(1) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075.

(2) *Umpoled Synthons*; Hase, T. A., Ed.; Wiley-Interscience: New York, 1987.

(3) Baldwin, J. E.; Hofle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125. Hartmann, J.; Stähle, M.; Schlosser, M. *Synthesis* **1974**, 888. Schöllkopf, U.; Haenssie, P. *Liebigs Ann. Chem.* **1972**, *763*, 208.

(4) Oshima, K.; Shimoji, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 2694.

(5) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.

(6) (a) For a review, see: Ager, D. J. in ref 2. Recent work: (b) Soderquist, J. A.; Hsu, G. J.-H. *Organometallics* **1982**, *1*, 830. McDougal, P. G.; Rico, J. G. *J. Org. Chem.* **1987**, *52*, 4817. Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269. Tamao, K.; Nakagawa, Y.; Arai, H.; Higuchi, N.; Ito, Y. *Ibid.* **1988**, *110*, 3712. Smith, A. B., III; Empfield, J. R.; Vaccaro, H. A. *Tetrahedron Lett.* **1989**, *30*, 7325. For a chiral version, see: McDougal, P. G.; Dicesare, J.; Kerrigan, J.; Starks, L. J. *Abstracts of Papers*; 199th National Meeting of the ACS, Boston, MA; American Chemical Society: Washington, DC, 1990; abstract no. ORGN 270. For an in situ generation of (2,2-difluoro-1-(tosyloxy)vinyl)lithium, see: Ichikawa, J.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1989**, *30*, 5437. (c) Trost, B. M.; Lavoie, A. C. *J. Am. Chem. Soc.* **1983**, *105*, 5075 and references cited therein. Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 303. McDougal, P. G.; Oh, Y.-I. *Tetrahedron Lett.* **1986**, *27*, 139. (d) McCombie, S. W.; Shankar, B. B.; Ganguly, A. K.; Padwa, A.; Bullock, W. H.; Dyszlewski, A. D. *Ibid.* **1987**, *28*, 4127 and references cited therein. For a formal 1-(tolylsulfinyl)vinyl α-anion, see: Cheng, H.-C.; Yan, T.-H. *Tetrahedron Lett.* **1990**, *31*, 673. (e) Krief, A. *Tetrahedron* **1980**, *36*, 2531. (f) Bates, R. B.; Beavers, W. A.; Blacksber, I. R. *Abstracts of Papers*; 169th National Meeting of the CS, Philadelphia, PA; American Chemical Society: Washington, DC, 1975. Boeckman, R. K., Jr.; Walters, M. A.; Koyano, H. *Tetrahedron Lett.* **1989**, *30*, 4787. Schmidt, R. R.; Speer, H. *Ibid.* **1981**, *22*, 4259. α-Metalated 1,2-dihydropyridines may be viewed as α-metalated enamine synthons, see: Comins, D. L.; Weglarz, M. A.; O'Connor, S. *Tetrahedron Lett.* **1988**, *29*, 1751. (g) Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595. Meyers, A. I.; Spohn, R. F. *Ibid.* **1985**, *50*, 4872.

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