Kinetic Resolution of Racemic Disubstituted 1-Pyrrolines *via* Asymmetric Reduction with a Chiral Titanocene Catalyst

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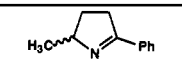
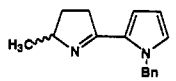
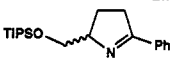
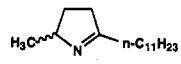
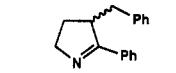
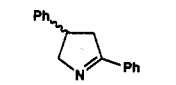
We recently reported the highly enantioselective hydrogenation of ketimines using chiral titanocene catalysts.[1] These results led us to explore the utility of this catalyst for the kinetic resolution of racemic imines.[2,3] In our earlier work, the reduction of cyclic imines was shown to proceed with particularly good enantioselectivity. This, combined with the interest, in terms of both their synthesis[4] and their biological activity,[5] made disubstituted 1-pyrrolines ideal racemic substrates for kinetic resolution.

We first studied the hydrogenation of (±)-5-methyl-2-phenyl-1-pyrroline[6a] (**1a**) (Table 1, entry 1). As previously reported,[1] the active catalyst was generated *in situ* from enantiomerically pure titanocene precatalyst **A** (5 mol %).[7] The hydrogenation was allowed to proceed in THF at ~65–75 °C and 80 psig of H_2 until the reaction had proceeded to 50% conversion.[8] The reaction was monitored by ^{1}H NMR analysis, and when ~50% conversion of **1a** to **2a** was reached, the reaction was stopped. After removal of solvent and chromatographic separation, pyrroline *R*-(+)-**1a** and *cis*-pyrrolidine 2*R*,5*S*-(−)-**2a** were isolated in good yields and with high levels of enantiomeric excess (Scheme 1).[9,10]

Table 1. Kinetic Resolution of Disubstituted 1-Pyrrolines[a]

entry	substrate		yield, %[b] (ee, %)[c] recovered 1	yield, %[b] (ee, %)[d] 2
1		(±)-**1a**	37 (99)	34 (99)
2		(±)-**1b**	42 (96)	44 (98)
3		(±)-**1c**	43 (98)	41 (98)
4[e]		(±)-**1d**	41 (>95)	41 (>95)
5		(±)-**1e**	-(75)[f]	42 (>95)[g]
6		(±)-**1f**	33 (49)	44 (99)[h]

[a] The reactions were carefully monitored by ^{1}H NMR (**1a–d**) or GC (**1e,f**) to 50% conversion (GC analysis of the crude mixture of **1a–d** is not optimal due to the partial conversion of **2** to **1**). [b] Yields of pure isolated materials (>95% pure), based on both enantiomers (50% is the maximum yield). All compounds were characterized by ^{1}H, ^{13}C NMR, HRMS, and IR spectroscopy (see supplementary material). [c] Enantiomeric excesses for **1a–c,e–f** were determined by HPLC using a Chiracel OD column. Recovered **1d** was reduced with DIBAL[10b] to the corresponding *cis*-2,5-pyrrolidine and the ee was determined by ^{1}H NMR analysis of the (*S*)-Mosher amide.[13] [d] Enantiomeric excesses were determined by HPLC (Chiracel OD column) for compounds **2a–c,e–f**; compound **2d** was analyzed using ^{1}H NMR spectrum of the (*S*)-Mosher amide.[13] [e] For conversions slightly higher than 50%, small amounts (~2%) of the 2-methyl-5-undecanyl-1-pyrroline isomer were detected in the ^{1}H NMR spectra of the crude reaction mixtures. [f] The yield of unreacted imine **1e** could not be determined because it racemizes on the deactivated silica gel column. The ee was determined by HPLC on the crude material (see supplementary material for details). [g] Reduced product **2e** consisted of a mixture of *cis* and *trans* isomers in a ratio of 85:15. Both *cis* and *trans* isomers had >95% ee. [h] Reduced product **2f** consisted of a mixture of *cis* and *trans* isomers in a ratio of 75:25. Both *cis* and *trans* isomers had 99% ee.

This kinetic resolution of 2,5-disubstituted pyrrolines was shown to be a relatively general process (Table 1). As can be seen from entries 1–3, substrates with varying combinations of aromatic groups at the 2 position and 5-alkyl substituents underwent effective kinetic resolution. To test whether this methodology could be extended to substrates in which the substituents at both the 2 and 5 positions of the starting pyrroline were unbranched alkyl groups, we prepared racemic **1d**[6d] (entry 4). That this did not proceed further for at least 20 h at either temperature. However, upon prolonged heating, reduction of the "mismatched" substrate took place. We attribute this to catalyst "decomposition", resulting in the formation of a new, nonselective catalyst which subsequently reduces the mismatched substrate.

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(1) (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562. (b) Willoughby, C. A.; Buchwald, S. L. *J. Org. Chem.* **1993**, *58*, 7627.

(2) For a recent example of kinetic resolution of acyclic imines reported while this study was in progress, cf.: Lensink, C.; de Vries, J. G. *Tetrahedron: Asymmetry* **1993**, *4*, 215.

(3) For leading references on kinetic resolution, see: (a) Van Nieuwenhze, M. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7864. (b) Kagan, H. B.; Fiaud, J. C. *Topics Stereochem.* **1988**, *18*, 249. For a related kinetic resolution of dihydropyrans, see: Morken, J. P.; Didiuk, M. T.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1994**, *116*, 3123.

(4) For recent examples of synthetic interest in pyrrolines, see: (a) Burk, R. M.; Overman, L. E. *Heterocycles* **1993**, *35*, 205. (b) Hua, D. H.; Park, J.-G.; Katsuhira, T.; Bcharathi, S. N. *J. Org. Chem.* **1993**, *58*, 2144.

(5) (a) Braekman, J. C.; Daloze, D. *Studies Nat. Prod. Chem.* **1990**, *6*, 421. (b) Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1982**, *38*, 1949. (d) Take, K.; Okumura, K.; Tsubaki, K.; Terai, T. *Chem. Pharm. Bull.* **1993**, *41*, 501.

(6) Optimum results, with respect to rate of reaction, are obtained when freshly purified substrates (either by distillation or chromatography) are employed. The pyrroline substrates were prepared as follows. (a) Racemic **1a** was prepared by addition of PhLi to (±)-5-methyl-*N*-((*E*)-2-phenylethenyl)-2-pyrrolidinone[6ci] following a procedure similar to one reported previously: Bielaski, J.; Brandänge, S.; Linblom, L. *Heterocycles* **1978**, *15*, 97. (b) Racemic **1b** was prepared by addition of pyrrole to (±)-5-methyl-2-pyrrolidinone, cf.: Rapoport, H.; Castagnoly, N. *J. Am. Chem. Soc.* **1962**, *84*, 2179. Treatment of the resulting imine with KH/BnBr in THF afforded (±)-**1b**. (c) Racemic **1c** was prepared from (±)-5-carbethoxy-2-pyrrolidinone [(i) Kwon, T. W.; Keusenkothen, P. F.; Smith, M. B. *J. Org. Chem.* **1992**, *57*, 6169] by the following sequence of reactions: (1) protection of the amide with an (*E*)-2-phenylethenyl group [(ii) Zezza, C. A.; Smith, M. B. *Synth. Commun.* **1987**, *17*, 729]; (2) reduction of the ester moiety;[6ci] (3) protection of the hydroxylic group (TIPSOTf/NEt_3/CH_2Cl_2/DMAP); (4) addition of PhLi.[6a] (d) Racemic **1d** (reported in Célérier, J. P.; Mars, E.; Lhommet, G. *J. Heterocycl. Chem.* **1988**, *25*, 1275) was prepared from (±)-5-methyl-1-(trimethylsilyl)-2-pyrrolidinone by a procedure related to that reported in: Hua, D. H.; Miao, S. W.; Bharathi, S. N.; Katsuhira, T.; Bravo, A. A. *J. Org. Chem.* **1990**, *55*, 3682. (e) Racemic **1e** was prepared from *N*-vinyl-2-pyrrolidinone as reported by: Haslego, M. L.; Maryanoff, C. A.; Scott, L.; Sorgi, K. L. *Heterocycles* **1993**, *35*, 643. (f) Racemic **1f** was prepared from 1,1-ethylenedioxy-1,3-diphenyl-4-aminobutane (see supplementary material). 1,1-Ethylenedioxy-1,3-diphenyl-4-aminobutane was prepared from 1,3-diphenyl-4-nitrobutan-1-one (Belsky, I. *J. Chem. Soc., Chem. Commun.* **1977**, 237) in two steps according to: Botteghi, C.; Paganelli, S.; Schionato, A.; Boga, C.; Fava, A. *J. Mol. Catal.* **1991**, *66*, 7.

(7) (a) Wild, F. R. W. P.; Zsolnai, J.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1982**, *232*, 233. (b) Collins, S.; Kuntz, A. B.; Hong, Y. *J. Org. Chem.* **1989**, *54*, 4154.

(8) To obtain the best results, it is important to monitor the reaction to 50% conversion. We found that for **1a**, when the reaction was run at 65 °C, it takes ~50 h to reach 50% conversion, compared to ~30 h at 75 °C. (The temperature was regulated for **1a,e,f** using a temperature regulator purchased from I^{2}R, Cheltenham, PA.) After 50% conversion was reached, the reduction

(9) (a) Unreacted **1a** and **1b** were both determined to have an *R* absolute configuration by independent synthesis. Commercially available (*S*)-(+)-5-(hydroxymethyl)pyrrolidinone was converted to (*R*)-5-methylpyrrolidinone as described in the following: (i) Silverman, R. B.; Levy, M. A. *J. Org. Chem.* **1980**, *45*, 815. (ii) McIntosh, J. M.; Acquaah, S. O. *Can. J. Chem.* **1988**, *66*, 1752. This was then converted to **1a** and to **1d** by the method given in refs 6a and 6d. Pyrrolines **1b** and **1c** isolated from the kinetic resolution protocol are assumed to be of the *R* configuration by analogy. (b) The *cis* relative configuration of the pyrrolidines obtained in the hydrogenation process was demonstrated for **2a** by preparing its known *N*-methyl derivative.[9a]

(10) (a) Tokuda, M.; Yamada, Y.; Takagi, T.; Suginome, H. *Tetrahedron* **1987**, *43*, 281. (b) Bacos, D.; Célérier, J. P.; Marx, E.; Saliou, C.; Lhomet, G. *Tetrahedron Lett.* **1989**, *30*, 1081. Reduction of racemic **1** using this procedure was also used to obtain samples of all the racemic amines.

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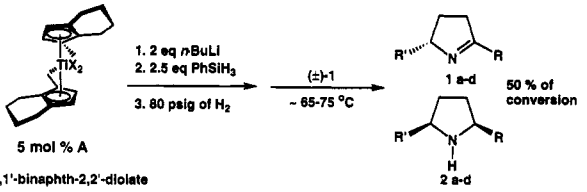
Scheme 1



pyrroline gave both recovered **1d** and pyrrolidine **2d** in high optical yield indicates that substrates of this type can also be efficiently kinetically resolved by this catalyst system.

We then examined the efficiency of kinetic resolution of pyrroline substrates with different substitution patterns. To this end, we prepared 3-benzyl-2-phenyl-1-pyrroline[6e] (**1e**) and 2,4-diphenyl-1-pyrroline[6f] (**1f**) and subjected these substrates to our standard kinetic resolution protocol. As shown by entry 5 in Table 1, a modest kinetic resolution was achieved for the 2,3-disubstituted pyrroline **1e** (75% ee for the unreacted **1e**). The resolution of 2,4-disubstituted pyrroline **1f** showed relatively poor selectivity (49% ee for the unreacted **1f**). Although kinetic resolution of 2,3- and 2,4-disubstituted substrates is not as efficient as that of the 2,5-disubstituted substrates, the reduction proved to be highly enantioselective; both *cis* and *trans* isomers of **2e** and **2f** (entries 5 and 6, Table 1) were produced with very high enantioselectivity (>95%). The reduction of both substrates **1e** and **1f** produced predominantly *cis* products. Substrate **1e** was reduced with a slightly higher level of diastereoselectivity (*cis*:*trans* 85:15) than was **1f** (*cis*:*trans* 75:25).

As previously described,[1] our working model postulates that a Ti(III) hydride is the active catalyst. The high enantiomeric excesses of both the recovered pyrroline and the reduced pyrrolidine for the 2,5-disubstituted cases (**1a–d**) indicate a very large difference in the rate of reaction of the enantiomers of the substrate.[3b] As shown in Figure 1, these results may be explained by considering the matched transition state **C** and the mismatched transition state **D**.[11] In **D**, the substituent at C5 is forced to reside in the wedge between the two tetrahydroindenyl moieties, while in **C**, it is pointed away from the bulky ligand.[12] This model predicts that substrates with a substituent at C3 should

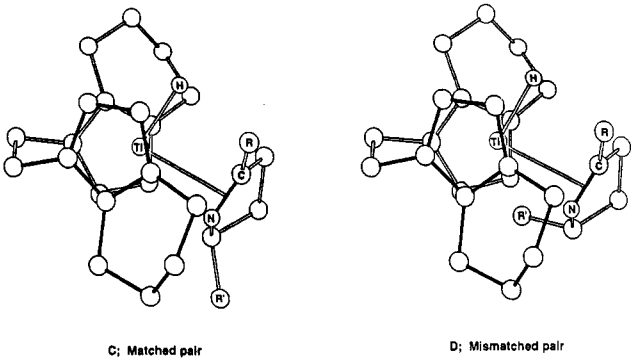


Figure 1. Ball and stick representation of the two diastereomeric imine titanium hydride complexes.

be more efficiently kinetically resolved than those with a substituent at C4. This prediction is consistent with the result that the ee of the recovered pyrroline obtained with substrate **1e** is higher than that for recovered substrate **1f** (Table 1).

In summary, we have developed an extremely efficient method for the kinetic resolution of 2,5-disubstituted 1-pyrrolines. At ~50% conversion, this process provides both pyrrolines **1** and *cis*-pyrrolidines **2** in good yields and with excellent enantiomeric excesses. We are currently examining the extension of this methodology to a variety of different classes of substrates.

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Supplementary Material Available: Experimental procedures for the preparation and spectroscopic characterization for compounds **1a–f** and **2a–f** (12 pages). This material is contained in many libraries on a microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(12) The diastereomeric excess for the mismatched pair could not be determined accurately due to the long reaction times made necessary by the very slow rate of the reaction and the instability of the catalyst species.

(13) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Am. Chem. Soc.* **1969**, *34*, 2543. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.