ORGANIC LETTERS

2001
Vol. 3, No. 12
1901−1903

Tandem Conjugate Reduction–Aldol Cyclization Using Stryker's Reagent

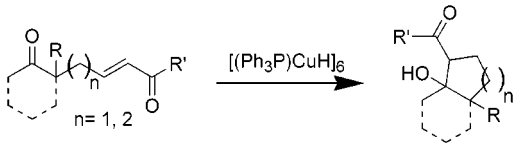
Pauline Chiu,* Chun-Pong Szeto, Zhe Geng, and Kin-Fai Cheng

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. China

pchiu@hkucc.hku.hk

Received April 5, 2001

ABSTRACT



Conjugate reduction by Stryker's reagent to form copper enolates, followed by intramolecular aldol cyclization, successfully generated five- and six-membered carbocycles in one pot efficiently. This tandem reaction is generally diastereoselective and provides good yields of the *β*-hydroxyketones without any dehydration at low temperatures.

Tandem reactions are highly desirable for increasing the efficiency of a synthetic plan by inducing multiple transformations of the substrate in one operation.[1] A well-known example of a tandem reaction is the conjugate addition of organocuprates, followed by alkylation of the resultant enolate to achieve the overall vicinal difunctionalization of a Michael acceptor.[2] In comparison, the analogous tandem conjugate reduction−alkylation reaction has not been as extensively explored.[3]

Conjugate reduction can be achieved by various reducing systems, the majority of which are hydrides generated in situ.[4] Among the reagents for conjugate reduction, the commercially available triphenylphosphinecopper hydride hexamer $[(Ph_3P)CuH]_6$ **1**, also known as Stryker's reagent, stands out as a well-characterized, stoichiometric source of hydride which chemoselectively reduces conjugate systems and is inert toward isolated olefins.[5] There has been continuing interest in the applications of this reagent since its introduction; its catalytic and its enantioselective versions have been reported in the literature.[6−9] The enolate intermediate, trapped as its silyl enol ether, has been induced to react under Mukaiyama conditions to accomplish a one-pot three-component reduction−alkylation reaction.[9]

Our approach to extending the synthetic applications of reagent **1** is to directly engage the copper enolate obtained upon conjugate reduction in further reactions rather than quenching or trapping them. Copper enolates in themselves are relatively little studied or used in organic chemistry.[10]

(1) (a) Ho, T. L. *Tandem Organic Reactions*; John Wiley & Sons: New York, 1992. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.

(2) Chapdelaine, M. J.; Hulce, M. *Org. React*. **1990**, *38*, 225.

(3) Some examples: (a) Stork, G.; Uyeo, S.; Wakamatsu, T.; Grieco. P.; Labovitz, *J. J. Am. Chem. Soc.* **1971**, *93*, 4945. (b) Tsuda, T.; Satomi, H.; Hayashi, T.; Saegusa, T. *J. Org. Chem*. **1987**, *52*, 439. (c) Matsuda, I.; Takahasi, K.; Sato, S. *Tetrahedron Lett.* **1990**, *31*, 5331. (d) Kiyooka, S.; Shimizu, A.; Torii, S. *Tetrahedron Lett*. **1998**, *39*, 5237. (e) Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc*. **1999**, *121*, 12202. For a recent catalytic asymmetric reductive aldol, see: (f) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc*. **2000**, *122*, 4528.

(4) Some representative examples: (a) Ikeno, T.; Kimura, T.; Ohtsuka, Y.; Yamada, T. *Synlett* **1999**, 96. (b) Mori, A.; Fujita, A.; Nishihara, Y.; Hiyama, T. *Chem. Commun*. **1997**, 2159. (c) Yamashita, M.; Tanaka, Y.; Arita, A.; Nishda, M. *J. Org. Chem*. **1994**, *59*, 3500. (d) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Meneses, R. *Synlett* **1999**, 1663, and references therein.

(5) (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc*. **1988**, *110*, 291. (b) Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett*. **1989**, *30*, 5677.

(6) (a) Mahoney, W. S.; Stryker, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8818. (b) Stryker, J. M.; Mahoney, W. S.; Daeuble, J. F.; Brestensky, D. M. In *Catalysis of Organic Reactions (Chem. Ind.)*; Pascoe, W. E., Ed.; Marcel Dekker: New York, 1992; Vol. 47, pp 24−44. (c) Chen, J. X.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2153. (d) Chen, J. X.; Daeuble, J. F.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2789.

(7) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627.

(8) (a) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 9473. (b) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797.

(9) Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779.

10.1021/ol015944n CCC: $20.00
Published on Web 05/16/2001

We have already reported the first example of a one-pot tandem reduction−intramolecular aldol cyclization in the context of a natural product synthesis, and now we wish to describe our further studies on the scope and applications of this reaction.[11]

A variety of appropriately substituted enedione systems undergo conjugate reduction, followed by intramolecular aldol cyclization in the presence of stoichiometric amounts of Stryker's reagent (Table 1). These reactions proceed smoothly at −40 to −25 °C in noncoordinating solvents such as toluene. When these reactions are performed at low temperatures, dehydration resulting in the loss of the two newly generated stereocenters is not a significant side reaction; thus good to excellent yields of the β-hydroxyketone products are obtained.[12]

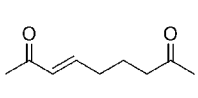
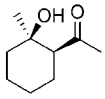
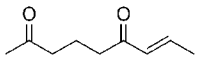
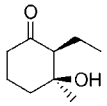
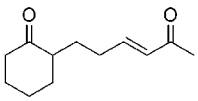
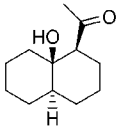
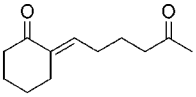
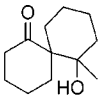
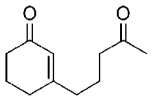
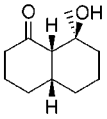
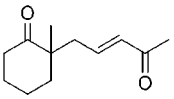
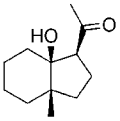
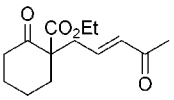
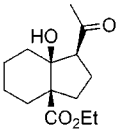
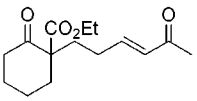
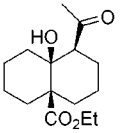
Selective enolate formation in compounds bearing multiple carbonyl groups is generally difficult to achieve using base-induced aldol reaction conditions.[13] In the reductive aldol cyclization induced by **1**, the enolate is exclusively derived from the reduction of the olefin; thus the generation of the enolate is unambiguous and entirely regioselective. For example, under base-induced aldol reaction conditions, the cyclization of 3,8-nonanedione would likely result in a mixture of regioisomeric products; however, only one regio- and stereoisomeric product from the reductive cyclization of 2-nonene-3,8-dione was observed in which the more hindered ketone was directed to be the enolate (entry 2). There was no evidence for the exchange of the initially formed enolate to other regioisomeric enolates via inter- or intramolecular deprotonation. Entries 3 and 4 show products from the complementary regiochemical modes of cyclization that can be achieved by the installation of the olefin in conjugation with either of the carbonyl groups to direct the formation of the enolate in the substrate.

The rate of the reduction−cyclization decreases with additional substituents on the double bond. The steric hindrance of the β-substituent introduced a severe retarding effect, the rate of the reduction step being seriously prohibited as evidenced by the low conversion rate (Table 1, entry 5).

As expected, conjugate reductions and aldol cyclizations leading to the formation of five-membered rings are extremely facile, while cyclizations to give six-membered rings are comparatively slower (Table 1, entries 7 and 8). Under these reductive conditions, substrates bearing shorter or longer tethers that could potentially cyclize to form four- or seven-membered rings only result in simple reduction (Scheme 1).

When the tandem conjugate reduction−aldol cyclization is conducted at low temperatures, the product is presumably the kinetically derived product. At higher temperatures, the copper aldolate intermediate can undergo a retro-aldol reaction to give the thermodynamically more stable product.

Table 1. Tandem Reduction−Aldol Cyclization of Enediones by Stryker's Reagent **1**

entry	substrate	T(°C)	t(hr)	product	yield[a] (%)
1		-40	1		80
2		-40	1		86
3		-40	1		72
4		-25	2		89[b]
5		0	12		19[c,d]
6		-40	2.5		66
7		-40	0.5		86[d]
8		-40	1		93[d]

[a] Isolated yields of pure products; structures determined by NMR analysis except where indicated otherwise. [b] One diastereomer obtained, structure not determined. [c] 5% reduction product and 69% recovered substrate also obtained. [d] Structures elucidated by X-ray crystallographic analyses of their 2,4-dinitrophenylhydrazone derivatives.

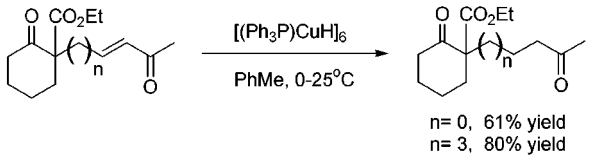
(10) There are very few studies of the preparation and chemistry of true copper enolates: (a) Mekelburger, H. B.; Wilcox, C. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 1.4, p 99. One well-studied and particularly effective example: (b) Kruger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (c) Pagenkopf, B. L.; Kruger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3124.

(11) (a) Chiu, P.; Chen, B.; Cheng, K. F. *Tetrahedron Lett.* **1998**, *39*, 9229. (b) For a case of a fragmentation to give a copper enolate that underwent an intramolecular aldol, see ref 6d. Other examples where the copper enolates from Stryker reduction were utilized synthetically: (c) Alkylation: Koenig, T. M.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 3237. (d) O-Acylation: Raimundo, B. C.; Heathcock, C. H. *Org. Lett.* **2000**, *2*, 27. (e) Michael addition: Kamenecka, T. M.; Ly, S. K.; Overman, L. E. *Abstract of Papers*, 212th National Meeting of the American Chemical Society, Orlando, FL; American Chemical Soceity: Washington, DC, 1996; ORGN 010. Ly, S. K. Ph.D. Dissertation, University of California, Irvine, CA, 1998.

(12) **Typical experimental procedure:** Stryker's reagent (65.0 mg, 0.033 mmol) was treated with 1.0 mL of dry toluene and cooled to −40 °C. Substrate **2** (23.4 mg, 0.088 mmol) in 1.0 mL of toluene was added, and the solution was stirred for 1 h. The reaction was quenched by adding a saturated aqueous NH_4Cl solution and stirring for 2 h open to air. Workup and purification by flash chromatography gave **3** (21.8 mg, 93%). For detailed experimental procedures, refer to Supporting Information.

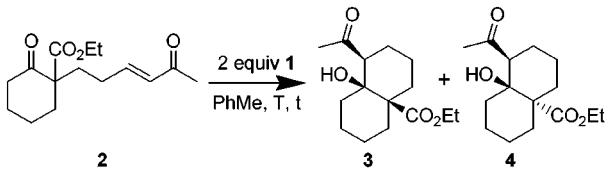
(13) For studies in the regioselectivity of base-induced intramolecular aldol reactions, see: Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 1.5, p 133.

Scheme 1. Stryker Reduction of Substrates with Tethers of Different Lengths



This was observed in the reaction of substrate **2** (Scheme 2). When the reaction is conducted at −40 °C, the all-*cis*

Scheme 2. Reductive Cyclization of **2** at Various Temperatures



2 **3** **4**

T (°C)	t (h)	isolated yields of **3** and **4**	
-40	1	93%	0
-25	0.5	79%	3%
-10	0.25	12%	58%

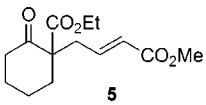
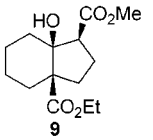
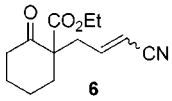
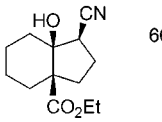
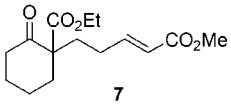
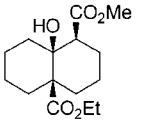
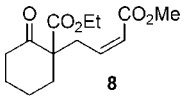
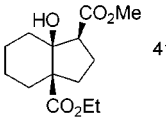
hydroxyketone **3** is obtained exclusively in excellent yield. When the reaction temperature is raised, another stereoisomer, **4**, is formed at the expense of **3**. When the reaction is carried out at −10 °C, substrate **2** is consumed quickly to give a mixture of isomeric products with the more stable hydroxyketone **4** bearing a *trans*-fused junction as the major product.[14]

Table 2 shows that conjugated esters and nitriles also undergo tandem conjugate reduction−aldol cyclization with Stryker's reagent. In general, the reactions proceeded at a much slower rate than with enone systems and needed to be conducted at room temperature for completion within a reasonable amount of time. Good to acceptable yields of reductively cyclized products were obtained for substrates which formed five-membered rings (entries 1 and 2), but more of the simple reduction products were obtained in the cyclization to form six-membered rings (entry 3).

In the studies of conjugated esters and nitriles, we observed that substrates bearing *trans* double bonds were reduced and proceeded to aldol cyclizations at faster rates than their *cis* isomeric counterparts. Although the reductive cyclization of either the *E*-enoate **5** or the *Z*-isomer **8** occurred to generate aldol product **9** with the same stereochemistry, the reduction of *E*-enoate **5** with two hydride equivalents of Stryker's reagent gave an 84% yield of **9**, while the *Z*-olefin **8** under the same conditions was still largely incomplete after 18 h

(14) The *trans*-fused hydroxyketone **4** (30.7799 kcal/mol) is slightly more stable thermodynamically than the *cis*-fused isomer **3** (30.9785 kcal/mol) by MM2 calculations (Macromodel v. 4.5 *MacroModel3D*). The structures of stereoisomers **3** and **4** have been determined on the basis of spectroscopic evidence; in addition, the structure of isomer **3** has been confirmed by X-ray crystallography of its 2,4-dinitrophenylhydrazone derivative.

Table 2. Tandem Reduction−Aldol Cyclization of Conjugated Esters and Nitriles by Stryker's Reagent **1**

entry	substrate	T(°C)	t(hr)	product	yield[a] (%)
1	 **5**	25 25	2[a] 18[b]	 **9**	74 84
2	 **6**	25	11		66[c]
3	 **7**	25	3		53[d]
4	 **8**	25	18[b]	 **9**	41[e]

[a] Reaction with 4 equiv (0.66 mol) of **1**. [b] Reaction with 2 equiv (0.33 mol) of **1**. [c] 11% recovered **6** (*cis*-isomer only) also obtained. [d] 35% reduction product also obtained. [e] 4% reduction product and 24% recovered **8** also obtained.

(Table 2, entries 1 and 4). When a 3:2 mixture of **5** and **8** was subjected to reduction, the recovered starting material consisted of only the *Z*-olefinic substrate **8**. Substrate **6** was subjected to reaction as an inseparable 3:2 mixture of the *E*- and *Z*-isomers (Table 2, entry 2). The starting material recovered after reductive cyclization consisted of only the *Z*-isomer.

This difference in the rates of reaction can be usefully exploited for the chemoselective reduction of *trans* enoate functional groups in the presence of *cis* substrates, as well as the possibility of achieving chemoselective partial reduction of ynone and ynoate systems. These applications of the reductive aldol cyclization will be reported in due course.

Acknowledgment. We thank Dr. K. K. Cheung and Dr. W. T. Wong for performing the X-ray crystallographic analyses. We also thank Dr. Zhengning Li for the preparation of Stryker's reagent and for obtaining some experimental results. The work described in this paper was supported by the University of Hong Kong (CRCG 1999-2000) and by a grant from the Research Grants Council of Hong Kong Special Administrative Region, China (Project No. HKU 7132/99P). C.P.S. thanks the University of Hong Kong for a postgraduate studentship.

Supporting Information Available: Experimental procedures; ^{1}H NMR, ^{13}C NMR, IR, and MS spectral data, structural determination of all products, ^{1}H and ^{13}C NMR spectra, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015944N