consisting of CTA^+ cations and tungstate anions. 4) With increasing furnace temperature, tungstate is reduced by pyrolytic carbon derived from CAT^+ to give W metal with a shape defined by the scrolls, which could serve as microreactors for the VPC process and thus are responsible for the ultimate wirelike shape of W. The VPC process should involve a tubular intermediate that results from confinement of the scrolls. However, with the removal of surfactant molecules and crystallization of tungsten metal, these tubular nanostructures would finally transform into the nanowire products.

To substantiate our hypothesis, we performed control experiments. The tungstate and surfactants were mixed mechanically, but no lamellar composite structures were present in these mixtures according to low-angle XRD data. The same VPC operations were performed on these mixtures. However, only W particles were observed. In addition, we performed a more stringent test of our model by preparing Ni, Co, Cu, and Cd nanowires (see Supporting Information). The fundamental experimental results were in good agreement with our suggested VPC model (see Supporting Information). The above studies illustrate that the controlled VPC treatment of inorganic–surfactant lamellar precursors might be a general approach for the synthesis of crystalline nanowires or nanotubes.

Experimental Section

Analytical-grade Na_2WO_4 (3 mmol) and CTAB (9 mmol) were dissolved in distilled water to form a homogeneous solution. The pH of the solution was adjusted to the range of 8–10 by addition of aqueous NH_3 or HCl. The mixture was stirred vigorously for 1 h and then sealed in a Teflon-lined stainless steel autoclave and kept at 140 °C for 6 d. The solid WO-L product was collected by filtration, washed with distilled water and absolute ethanol, and then dried in vacuo at 80 °C for 12 h. The calculated yield was about 85–90 % on the basis of W.

The VPC treatment was carried out in a conventional tube furnace (see Figure 2). The as-prepared WO-L (400 mg) was placed in a quartz boat. The quartz boat was placed in the hot zone inside the quartz tube and the content calcined and pyrolyzed for 10 h at 100 to 850 °C in a high-purity argon atmosphere (99.999 %) with a pressure range of 10^{-2}–10^{-3} atm. The furnace temperature was first increased to 400 °C over 4 h and then held at that temperature for 2 h to ensure completion of the rolling process of the lamellar precursor. Then the temperature was raised to 850 °C over 2 h and kept at that temperature for 2 h. Finally, the temperature was allowed to descend to room temperature. In the whole process, the reaction temperature was controlled exactly at ±1 K by a built-in temperature-control unit in the tube furnace.

Received: July 17, 2001
Revised: November 5, 2001 [Z17528]

[1] C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **1992**, *359*, 710–712.
[2] M. E. Davis, *Nature* **1993**, *364*, 391–393.
[3] Q. Huo, D. I. Margolese, U. Ciesla, P. Feng, T. E. Gier, P. Sieger, R. Leon, P. M. Petroff, F. Schüth, G. D. Stucky, *Nature* **1994**, *368*, 317–321.
[4] P. T. Tanev, M. Chibwe, T. J. Pinnavaia, *Nature* **1994**, *368*, 321–323.
[5] H. Yang, A. Kuperman, N. Coombs, S. Mamiche-Afara, G. A. Ozin, *Nature* **1996**, *379*, 703–705.
[6] T. Sun, J. Y. Ying, *Nature* **1997**, *389*, 704–706.
[7] P. Yang, D. Zhao, D. I. Margolese, B. F. Chmelka, G. D. Stucky, *Nature* **1998**, *396*, 152–155.
[8] P. Yang, G. Wirnsberger, H. C. Huang, S. R. Cordero, M. D. McGehee, B. Scott, T. Deng, G. M. Whitesides, B. F. Chmelka, S. K. Buratto, G. D. Stucky, *Science* **2000**, *287*, 465–467.
[9] S. Iijima, *Nature* **1991**, *354*, 56–58.
[10] R. Tenne, L. Margulis, M. Genut, G. Hodes, *Nature* **1992**, *360*, 444.
[11] Y. R. Hachohen, E. Grunbaum, J. Sloan, J. L. Hutchison, R. Tenne, *Nature* **1998**, *395*, 336.
[12] U. Ciesla, D. Demuth, R. Leon, P. Petroff, G. D. Stucky, K. Unger, F. Schüth, *J. Chem. Soc. Chem. Commun.* **1994**, 1387–1388.
[13] A. Stein, M. Fendorf, T. P. Jarvie, K. T. Mueller, A. J. Benesi, T. E. Mallouk, *Chem. Mater.* **1995**, *7*, 304–313.

Dynamic Kinetic Resolution and Desymmetrization of Enantiotopic Groups by Cyclodehydration of Racemic or Prochiral *δ*-Oxoesters with (*R*)-Phenylglycinol: Enantioselective Synthesis of Piperidines**

Mercedes Amat,* Margalida Cantó, Núria Llor, Viviana Ponzo, Maria Pérez, and Joan Bosch

The development of efficient methods to produce an optically pure enantiomer is of fundamental importance, particularly for the synthesis of bioactive natural or synthetic products. Today, enzyme-mediated desymmetrizations of either prochiral or *meso* substrates, generally diesters, and enzyme-catalyzed kinetic resolutions of racemates constitute classical approaches for the synthesis of enantiopure compounds, and have become powerful synthetic tools.[1] In contrast, in spite of the impressive advances in the field of chemical, nonenzymatic, enantioselective desymmetrizations over the last few years, the chemical differentiation of two enantiotopic functional groups has been little developed.[2] On the other hand, the major drawback of kinetic resolution, like conventional resolution processes, is that the maximum yield of one enantiomer is always limited to 50 %. However, this situation dramatically changes when racemic substrates have a chirally labile stereogenic center that is capable of undergoing racemization in situ during the reaction (dynamic kinetic resolution (DKR)).[3]

In the context of our studies on the synthesis of enantiopure piperidine derivatives from chiral nonracemic bicyclic lactams formed by cyclodehydration of *δ*-oxoesters and (*R*)- or (*S*)-

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[**] This work was supported by the DGICYT, Spain (BQU2000-0651), and the CUR, Generalitat de Catalunya (2001SGR-0084). We also thank the Ministry of Education, Culture, and Sport for fellowships to M.C. and M.P., as well as the CICYT, Spain, for a postdoctoral fellowship to V.P.

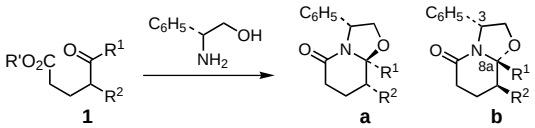
Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

  1433-7851/02/4102-0335 $ 17.50+.50/0

phenylglycinol,[4] we report herein the preparation of polysubstituted lactams by DKR of racemic δ-oxoacid derivatives, enantioselective desymmetrization of prochiral δ-oxodiesters, and tandem DKR – diastereotopic differentiation of racemic δ-oxodiesters, which ultimately leads to diversely substituted enantiopure piperidines.

Cyclodehydrations[5] with a variety of racemic aldehyde esters and ketoacids that bear a substituent (alkyl or aryl) at the epimerizable carbon atom α to the aldehyde (**1a–c**) or ketone (**1d–f**)[6] group (Table 1) stereoselectively afforded a lactam as the major product, accompanied by minor amounts of a second stereoisomer ($\approx$4:1),[7] which clearly indicates that DKR had occurred.[8]

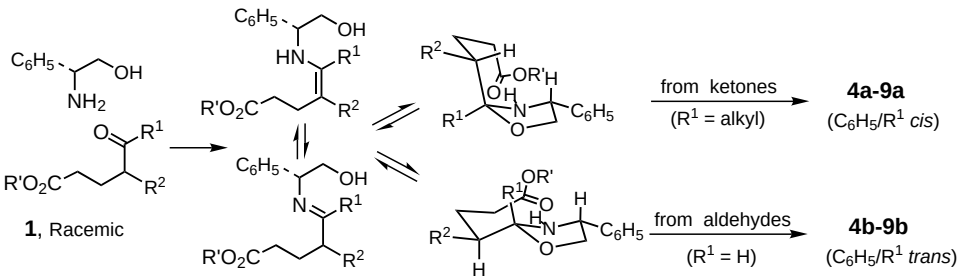
Table 1. DKR by cyclodehydration of racemic δ-oxoacid derivatives with (*R*)-phenylglycinol.



Entry	Substrate	R′	R^1	R^2	*t* [h]	Lactam	**a/b**	Yield [%]
1	**1a**	Me	H	Et	18	**4**	20:80[b]	80
2	**1b**	Me	H	$CH_2CH_2C(S_2C_3H_6)CH_3$	14	**5**	17:83[c]	70
3	**1c**	Me	H	C_6H_5	24	**6**	16:84[b]	58
4	**1d**	H	Me	Et	24	**7**	78:22[c]	60
5	**1e**[a]	Me	Me	*p*-$MeOC_6H_4$	14	**8**	80:20[b]	76
6	**1f**	H		$-(CH_2)_4-$	24	**9**	79:21[c,d]	70

[a] Catalytic amounts of *p*-TsOH were added. [b] Calculated by means of ^{1}H NMR spectroscopy. [c] Calculated by using HPLC. [d] The configuration of **9a** was confirmed by X-ray crystallographic analysis.

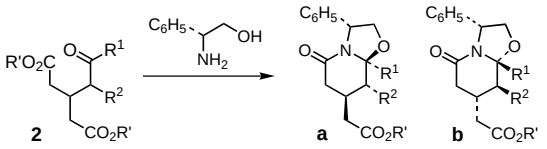
The stereochemical outcome of these reactions[9] can be accounted for by considering that the mixture of four diastereomeric oxazolidines formed initially is in equilibrium through the corresponding imines – enamines, and that subsequent lactamization takes place faster through a chairlike transition state in which the substituent R^2 is equatorial, thus leading predominantly to isomers in which R^1 and R^2 are *cis* (Scheme 1). The preferential formation of isomers **b** (C_6H_5 and R^1 = H are *trans*) from aldehydes **1a–c** (Table 1, entries 1–3) and isomers **a** (C_6H_5 and R^1 = alkyl are *cis*) from ketones **1d–f** (Table 1, entries 4–6)[10] indicates that lactamization occurs faster from the diastereomeric oxazolidine that allows the approach of the carboxylate group to the nitrogen atom by the most accessible face, that is *anti* with respect to C_6H_5 (from aldehyde esters) or to both C_6H_5 and R^1 (from ketoacids).



Scheme 1. Imine – enamine equilibrium and subsequent lactamization in the formation of **4–9**.

To study enantioselective desymmetrizations of prochiral δ-oxodiesters with (*R*)-phenylglycinol, we selected the glutaric and pimelic acid derivatives **2a–b** and **3a**, respectively.[6] Interestingly, cyclodehydration[5] of aldehyde diester **2a** and ketodiester **2b** with (*R*)-phenylglycinol stereoselectively afforded lactams **10b** and **11a**, respectively, as the major products, together with minor amounts (4:1) of a second diastereomer, **10a** and **11b**, respectively (Table 2, entries 1 and 2). Similarly, cyclodehydration of the prochiral aldehyde **3a** gave lactams **14** in very high stereoselectivity (**14a**/**14b** 1:9; Table 3, entry 1).[7]

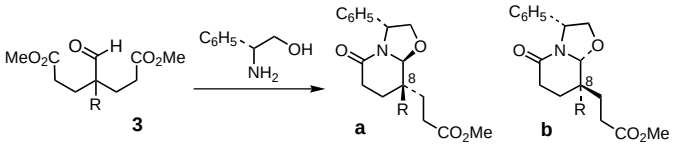
Table 2. Enantioselective desymmetrization of prochiral δ-oxodiesters and tandem DKR – diastereoselective differentiation of racemic δ-oxodiesters.



Entry	Substrate	R′	R^1	R^2	*t* [h]	Lactam	**a/b**	Yield [%]
1	**2a**	Me	H	H	8	**10**	20:80[c]	95
2	**2b**[a]	Et	Me	H	18	**11**	82:18[c,d]	77
3	**2c**	Et	H	Et	14	**12**	20:80[e]	77
4	**2d**[b]	Et	Me	*n*Pr	24	**13**	85:15[e]	54

[a] Catalytic amounts of *p*-TsOH were added. [b] Catalytic amounts of AcOH were added. [c] Calculated by means of HPLC. [d] The configuration of **11a** was confirmed by X-ray crystallographic analysis. [e] Calculated by using ^{1}H NMR spectroscopy.

Table 3. Enantioselective desymmetrization of prochiral 4-formylpimelic acid derivatives by cyclodehydration with (*R*)-phenylglycinol.



Entry	Substrate	R	*t* [h]	Lactam	**a/b**	Yield [%]
1	**3a**	H	20	**14**	10:90[a]	67
2	**3b**	Et	24	**15**	10:90[b,c]	50

[a] Calculated by means of HPLC. [b] Calculated by using ^{1}H NMR spectroscopy. [c] Isomers **15a** and **15b** were isolated accompanied by their respective C-8 epimers (**15a′** and **15b′**; 1:1 mixtures).

The above results can be rationalized by taking into account that, after the formation of the corresponding oxazolidines, lactamization occurs faster through a chairlike transition state in which the diastereotopic acetate (Scheme 2; from **2a** and **2b**) or propionate (Scheme 3; from **3a**) chain that does not undergo cyclization is equatorial. In accordance with this interpretation, the presence of an ethyl substituent at the prochiral carbon atom in **3b**[6] suppresses the discrimination between the two propionate chains (Table 3, entry 2). In this case, either the ethyl

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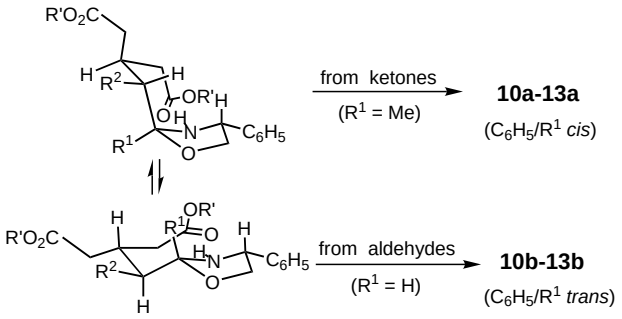
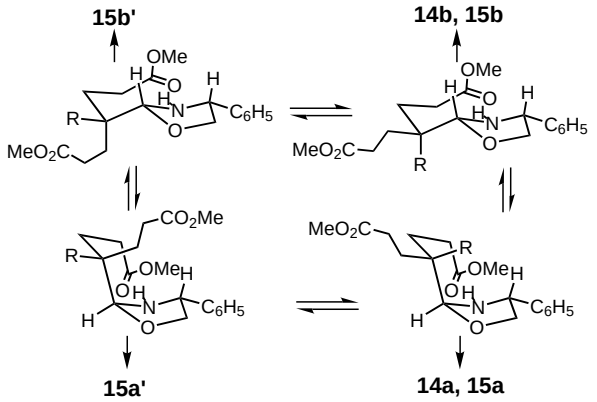


Scheme 2. Lactamization step in the formation of **10**–**13**.

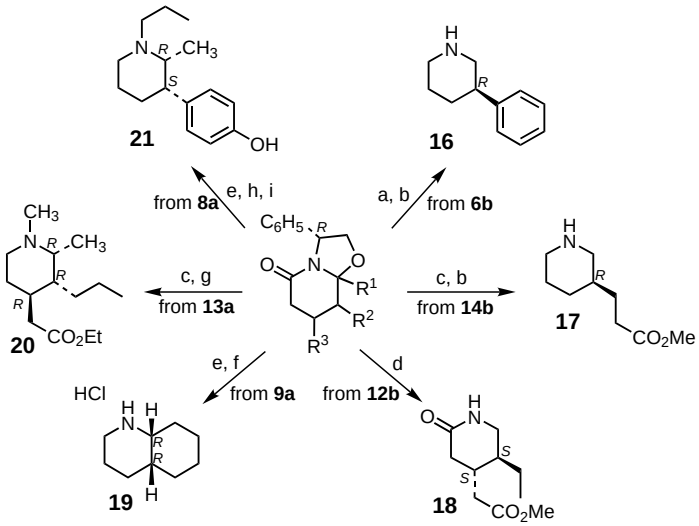


Scheme 3. Lactamization step in the formation of **14** and **15**.

substituent or one of the propionate chains is axially oriented (Scheme 3).

Finally, as could be expected from the above results, treatment of racemic δ-oxodiesters **2c** or **2d**[6] with (*R*)-phenylglycinol under the usual conditions predominantly afforded one of the eight possible stereoisomers, **12b** or **13a**, respectively (Table 2, entries 3 and 4). Three stereogenic centers with a well-defined absolute configuration have been generated in a single synthetic step. Minor amounts of the respective isomers **12a** or **13b** were also isolated.[7] These reactions involve DKR, with epimerization of the configurationally labile stereocenter in the substrate, and differentiation of the two diastereotopic acetate chains via a transition state in which the substituents R^2 and CH_2CO_2Et of the incipient chairlike six-membered lactam are equatorial (Scheme 2, R^2 = alkyl). In all cases, isomers **b** (C_6H_5 and R^1 = H are *trans*) are the major products in the cyclodehydrations from aldehydes, whereas bicyclic *cis* C_6H_5/Me lactams **a** are the main products from ketones.

The substituted chiral lactams **4**–**14** are immediate precursors of a variety of valuable enantiopure piperidine and perhydroquinoline derivatives, including functionalized 3-alkyl-, 3-aryl-, 2,3-dialkyl-, and 2-alkyl-3-arylpiperidines, as well as diversely substituted 4-piperidineacetates. Thus, after removal of the chiral auxiliary, bicyclic lactams **6b**, **14b**, and **12b** were converted into 3-phenylpiperidine **16**, 3-piperidinepropionate **17**, which is an intermediate in the synthesis of anti-obesity drugs,[11] and *trans*-3-ethyl-4-piperidineacetate **18**, the enantiomer of a crucial intermediate in the synthesis of benzo[*a*]- and indolo[2,3-*a*]quinolizidine alkaloids[12] (Scheme 4). Similarly, after stereoselective opening of the oxazolidine ring, lactams **9a**, **13a**, and **8a** were converted into *cis*-perhydroquinoline **19**, polysubstituted piperidine **20**, and *cis*-2-alkyl-3-arylpiperidine **21**, an analogue of the antipsychotic drug preclamol [(−)-3PPP].[13]



Scheme 4. Reagents and conditions: a) $LiAlH_4$, THF, 70%; b) H_2, $Pd(OH)_2$, EtOAc, 73% (**16**), 91% (**17**); c) BH_3, THF, 61% (from **14b**), 70% (from **13a**); d) Ca, liquid NH_3, then Et_3SiH, $TiCl_4$, THF, 53%; e) AlH_3, THF, 70% (from **9a**), 87% (from **8a**); f) HCl, MeOH, then H_2, Pd/C, 85%; g) H_2, Pd/C, MeOH, 73%; h) H_2, $Pd(OH)_2$, CH_3CH_2CHO, EtOAc, 79%; i) aq. HBr, 82%.

Simple chiral, aminoalcohol-derived bicyclic lactams that are either unsubstituted at the piperidine carbon atoms or bear an alkyl substituent at the angular C8a position have already been demonstrated to be extremely useful building blocks for the enantioselective construction of a number of natural and non-natural products.[4, 14] These syntheses require a later stereocontrolled formation of C–C bonds at the carbon atom positions of the nitrogen heterocycle. Advantageously, the chiral synthons described herein already incorporate the carbon substituents on the heterocyclic ring, thus expanding the potential of chiral bicyclic lactams for the enantioselective synthesis of piperidine derivatives.[15] Although the diastereoselectivity of the above cyclodehydrations ranges from only 4:1 to 9:1, taking into account that both enantiomers of phenylglycinol are commercially available and that this auxiliary is easily removable, this method provides a convenient straightforward access to polysubstituted piperidines in both enantiomeric series.

Received: July 30, 2001 [Z17626]
Revised: October 29, 2001

[1] a) M. Ohno, M. Otsuka, *Org. React.* **1989**, *37*, 1–55; b) E. Schoffers, A. Golebiowski, C. R. Johnson, *Tetrahedron* **1996**, *52*, 3769–3826.
[2] For reviews, see: a) R. S. Ward, *Chem. Soc. Rev.* **1990**, *19*, 1–19; b) S. R. Magnuson, *Tetrahedron* **1995**, *51*, 2167–2213; c) M. C. Willis, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1765–1784.
[3] a) R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56; b) R. S. Ward, *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490; c) S. Caddick, K. Jenkins, *Chem. Soc. Rev.* **1996**, *25*, 447–456.

  1433-7851/02/4102-0337 $ 17.50+.50/0

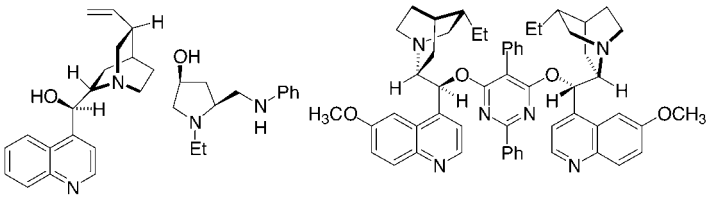
[4] a) M. Amat, J. Bosch, J. Hidalgo, M. Cantó, M. Pérez, N. Llor, E. Molins, C. Miravitlles, M. Orozco, J. Luque, *J. Org. Chem.* **2000**, *65*, 3074 – 3084; b) M. Amat, M. Pérez, N. Llor, J. Bosch, E. Lago, E. Molins, *Org. Lett.* **2001**, *3*, 611 – 614, and previous papers in this series.
[5] The reactions were carried out by heating a solution of the δ-oxoacid derivative and (*R*)-phenylglycinol in toluene at reflux: D. Romo, A. I. Meyers, *Tetrahedron* **1991**, *47*, 9503 – 9569.
[6] For the preparation of the starting δ-oxoacid derivatives, see Supporting Information.
[7] The isomers were separated by means of column chromatography and gave satisfactory analytical and/or spectroscopic data.
[8] For related examples which lead to tricyclic five-membered lactams, see: a) J. A. Ragan, M. C. Claffey, *Heterocycles* **1995**, *41*, 57 – 70; b) M. D. Ennis, R. L. Hoffman, N. B. Ghazal, D. W. Old, P. A. Mooney, *J. Org. Chem.* **1996**, *61*, 5813 – 5817.
[9] For mechanistic considerations in related cyclodehydrations from unsubstituted ketoacids, see: A. I. Meyers, S. V. Downing, M. J. Weiser, *J. Org. Chem.* **2001**, *66*, 1413 – 1419.
[10] Similar differences in stereoselectivity between unsubstituted aldehyde[4a] and ketoacid derivatives have been observed in related cyclodehydrations: a) A. A. Bahajaj, P. D. Bailey, M. H. Moore, K. M. Morgan, J. M. Vernon, *J. Chem. Soc. Chem. Commun.* **1994**, 2511 – 2512; b) M. J. Munchhof, A. I. Meyers, *J. Org. Chem.* **1995**, *60*, 7084 – 7085; c) N. Yamazaki, T. Ito, C. Kibayashi, *Tetrahedron Lett.* **1999**, *40*, 739 – 742.
[11] H. Zarrinmayeh, A. M. Nunes, P. L. Ornstein, D. M. Zimmerman, M. B. Arnold, D. A. Schober, S. L. Gackenheimer, R. F. Bruns, P. A. Hipskind, T. C. Britton, B. E. Cantrell, D. R. Gehlert, *J. Med. Chem.* **1998**, *41*, 2709 – 2719.
[12] For reviews, see: a) T. Fujii, M. Ohba, *Heterocycles* **1988**, *27*, 1009 – 1033; b) T. Fujii, M. Ohba, *Heterocycles* **1998**, *47*, 525 – 539.
[13] *Drugs Future* **1987**, *12*, 88 – 89.
[14] For reviews, see: a) A. I. Meyers, G. P. Brengel, *Chem. Commun*. **1997**, 1 – 8; b) A. I. Meyers, C. J. Andres, J. E. Resek, C. C. Woodall, M. A. McLaughlin, P. H. Lee, D. A. Price, *Tetrahedron* **1999**, *55*, 8931 – 8952; c) M. D. Groaning, A. I. Meyers, *Tetrahedron* **2000**, *56*, 9843 – 9873.
[15] For reviews, see: a) P. D. Bailey, P. A. Millwood, P. D. Smith, *Chem. Commun.* **1998**, 633 – 640; b) S. Laschat, T. Dickner, *Synthesis* **2000**, 1781 – 1813.

A Highly Enantioselective and General Conjugate Addition of Thiols to Cyclic Enones with an Organic Catalyst**

Paul McDaid, Yonggang Chen, and Li Deng*

Enantioselective conjugate addition is a fundamentally important transformation in asymmetric synthesis.[1] Catalytic enantioselective conjugate addition to cyclic enones has attracted considerable attention as a general and attractive strategy for the synthesis of optically active cyclic building blocks. A number of general and highly enantioselective conjugate additions of carbon nucleophiles to cyclic enones catalyzed by transition metals have been reported recently.[2] Excellent enantioselectivity has also been obtained in the conjugate addition of carbon nucleophiles to cyclohexenone and α,β-unsaturated aldehydes with organic catalysts.[3] However, the development of a general and highly enantioselective 1,4-addition of thiols to cyclic enones remains a challenging goal despite numerous attempts involving metal-based catalysts,[4] phase-transfer catalysts,[5] and organic catalysts.[6–11] We describe here significant progress toward accomplishing this goal using a readily available chiral organic catalyst.

Pioneering studies by Wynberg et al.[6] and Mukaiyama et al.[7] on the asymmetric 1,4-addition of thiols promoted by organic catalysts pinpointed chiral cyclic amines bearing a β-hydroxy group such as cinchonidine (**1**) and the proline-derived compound **2** as promising catalysts. The highest



1 **2** (DHQD)$_2$PYR **3**

enantioselectivities obtained with catalysts **1** and **2** in the conjugate additions of thiols to 5,5-dimethylcyclohexenone and cyclohexenone, respectively, are 75 and 88% *ee*.[6, 7] Unfortunately, in additions to other cyclic enones enantioselectivity was found to decrease significantly (<70% *ee*) with either catalyst.[6, 7] Since modification or removal of the hydroxy group of catalysts **1** and **2** led to drastically reduced catalyst efficiency, the enantioselective catalysis of **1** and **2** was attributed to a bifunctional mechanism involving the simultaneous activation of the cyclic enone and the thiol by the hydroxy and the amino groups, respectively.[6, 7] However, we recently observed that commercially available ethers of mono- and biscinchona alkaloids are more effective than natural cinchona alkaloids as chiral Lewis base catalysts for asymmetric nucleophile – electrophile reactions.[12] These observations prompted us to explore the possibility of using a modified cinchona alkaloid to catalyze highly enantioselective 1,4-additions of thiols to cyclic enones.

We first examined natural and modified cinchona alkaloids for their ability to promote enantioselective conjugate addition of thiophenol to cyclohexenone [Eq. (1)]. As illustrated in Table 1, modified cinchona alkaloids bearing no hydroxy groups are comparable to cinchonidine (**1**) in their catalytic activity. Especially notable is that the bis(dihydroquinidinyl)pyrimidine derivative (DHQD)$_2$PYR (**3**) was shown to be more effective than cinchonidine (**1**). Lacking a hydrogen donor, (DHQD)$_2$PYR (**3**) is unable to promote the enantioselective conjugate addition by means of a bifunctional catalysis mechanism similar to that proposed for **1** and **2**.[6, 7] Furthermore, reactions promoted by **3**, which was derived from quinidine, gave in excess the *R* isomer of the

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[**] This work was financially supported by National Institutes of Health (GM-61591), Research Corporation (RI-0311), and the Harcourt General Charitable Foundation.

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  1433-7851/02/4102-0338 $ 17.50+.50/0