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Stereoselective Synthesis of Pyrrolidine Derivatives via Reduction of Substituted Pyrroles

Chao Jiang and Alison J. Frontier*

Department of Chemistry, University of Rochester, Rochester, New York 14627

frontier@chem.rochester.edu

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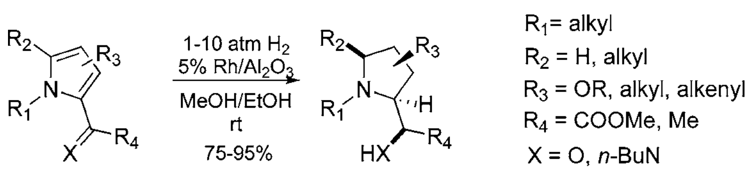
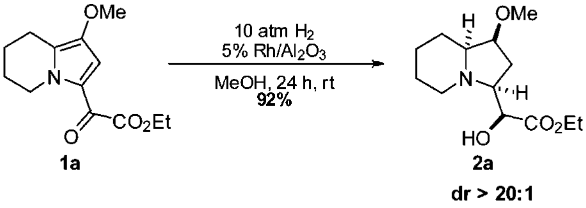
ABSTRACT



The heterogeneous catalytic hydrogenation of highly substituted pyrrole systems was studied. These aromatic systems could be fully reduced with excellent diastereoselectivity to afford functionalized pyrrolidines with up to four new stereocenters. It is likely that the reaction is a two-step hydrogenation sequence, and that initial reduction of the C═X bond provides a stereocenter that directs the subsequent reduction of the pyrrole.

Hydrogenative reduction of pyrroles to pyrrolidines using heterogeneous catalyst systems is a well-known process,[1] and it has been shown that hydrogen is typically delivered from just one face of the aromatic system. In this way, 2,5-disubstituted pyrroles are converted into *cis*-2,5-dialkylpyrrolidines.[2−4] One might expect that pyrroles with substituents containing stereogenic centers might undergo diastereoselective reduction, leading to a convenient method for stereoselective synthesis of substituted pyrrolidines of high complexity. A number of studies toward this goal have been conducted, with varying degrees of success with respect to diastereoselective pyrrole reduction.[5−9] Jefford,[5] Taylor[6] and Angle[7] have shown that, in bicyclic pyrroles, existing stereocenters can exert a strong directing effect to allow reduction to occur with high diastereoselectivity. However, only one study was found describing hydrogenation of pyrroles with a stereogenic centers on an acyclic chain. In this report, one pyrrole was reduced with high diastereoselectivity, while reduction of a closely related structure was unselective.[10]

Scheme 1. Diastereoselective Reduction of Pyrrole **1a**



During studies toward the synthesis of pyrrolidine-containing targets, our group found that hydrogenation of substituted pyrrole **1a**, with an α-ketoester substituent at the 2-position (see Scheme 1), led to reduction of both the ketone and the pyrrole ring with high diastereoselectivity. The hydrogenation reaction of the pyrrole **1a** was achieved with rhodium-on-

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[1] Gribble, G. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, pp 603−634.

[2] Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1979**, *101*, 1259−1265.

[3] Kaiser, H.-P.; Muchowski, J. M. *J. Org. Chem.* **1984**, *49*, 4203−4209.

[4] Gilchrist, T. L.; Lemos, A.; Ottaway, C. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3005−3008.

[5] (a) Jefford, C. W. *Curr. Org. Chem.* **2000**, *4*, 205−230. (b) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513−3518. (c) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 3119−3122. (d) Jefford, C. W.; Thornton, S. R.; Sienkiewicz, K. *Tetrahedron Lett.* **1994**, *35*, 3905−3908. (e) Jefford, C. W.; Sienkiewicz, K.; Thornton, S. R. *Tetrahedron Lett.* **1994**, *35*, 4759−4762. (f) Jefford, C. W.; Sienkiewicz, K.; Thornton, S. R. *Helv. Chim. Acta* **1995**, *78*, 1511−1524.

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alumina to give a single diastereomer **2a** (Scheme 1). The relative stereochemistry of the four stereocenters formed in this reaction was determined by an X-ray crystallography study of amine **2a**. The hydrobromide complex of **2a** was available via treatment of **2a** with benzyl bromide in refluxing ethanol,[11] and the crystal structure is shown in Figure 1. Since highly substituted pyrrolidines are valuable building blocks for the synthesis of chiral ligands, drugs, and other bioactive molecule,[12] further examination of this potentially general diastereoselective reduction of pyrroles was conducted.[13]

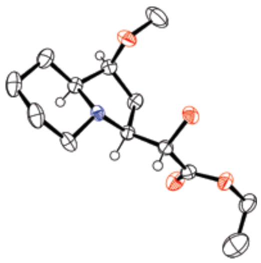
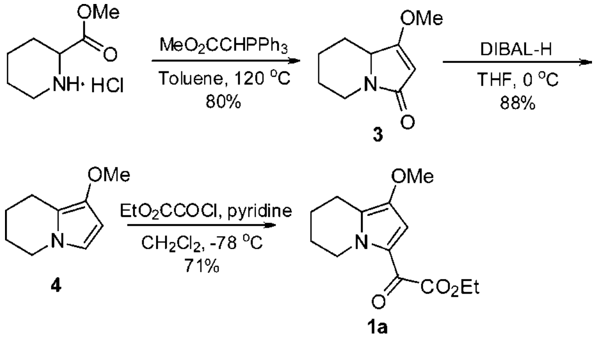


Figure 1. ORTEP drawing of the hydrobromide complex of **2a**.

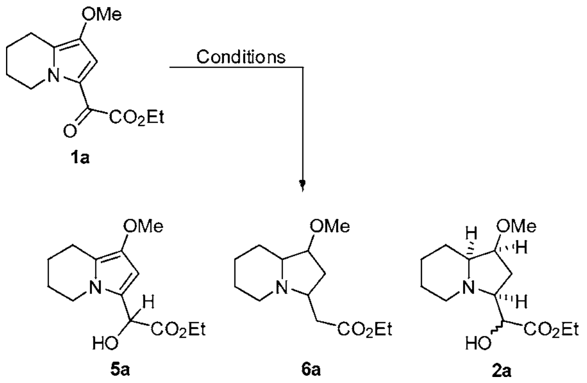
Bicyclic pyrrole **1a** was synthesized from pipecolic acid methyl ester in a three-step sequence (Scheme 2). Treatment of the ester with methoxycarbonylmethylene (triphenyl) phosphorane in refluxing toluene gave tetronic acid derivative **3** in 80% yield.[14] Reduction of **3** with DIBAL-H gave unstable pyrrole **4**,[15] which was immediately treated with ethyl or methyl oxalyl chloride to give α-ketoester **1a** in 71% yield.[16]

Scheme 2. Synthesis of Pyrrole **1a**



Different catalysts and reaction conditions were screened based on literature procedures (Table 1). Hydrogenation of **1a** gave varying ratios of undesired products **5a** and **6a** along with the desired pyrrolidines **2a**. It was found that Pt/Al_2O_3 reduced only the ketone to give primarily **5a**, along with both diastereomers of **2a** (entry 1). The major product of

Table 1. Catalyst Screening



entry	conditions	products (ratio)[a]	% yield	references
1	H_2 (10 atm), Pt/Al_2O_3, EtOH, 12 h	**5a**:**2a** (2:1)	94	
2	H_2 (3.7 atm), Rh/Al_2O_3, HOAc/MeOH, 16 h	**6a**:**2a** (1:10)	90	6b, 5c,d
3	H_2 (20 atm), Rh/Al_2O_3, TFA, 24 h	**6a**:**2a** (1:6.7)	84	4
4	H_2 (1 atm), Pd/C, MeOH, 12 h	**6a**:**2a** (1:3.3)	88	6a,b, 17
5	H_2 (3.7 atm), Pd/C, HOAc, 16 h	*b*		5d−f, 6b
6	H_2 (10 atm), Rh/C, EtOH, 24 h	**2a**	87	9
7	H_2 (10 or 1 atm), Rh/Al_2O_3, MeOH, 2 h	**2a**	92	2, 6a,b, 8, 10

[a] Ratio was determined by ^1H NMR of crude mixture. [b] Only decomposition products were observed.

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(6) (a) Bond, T. J.; Jenkins, R.; Ridley, A. C.; Taylor, P. C. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2241−2242. (b) Bond, T. J.; Jenkins, R.; Taylor, P. C. *Tetrahedron Lett.* **1994**, *35*, 9263−9266.

(7) Angle, S. R.; Boyce, J. P. *Tetrahedron Lett.* **1995**, *36*, 6185−6188.

(8) Artis, D. R.; Cho, I.-S.; Jaime-Figueroa, S.; Muchowski, J. M. *J. Org. Chem.* **1994**, *59*, 2456−2466.

(9) Castano, A. M.; Cuerva, J. M.; Echavarren, A. M. *Tetrahedron Lett.* **1994**, *35*, 7435−7438.

(10) Mori, M.; Hori, M.; Sato, Y. *J. Org. Chem.* **1998**, *63*, 4832−4833.

(11) Kantor, S. W.; Hauser, C. K. *J. Am. Chem. Soc.* **1951**, *73*, 4122−4131.

(12) For a comprehensive discussion of the importance of pyrrolidines and strategies for their synthesis, see: Schomaker, J. M.; Bhattacharjee, S.; Yan, J.; Borhan, B. *J. Am. Chem. Soc.* **2007**, *129*, 1996−2003.

(13) For a selection of recently reported methods for the stereoselective synthesis of pyrrolidines, see: (a) Reference 12. (b) Enders, D.; Thiebes, C. *Pure Appl. Chem.* **2001**, *73*, 573−578. (c) Vasse, J. L.; Joosten, A.; Denhez, C.; Szymoniak, J. *Org. Lett.* **2005**, *7*, 4887−4889. (d) Gebauer, J.; Dewi, P.; Blechert, S. *Tetrahedron Lett.* **2005**, *46*, 43−46. (e) Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953−955. (f) Galliford, C. V.; Beenen, M. A.; Nguyen, S. T.; Scheidt, K. A. *Org. Lett.* **2003**, *5*, 3487−3490. (g) Coldham, I.; Hufton, R.; Price, K. N.; Rathmell, R. E.; Snowden, D. J.; Vennall, G. P. *Synthesis* **2001**, 1523−1531. (h) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471−1474. (i) Besev, M.; Engman, L. *Org. Lett.* **2002**, *4*, 3023−3025.

(14) (a) Schobert, R.; Muller, S.; Bestmann, H.-J. *Synlett* **1995**, 425−426. (b) Löffler, J.; Schobert, R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2799−2802.

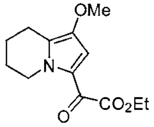
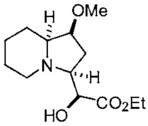
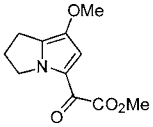
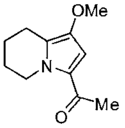
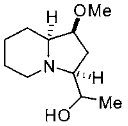
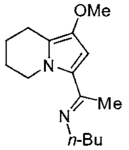
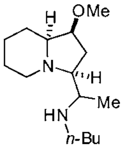
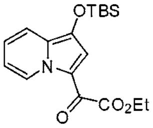
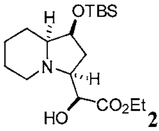
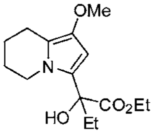
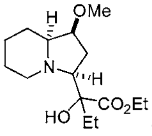
(15) Kochhar, K. S.; Pinnick, H. W. *J. Org. Chem.* **1984**, *49*, 3222−3224.

(16) Harrison, C.-A.; Jackson, P. M.; Moody, C. J.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1131−1136.

reduction using Rh/Al_2O_3 with HOAc or TFA was **2a**, as a mixture of two diastereomers, along with **6a** (entries 2 and 3). Pd/C gave the same result in alcoholic solvents (entry 4). Reduction with Pd/C in acetic acid led to decomposition (entry 5). Reduction with Rh/Al_2O_3 or Rh/C in alcohol gave the best results, delivering a single diastereomer of **2a** as the only product with yields of 92 and 88% (entries 6 and 7). Rh/Al_2O_3-catalyzed reductions could also be carried out under 1 atm of hydrogen pressure at room temperature: the reaction was complete in 2 h and gave **2a** with the same yield and selectivity as the reductions under 10 atm of hydrogen pressure.

Bicyclic pyrrole substrates with different substitution patterns were synthesized to study the scope of this heterogeneous catalytic reaction with rhodium-on-alumina (Table 2). The hydrogenation reaction of the pyrrole **1b**, with a fused five-membered ring, gave a complex mixture that was hard to analyze (entry 2). The hydrogenation reaction of the pyrrole **1c**, with an acetyl group at the 2-position instead of an α-ketoester, gave a single diastereomer **2c** (entry 3). The hydrogenation reaction of pyrrole **1d**, with an imino group at the 2-position, gave only diastereomer **2d** (entry 4). The hydrogenation reaction of indolizine **1e**,[18] with a TBSO group at the 4-position, gave one diastereomer **2e** (entry 5). The hydrogenation reaction of pyrrole **1f**, with a tertiary alcohol substitution at the 2-position, gave **2f** as a 9:1 ratio of two diastereomers (entry 6).

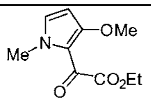
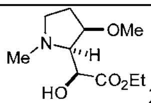
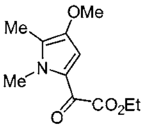
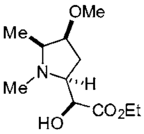
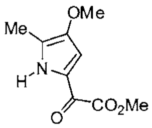
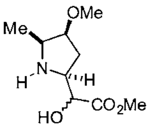
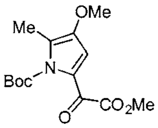
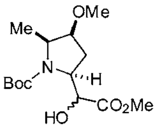
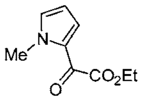
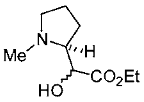
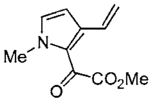
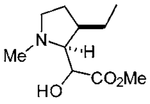
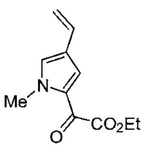
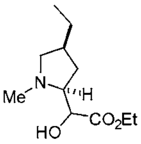
Table 2. Stereoselective Reduction of Bicyclic Pyrroles[a]

entry	pyrrole	ratio	% yield	product[b]
1	 **1a**	>20:1	92	 **2a**
2	 **1b**	--	--	--
3	 **1c**	>20:1	90	 **2c**
4	 **1d**	>20:1	75	 **2d**
5	 **1e**	>20:1	91	 **2e**
6	 **1f**	9:1	91	 **2f**

[a] Reaction conditions: 10 atm H_2, 5% Rh/Al_2O_3 (w/w), room temperature, MeOH or EtOH. [b] Stereochemistry of product in entry 5 was tentatively assigned based on structure determination of **2a**.

Acyclic alkyl-substituted pyrroles were also studied under the same conditions with rhodium-on-alumina (Table 3). The hydrogenation of *N*-methyl pyrrole **1g**, with a methoxy group at the 3-position, gave one diastereomer **2g** with three stereocenters (entry 1). The hydrogenation of *N*-methyl pyrrole **1h**, with a methyl group at the 5-position, gave one diastereomer **2h** with four stereocenters (entry 2). Hydrogenations of pyrroles with substitution other than methyl (i.e., **1i** and **1j**) gave mixtures of two diastereomers (**2i** and **2j**, respectively, entries 3 and 4). Pyrrole **1k**, which is unsubstituted at the 3-, 4-, and 5-positions, also gave a mixture of two diastereomers **2k** (entry 5). Hydrogenations of pyrroles

Table 3. Stereoselective Reduction of Substituted Pyrroles[a]

entry	pyrrole	ratio	% yield	product[b]
1	 **1g**	>20:1	91	 **2g**
2	 **1h**	>20:1	90	 **2h**
3	 **1i**	~3:1	90	 **2i**
4	 **1j**	~2:1	95	 **2j**
5	 **1k**	~1:1	93	 **2k**
6	 **1l**	>20:1	92	 **2l**
7	 **1m**	>20:1	91	 **2m**

[a] Reaction conditions: 10 atm H_2, 5% Rh/Al_2O_3 (w/w), room temperature, MeOH or EtOH. [b] Stereochemistry of products in entries 1 and 2 was tentatively assigned based on structure determination of **2a**.

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(17) Mori, M.; Hashimoto, A.; Shibasaki, M. *J. Org. Chem.* **1993**, *58*, 6503−6504.

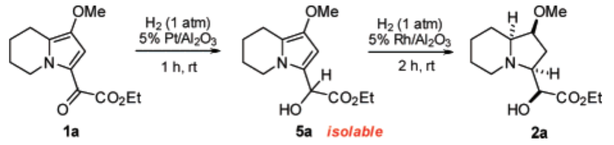
(18) The indolizine substrates were synthesized according to the procedure of: Gevorgyan, Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050−12051. For details, see the Supporting Information.

with a vinyl group at the 3- and 4-positions (i.e., **1l** and **1m**) gave one diastereomer (**2l** and **2m**, respectively, entries 6 and 7).

It is important to emphasize that it was not possible to determine the structures of pyrrolidines **2** by simple spectroscopic techniques. X-ray crystallographic analysis of **2a** was carried out, but other compounds **2** did not crystallize readily. Therefore, the relative stereochemistry of compounds **2c**−**2h**, **2l**, and **2m** has not yet been unambiguously assigned. Tentative assignments have been made based on the stereochemical result of the closely analogous hydrogenation of **1a** (see Tables 2 and 3) because it seems reasonable to propose that all of these highly selective reductions are likely to produce products with the same relative stereochemistry. Efforts to obtain data that confirm these assignments are underway.

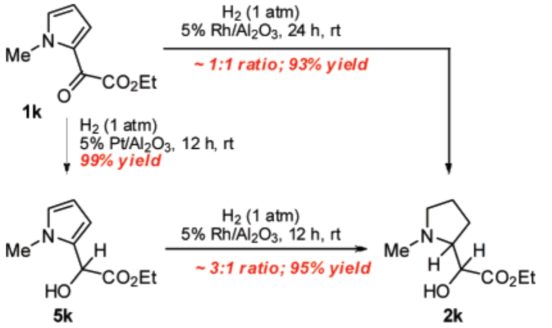
During optimization experiments, it was found that, using either Rh/Al_2O_3 or Pt/Al_2O_3, hydrogenation of the ketone occurs first to give unstable pyrrole **5a**, which can be isolated (Scheme 3). Further reduction delivers pyrrolidine **2a**. While hydroxyl groups often direct hydrogenation of neighboring olefins,[19,20] it is difficult to assess directing effects in this case because of the unknown orientation of the side chain during reduction. Simple analysis suggests that hydrogen is delivered to the face *anti* to the hydroxyl group, indicating that the stereocenter on the side chain may hinder approach to one face of the pyrrole rather than complexing to the catalyst.

Scheme 3. Stepwise Reduction of Pyrrole **1a**



Another interesting observation was made during the unselective reduction of **1k**. Hydrogenation product **2k** was not generated selectively during hydrogenation using Rh/Al_2O_3 (Scheme 4). In contrast, partial reduction to **5k** could be achieved using Pt/Al_2O_3 as catalyst, *and hydrogenation of* ***5k*** *was more diastereoselective than hydrogenation of* ***1k****.*

Scheme 4. Diastereoselectivity in the Hydrogenation of **1k**



Taken together, the results shown in Schemes 3 and 4 suggest that (1) the pyrrole alcohol stereocenter must be present for diastereoselective reduction to occur, *but* (2) the diastereoselectivity of the reduction is not completely controlled by the alcohol stereocenter. Finally, it appears that (3) the electron-donating methoxy group may slow the reduction rate of the pyrrole ring relative to the ketone carbonyl.

In summary, an efficient and diastereoselective heterogeneous catalytic hydrogenation reaction of highly substituted pyrrole systems has been developed to synthesize pyrrolidine derivatives stereoselectively. Efforts to expand the scope of the hydrogenation and develop a convenient enantioselective protocol for the reduction of substituted pyrroles are underway.

Acknowledgment. We thank the University of Rochester for support of this work. The authors thank Tulay Aygan Atesin (University of Rochester) for conducting preliminary studies on the hydrogenation of pyrrole **1a**. We also thank Dr. William Brennessel (University of Rochester) for carrying out an X-ray crystallographic study of compound **2a**, and Dr. Alice Bergmann (SUNY at Buffalo) for the collection of high-resolution mass spectra.

Supporting Information Available: Experimental procedures and spectral data for all new compounds, including crystallographic data for **2a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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