A Three-Step Procedure for Asymmetric Catalytic Reductive Amidation of Ketones

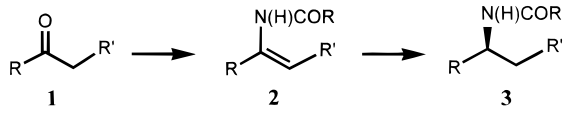
Mark J. Burk,* Guy Casy, and Nicholas B. Johnson

Chirotech Technology Ltd. and Chiroscience R&D Ltd., Cambridge Science Park, Milton Road, Cambridge CB4 4WE, U.K.

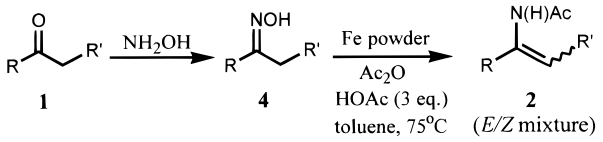
Received May 20, 1998

The value of optically active amines as resolving agents, as chiral auxiliaries, and as components of many important biologically active compounds is well documented. Accordingly, the development of practical methods for the production of enantiomerically pure amines is of cardinal interest. We recently have described the effectiveness of cationic Me-DuPHOS-Rh and Me-BPE-Rh catalysts for highly enantioselective hydrogenation of *N*-Ac-α-arylenamides to the corresponding *N*-Ac-α-arylalkylamines.[1] Despite the ostensible utility of this hydrogenation procedure, the dearth of efficient methods for synthesis of the enamide substrates[2,3] essentially has rendered this process unavailing, particularly for industrial manufacture of enantiomerically pure amines.

In addition to the demonstrated use of enamides in asymmetric hydrogenation reactions,[1,4] they have found application in numerous other areas of organic synthesis.[5] In an effort to provide practical access to prochiral enamides of type **2**, we now have developed an efficacious two-step route from simple ketones. We disclose preliminary results that indicate that a range of new enamides may be prepared readily and hydrogenated with high enantioselectivities using the Me-DuPHOS-Rh and/or Me-BPE-Rh catalyst systems. Conceptually, the combined three-step procedure offers a novel method for asymmetric catalytic reductive amidation of ketones (**1** → **3**).



Below we generically depict the method for enamide synthesis, which involves transformation of a ketone into an oxime of type **4** followed by subsequent reduction with iron metal in the presence of acetic anhydride.[6]



We have identified several reaction parameters that appear vital for success in the oxime reduction step. For instance, performing the reaction at moderate temperatures (≤75 °C) attenuates otherwise problematic product decomposition. Also, the introduction of acetic acid (3 equiv/mol of oxime) leads to definite enhancement of the oxime reduction rates. Finally, the use of a cosolvent (e.g., toluene) is an important factor that, under these conditions, greatly facilitates product isolation. The initial reduction mixture generally consists of both monoacetyl and diacetyl products that, through a simple 2 M NaOH wash, are converged into the desired monoacetyl enamides **2** in moderate to good yields (40−85%, unoptimized) and importantly in a high state of purity.

Figure 1 shows representative examples of varied enamides that have been produced using this method. Both acyclic and cyclic ketones may be cleanly converted to enamides via this method. When R′ is a non-hydrogen atom, the enamides are formed as *E*/*Z* mixtures. With regard to use of the latter enamides in asymmetric hydrogenation reactions, the DuPHOS-Rh and BPE-Rh catalysts have been found to be uniquely capable of reducing mixtures of *E* and *Z* enamides with high enantioselectivities.[1] Preliminary studies indicate that when both R and R′ groups of oxime **4** possess enolizable protons, regioisomeric enamides are formed. It is important to note that in most cases crude enamides **2** isolated via this procedure were crystalline solids of suitable purity to be employed directly in asymmetric catalytic hydrogenation reactions (vide infra).

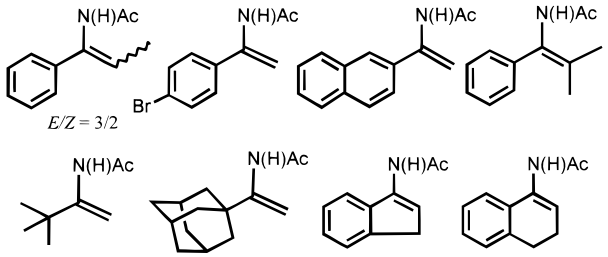


Figure 1. Representative enamides produced through reduction of ketone oximes.

(1) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142. DuPHOS refers to 1,2-bis(*trans*-2,5-disubstituted phospholano)-benzene ligands, whereas BPE indicates 1,2-bis(*trans*-2,5-disubstituted phospholano)ethane ligands. See ref 7 below for further information on these ligands.

(2) (a) Boar, R. B.; McGhie, J. F.; Robinson, M.; Barton, D. H. R.; Horwell, D. C.; Stick, R. V. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1237. (b) Heng-Suen, Y.; Kagan, H. B. *Bull. Soc. Chem. Fr.* **1965**, 1460. (c) Lenz, G. R. *Synthesis* **1978**, 489 and references therein. (d) Brettle, R.; Mosedale, A. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2185.

(3) (a) Heng-Suen, Y.; Horeau, A.; Kagan, H. B. *Bull. Soc. Chem. Fr.* **1965**, 1454. (b) Kagan, H. B.; Langlois, N.; Dang, T. P. *J. Organomet. Chem.* **1975**, *90*, 353.

(4) (a) Koenig, K. E. In *Asymmetric Synthesis*; Morrison, J. D, Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 3. (b) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117. (c) Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J. Org. Chem.* **1994**, *59*, 297. (d) Tschaen, D. M.; Abramson, L.; Cai, D.; Desmond, R.; Dolling, U.-H.; Frey, L.; Karady, S.; Shi, Y.-J.; Verhoeven, T. R. *J. Org. Chem.* **1995**, *60*, 4324.

(5) (a) Jutz, C. *Adv. Org. Chem.* **1976**, *9*, 225. (b) Meth-Cohn, O.; Westwood, K. T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1173. (c) Muller, H.-R.; Seefelder, M. *Justus Leibigs Ann. Chem.* **1969**, 728, 88. (d) Boar, R. B.; McGhie, J. F.; Robinson, M.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1242. (e) Sano, T.; Tsuda, Y. *Heterocycles* **1976**, *4*, 1361. (f) Sano, T.; Toda, J.; Kashiwaba, N.; Ohshima, T.; Tsuda, Y. *Chem. Pharm. Bull.* **1987**, *35*, 479. (g) Cook, A. G. In *Enamines*, 2nd ed.; Cook, A. G., Ed.; Marcel Dekker: New York, 1988; p 388. (h) Vilsmaier, E. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; Part 2, p 1356. (i) Mpango, G. B.; Mahalanabis, K. K.; Mahdavi-Damghani, Z.; Sniekus, V. *Tetrahedron Lett.* **1980**, *21*, 4823. (j) Baldwin, J. E.; DuPont, W. A. *Tetrahedron Lett.* **1980**, *21*, 1881. (k) Jurczak, J.; Golebioski, A. *Chem. Rev.* **1989**, *89*, 149.

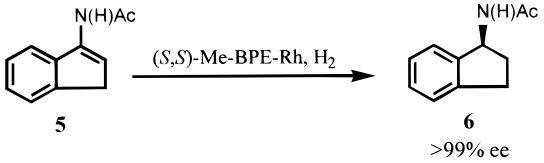
(6) The use of iron metal for reduction of a specific steroidal oxime has been reported; see: Barton, D. H. R.; Zard, S. Z. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2191. For reduction of nitroolefins using iron powder in acetic anhydride, see: Laso, N. M.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 1605.

(7) (a) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (b) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266. (c) Burk, M. J.; Feaster, J. E.; Nugent, W.A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (d) Burk, M. J.; Martinez, J. P.; Feaster, J. E.; Cosford, N. *Tetrahedron* **1994**, *50*, 4399. (e) Burk, M. J.; M. F. Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. (f) Burk, M. J.; Harper, T. G. P.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423. (g) Burk, M. J.; Gross, M. F.; Harper, T. G. P.; Kalberg, C. S.; Lee, J. R. Martinez, J. P. *Pure Appl. Chem.* **1996**, *68*, 37. (h) Burk, M. J.; Allen, J. G.; Kiesman, W. F. *J. Am. Chem. Soc.* **1998**, *120*, 657.

S0022-3263(98)00933-5 CCC: $15.00
Published on Web 08/20/1998

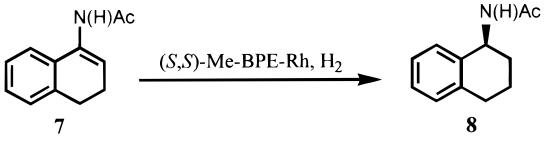
The synthetic procedure delineated above provides ready access to many different types of enamides that previously were unknown and have not been scrutinized in asymmetric hydrogenation reactions. Accordingly, we have surveyed the efficacy of the DuPHOS-Rh and BPE-Rh catalysts[7] for hydrogenation of several new enamides **2**.

Initial experiments focused upon enamides derived from the cyclic ketones 1-indanone and α-tetralone, respectively. Enantioselective hydrogenation of these types of enamides was unprecedented to our knowledge and could provide facile access to valuable amines that have proven useful in drug design efforts.[8] Preliminarily we examined a series of DuPHOS-Rh and BPE-Rh catalysts using a standard set of parameters (catalyst precursor = [(COD)Rh(diphosphine)]-BF_4, MeOH, 20 °C, S/C = 500, 200 psi H_2, 18 h). Under these conditions, we observed smooth hydrogenation of **5** to the desired 1-aminoindane derivative **6**. The least sterically encumbered Me-BPE-Rh catalyst was found to furnish the product with the highest enantioselectivity (>99% ee). High enantioselectivity also was achieved with the corresponding Me-DuPHOS-Rh catalyst, which yielded **6** with 98% ee, while the more sterically congested Et-DuPHOS-Rh catalyst provided **6** with slightly lower selectivity (95% ee).



We next examined the α-tetralone-derived enamide **7**. Under the same conditions outlined above, hydrogenation in the presence of (*S*,*S*)-Me-BPE-Rh afforded the desired product (*S*)-**8**, but surprisingly only moderate enantioselectivity was achieved (69% ee). Interestingly, in a parallel experiment, the more structurally rigid Me-DuPHOS-Rh catalyst effected only 50% conversion to **8**, and no asymmetric induction was achieved (0% ee).

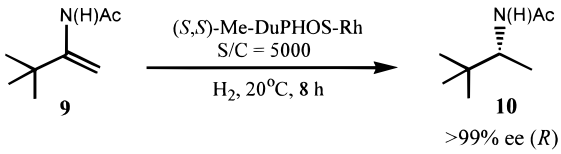
Table 1. Temperature Effects in the Me-BPE-Rh-Catalyzed Hydrogenation of 7



entry	*T* (°C)	% ee
1	50	54
2	20	69
3	10	90
4	0	92

As seen in Table 1, temperature had a large influence upon enantioselectivity in the hydrogenation of **7** using the Me-BPE-Rh catalyst. Higher temperatures resulted in a diminution of the selectivity to 54% ee. In contrast, a moderate reduction of temperature led to a striking increase in the enantioselectivity, with **8** being produced in 90% ee at 10 °C and 92% ee at 0 °C, respectively, and with little apparent decrease in rate. Such a significant enhancement of selectivity (Δee = 21%) over a 10 °C temperature range (entries 2−3) does not appear to be consistent with simple Arrhenius kinetic behavior and suggests that a mechanistic interchange may be occurring as the temperature is lowered. More detailed study clearly is required to ascertain these points.

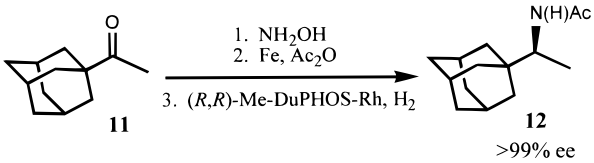
Another series of previously uncharted enamides are those derived from dialkyl ketones. Equation 1 displays the asymmetric hydrogenation of enamide **9**, which was prepared from pinacolone. A screen of our catalyst series revealed that Me-DuPHOS-Rh was paramount for this transformation. For example, when the (*R*,*R*)-Me-DuPHOS-Rh catalyst was employed at S/C = 1000, hydrogenation of **9** was complete within 5 min to afford (*S*)-**10** in >99% ee. Similarly, at S/C = 5000 the (*S*,*S*)-Me-DuPHOS-Rh catalyst induced complete conversion to (*R*)-**10** within 8 h at 20 °C with identical enantioselectivity (>99% ee).



(1)

In addition to the high catalytic efficiency and high enantioselectivity, another interesting aspect of this reaction is that *the Me-DuPHOS-Rh catalyst yielded product **10** with absolute configuration opposite to that predicted* on the basis of our previous results involving asymmetric hydrogenation of α-aryl enamides.[1] Hence, hydrogenation of **9** with the (*S*,*S*)-Me-DuPHOS-Rh catalyst rendered (*R*)-**10**, whereas hydrogenation of the corresponding phenyl-substituted enamide with the same catalyst provides the (*S*)-phenylethylamine derivative. Simple transmutation of an aromatic group on an enamide of type **2** (R = Ar) to a bulky alkyl substituent (e.g., R = *t*-Bu as in **9**) results in a reversal of the absolute stereochemistry observed in these hydrogenation reactions. Further mechanistic study will be required to provide a clear understanding of this observation.

Equation 2 illustrates the complete three-step reductive amidation process for conversion of 1-acetyladamantane (**11**) to the novel amine derivative **12** with high efficiency and high enantioselectivity (>99% ee), and again with converse absolute stereochemistry.



(2)

Overall, we have described the development of a practical three-step process for asymmetric catalytic reductive amidation of ketones. Several novel enamides were prepared and hydrogenated with high enantioselectivities for the first time. We presently are extending this process to other ketones and also to enamides bearing different *N*-acyl groups. These results will be reported in due course.

Acknowledgment. We gratefully acknowledge the vital analytical support provided by Catherine Rippe, Sean Savage, and Colin Dewar of ChiroTech's Analytical Team. We also thank Dr. Philip Gilbert for NMR analyses and Mr. Frank Sheldon for preliminary synthetic work.

Supporting Information Available: Experimental procedures, spectral data, and methods for enantiomeric excess determinations (10 pages).

JO9809332

(8) (a) Makovec, F.; Peris, W.; Frigerio, S.; Giovanetti, R.; Letari, O.; Mennuni, L.; Revel, L. *J. Med. Chem.* **1996**, *39*, 135. (b) Manara, L.; Badone, D.; Baroni, M.; Boccardi, G.; Cecchi, R.; Croci, T.; Guidice, A.; Guzzi, U.; Le Fur, G. *Pharmacol. Commun.* **1995**, *6*, 253. (c) Smith, R. A.; White, R. L.; Krantz, A. *J. Med. Chem.* **1988**, *31*, 1558. (d) Trivedi, B. K.; Blankley, C. J.; Bristol, J. A.; Hamilton, H. W.; Patt, W. C.; Kramer, W. J.; Johnson, S. A.; Bruns, R. F.; Cohen, D. M.; Ryan, M. J. *J. Med. Chem.* **1991**, *34*, 1043. (e) Gorin, F. A.; Balasubramanian, T. M.; Cicero, T. J.; Schwietzer, J.; Marshall, G. R. *J. Med. Chem.* **1980**, *23*, 1113.