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Asymmetric Hydrogenation of Tetrahydropyrazines: Synthesis of (S)-Piperazine-2-tert-butylcarboxamide, an Intermediate in the Preparation of the HIV Protease Inhibitor Indinavir.

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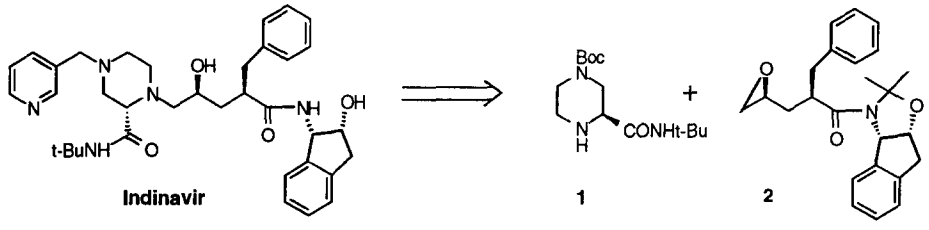
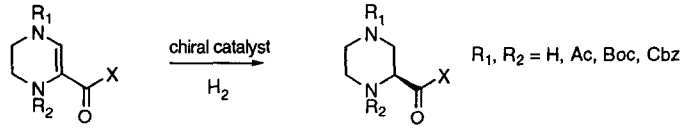
Abstract: *Hydrogenation of tetrahydropyrazine **4g** with [(R)-BINAP(COD)Rh]TfO gave piperazine **6g** in 96% yield and 99% ee. Simple hydrogenolytic deprotection and crystallization afforded the key chiral (S)-N-Boc-piperazine MK-639 intermediate **1** in high yield and enantiomeric purity.*

Of the many potential therapeutic targets in the treatment of AIDS, inhibition of the HIV protease enzyme continues to show the most promise as an effective means of antiretroviral therapy.[1] The progression of the Merck HIV protease inhibitor Indinavir Sulfate (formerly L-735,524)[2] to phase III clinical trials has necessitated the development of practical and efficient methodology for the large scale preparation of this complex molecule.



Indinavir **1** **2**

At present, Indinavir is constructed by coupling epoxide **2**[3] with (S)-2-*tert*-butylcarboxamide-4-*tert*-butoxycarbonylpiperazine (**1**). While **1** has been previously prepared utilizing classical chemical resolution methodology,[4] an asymmetric catalytic hydrogenation of tetrahydropyrazine derivatives, e.g. **3** or **4**, appeared to be an attractive alternative.

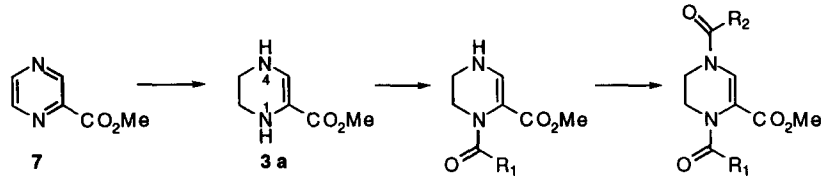


3 X = OMe
4 X = NHt-Bu

5 X = OMe
6 X = NHt-Bu

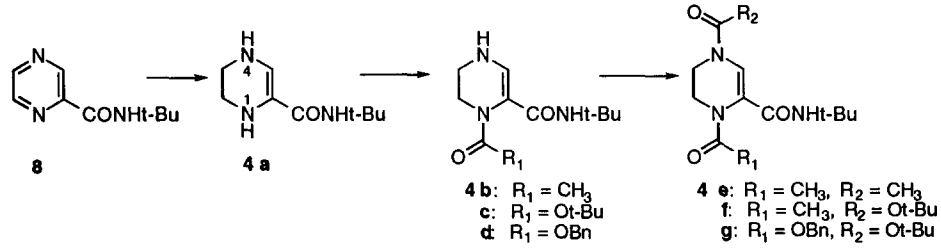
While standard acyclic α-(acylamino)acrylic acids and their methyl esters have been efficiently reduced asymmetrically with a variety of Rh/chiral bisphosphine catalysts,[5] analogous reductions of tetrahydropyrazine derivatives **3** or **4** have not been reported. In addition, the cyclic nature of the tetrahydropyrazine system, and

the contribution of the vinylogous urethane (X = OMe) or urea (X = NHt-Bu) can be expected to perturb the catalyst-olefin interaction and hence the reduction.



The tetrahydropyrazine substrates **3** and **4** were readily obtained by partial hydrogenation of the corresponding pyrazines with Pd/C. In the case of pyrazine ester **7**, the hydrogenation stopped cleanly at **3a**[6] and the two nitrogen atoms were readily differentiated by sequential protection. The lone pair of N4 is conjugated with the ester carbonyl group and is consequently less basic than N1. Protection of N1 as its acetamide, Cbz or Boc carbamate, **3 b-d**, was accomplished under standard conditions; however, subsequent protection of N4 (Ac_2O or Boc_2O) required the presence of DMAP and gave **3 e-h**.

While the partial hydrogenation of pyrazine amide **8** to **4a** is possible under tightly controlled hydrogenation conditions,[7] tetrahydropyrazine **4a** was also readily trapped as **4b** or **4c** by hydrogenation of **8** in a Parr shaker with Pd/C in the presence of Ac_2O or Boc_2O, respectively. Again, N4 was protected as its corresponding acetamide or Boc derivative using Ac_2O or Boc_2O in the presence of DMAP to give **4 e** or **f**, respectively.[8]



A systematic study was undertaken to study the influence of substrate substitution pattern, reaction conditions, and various Rh catalysts on the hydrogenation. Since commonly studied chiral hydrogenation substrates contain an acetamide and a CO_2Me group, **3f** was chosen as the model substrate. The corresponding piperazine **5** was obtained with [(chiral bisphosphine)(COD)Rh]TfO catalysts; however, the observed ee's were unexpectedly low (Table 1).[9] Even Et-DUPHOS and BINAP ligands, which give >98%ee with simple acyclic α-(acylamino)acrylic acids, resulted in <60% ee.

Table 1: Hydrogenation of **3f** with [(chiral bisphosphine)(COD)Rh]TfO

Catalyst	Boc-BPPM	PROPHOS	SKEWPHOS	Et-DUPHOS	DIOP	BINAP
ee	21	22	23	50	55	56
yield	87	41	86	97	90	88

Conditions: 3 mol% catalyst, 70 bar H_2 at 40°C, CF_3CH_2OH(TFE)

Next, the influence of reaction conditions was examined using the Et-DUPHOS/Rh catalyst with substrate **3f**. The ee increased from a level of ca. 48% in MeOH or TFE to ca. 58% in the less polar IPA or t-amylalcohol solvents; however, addition of non-alcoholic solvents (CH_2Cl_2/IPA) either did not improve the observed ee, or inhibited the reaction (toluene/IPA). In contrast to what is expected from the accepted mechanism for these reactions, the observed ee's were virtually identical at both 3 and 70 bar.[10]

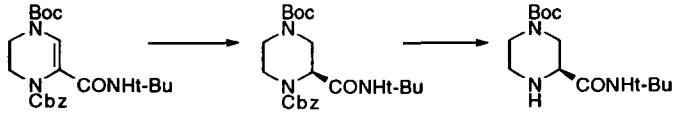
As neither catalyst nor reaction condition variation resulted in a satisfactory chiral hydrogenation, the influence of the substrate structure was examined next with [Et-DUPHOS(COD)Rh]TfO (Table 2). Consequently, the hydrogenations of the N1 acylated substrates **3 f-h** were examined.[11] The observed ee's were largely independent on the substitution at N1, and acetamide **3f**, and Cbz and Boc derivatives **3g** and **3h** all gave ca. 50% ee. The effect of the electronic character of the olefin was then explored by evaluation of several differentially substituted N4 derivatives on both the Me ester and the *tert*-butylcarboxamide. Decreasing the availability of the N4 lone pair for conjugation with the ester or amide by going from N-H to Boc or acetamide improved the observed ee. The exception was **3e**, where the olefin has become so electron poor, that it is a poor hydrogenation substrate. Interestingly, the optical inductions observed with the vinylogous urea derivatives **4** were slightly better than those of the corresponding vinylogous urethanes **3**.

Table 2: Substrate Dependence of Hydrogenation with [Et-DUPHOS (COD) Rh]TfO

Substrate	ee	yield	Substrate	ee	yield
3b	32	95	**4b**	39	97
3e	47	78	**4e**	69	98
3f	50	97	**4f**	70	95
3g	56	57	**4g**	65	83
3h	49	94			

Conditions: 3 mol% catalyst, 70 bar H_2 at 40°C, CF_3CH_2OH solvent

The above results (Table 1 and 2) coupled with the need for appropriate substitution in order to prepare the MK-639 intermediate **1**, led us to attempt to reduce **4g** in the presence of [(R)-BINAP(COD)Rh]TfO.[12] ***Hydrogenation with 2% catalyst in MeOH at 70 bar gave a 96% yield of 6g in 99% ee.***[13] Hydrogenolytic removal (Pd/C, MeOH) of the Cbz group, followed by crystallization gave **1** in 99% yield and >99% ee.



4g **6g** **1**

In summary, an efficient asymmetric synthesis of the key piperazine intermediate **1** for the HIV-protease inhibitor Indinavir Sulfate was developed utilizing a novel and efficient asymmetric catalytic hydrogenation of the cyclic vinylogous urea **4g**.

Acknowledgments: Helpful discussions with Professor David A. Evans are gratefully acknowledged.

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8. For preparation of **4d** and **4g**, see footnote 12.
9. (a) The separately prepared catalyst[5b] was added to a degassed solution of substrate **3f** in TFE (0.1 molar) . After three vacuum/H_2 purges, the reaction mixture was pressurized to 70 bar of H_2 and heated to 40°C for 18 h. The reaction mixture was concentrated and purified by flash chromatography (EtOAc/hexane 80/20). The ee was determined on a Chiracell AD column (hexane/IPA 80/20, 0.4 mL/min, 225 nm detection, 30°C, retention time: **3f** 13.1 min, enantiomers 13.9 and 16.0 min). An authentic racemic standard was produced by hydrogenation of **3f** with Pd/C (EtOH, 40°C). The absolute configuration of the products was not determined for this substrate. (b) PROPHOS: 1,2-bis(diphenylphosphino)propane; SKEWPHOS: 2,4-bis(diphenyphosphino)pentane; Boc-BPPM: (2S,4S)-*tert*-Butyl 4-(diphenylphosphino)-2-(diphenylphosphinomethyl)-1-pyrrolidine-carboxylate; Et-DUPHOS: 1,2-Bis((2S,5S)-2,5-diethylphospholano)benzene; DIOP: (R,R)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphine)-butane; BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binapthyl.
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11. Attempts to reduce **4a** • 2TfOH with a series of chiral Ru and Rh catalysts were largely unsuccessful (10-50%ee).
12. **Preparation of 4a** • 2HCl: Into a slurry of **4c** (18.58 g, 0.066 Mol) in 200 mL EtOAc was bubbled an excess of HCl gas at 10-15°C. The resulting slurry was aged over night at 20°C and filtered. The filtrate was washed with EtOAc and hexane and dried in a N2 stream to give **4a** • 2HCl (16.42g, 98%).
Preparation of 4d: A slurry of **4a** • 2HCl (12.09 g, 0.047 Mol) in 160 mL EtOAc was degassed in a N_2 stream and cooled to 5°C. Et_3N (16.5 mL, 0.12 Mol) and N-(benzyloxycarbonyloxy)succinimide (12.35 g, 0.05 Mol) were added and the reaction mixture was stirred at 22°C overnight. The reaction mixture was washed with H_2O, 5% citric acid, 5% $NaHCO_3$ and brine. After drying ($MgSO_4$), the organic phase was filtered through a plug of SiO_2 and evaporated. Crystallization from EtOAc/cyclohexane 10/90 gave **4d** (9.39g, 63% yield). Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.23; H, 7.31; N, 13.17. mp 161-162 °C.
Preparation of 4g: To a slurry of **4d** (18.59 g, 0.059 Mol) in 120 mL isopropyl acetate was added Boc_2O (29 mL, 0.12 Mol) and diisopropylethylamine (1 mL). On heating to reflux the reaction mixture turned homogeneous and was refluxed for 18 h. The reaction mixture was evaporated and chromatographed (SiO_2, EtOAc/hexane 50/50) to give **4g** as an oil (24.5 g, 100%). Crystallization from cyclohexane / isopropyl acetate 10/1gave **4g** as a white solid. Anal. Calcd for $C_{22}H_{31}N_3O_5$: C, 63.29; H, 7.48; N, 10.06. Found: C, 63.30; H, 7.40; N, 9.94. mp 99-100 °C.
13. **Preparation of 6g**: A solution of **4g** (0.433 g, 1.04 mmol) in 10 mL of MeOH in a high pressure hydrogenation tube was degassed with N_2 for 10 min. The catalyst ([(R)-BINAP (COD) Rh]TfO, 21 mg, 2 mol%) was added. After 3 vacuum/H_2 flushes the system was pressurized to 70 bar of H_2 and heated to 40°C. After 18 h the solution was evaporated and chromatographed (SiO_2, EtOAc/hexane 50/50) to give 417 mg (96%) of a white solid of 99% ee. The ee was determined using a Hewlett Packard-SFC with a Daicel Chiracell OD(H) column (300 bar CO_2, 2.5 % MeOH at 1 mL/min, RT (S) enantiomer 20.7 min, (R) 22.2 min). Anal. Calcd for $C_{22}H_{33}N_3O_5$: C, 62.99; H, 7.93; N, 10.02. Found: C, 63.04; H, 7.86; N, 10.05. mp 136-137 °C.

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