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Asymmetric Hydrogenation of Protected Allylic Amines

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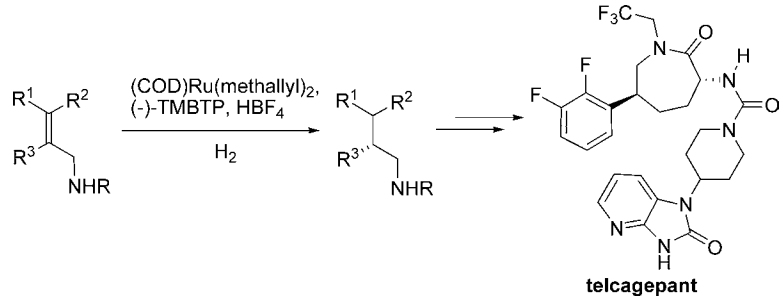
ABSTRACT

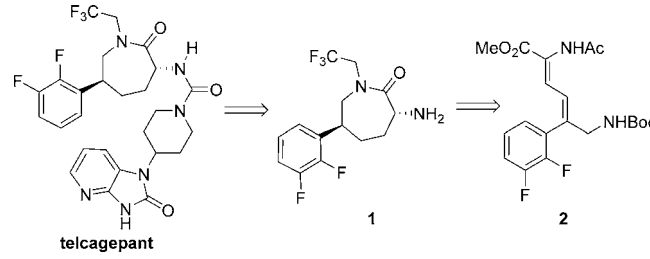


A general method for the enantioselective hydrogenation of protected allylic amine derivatives is described. This procedure relies on the generation of a cationic ruthenium complex with the axially chiral ligand (−)-TMBTP. The utility is highlighted by the highly enantioselective hydrogenation of a diene substrate that can then be elaborated to prepare Telcagepant, a compound currently in Phase III clinical trials. The scope of the hydrogenation reaction was studied, and a variety of substituted allylic amine derivatives could be hydrogenated with enantiomeric ratios of 92:8 or higher.

Telcagepant is an antagonist of the calcitonin gene-related peptide (CGRP) receptor currently in Phase III clinical trials and has the potential to become a novel therapy for the treatment of migraine headaches (Scheme 1).[1]

Although caprolactams are core structures in several pharmaceutical agents, the novel *trans* stereochemistry and trifluoroethylated amide of telcagepant represent significant synthetic challenges in the development of an efficient scalable synthesis.[2] We envisioned a synthesis of caprolactam **1** proceeding via an asymmetric hydrogenation of differentially protected diene **2** (Scheme 1). While the enamide hydrogenation is well precedented, reports of a general catalyst system for the asymmetric hydrogenation of trisubstituted allylic amine derivatives remain lacking and represent a significant gap in contemporary asymmetric hydrogenation chemistry. Examples of this type of transformation mainly involve 1,1-disubstituted derivatives bearing protecting groups that are not readily removed.[3]

Scheme 1. Retrosynthesis of Telcagepant



(1) Paone, D. V.; Shaw, A. W.; Nguyen, D. N.; Burgey, C. S.; Deng, Z. J.; Kane, S. A.; Koblan, K. S.; Salvatore, C. A.; Hershey, J. C.; Wong, B.; Roller, S. G.; Miller-stein, C.; Graham, S. L.; Vacca, J. P.; Williams, T. M. *J. Med. Chem.* **2007**, *50*, 5564–5567.

(2) For the first synthesis, see: (a) Burgey, C. S.; Paone, D. V.; Shaw, A. W.; Deng, J. Z.; Nguyen, D. N.; Potteiger, C. M.; Graham, S. L.; Vacca, J. P.; Williams, T. M. *Org. Lett.* **2008**, *10*, 3235–3238. (b) For an alternate approach, see: Janey, J. M.; Orella, C. J.; Njolito, E.; Baxter, J. M.; Rosen, J. D.; Palucki, M.; Sidler, R. R.; Li, W. L.; Kowal, J. J.; Davies, I. W. *J. Org. Chem.* **2008**, *73*, 3212–3217.

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From the outset of this program we focused on control of the olefin geometry as an important element to enable success of the asymmetric hydrogenation. A high-yielding synthesis of the geometrically pure diene was developed (Scheme 2), and our screening began to gauge the reactivity profile of this unique substrate.[4]

Scheme 2. Synthesis of Caprolactam **1**

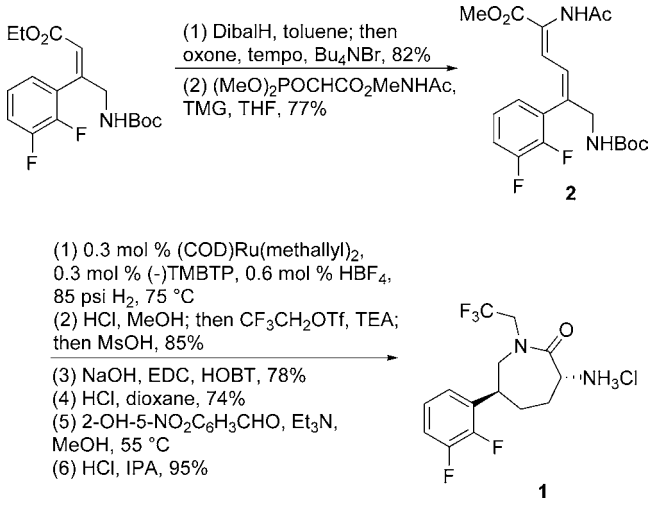
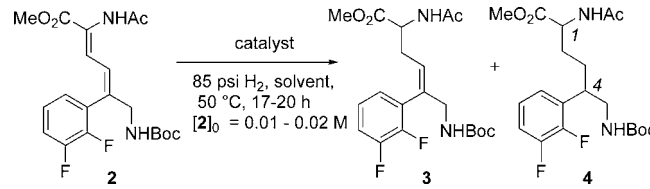


Table 1 shows representative results of initial catalyst screens employing diene **2**. Typical cationic rhodium and iridium phosphine complexes (Table 1, entries 1 and 2) had insufficient reactivity to hydrogenate the allylic amine portion of the diene. Since literature reports indicate that cationic ruthenium systems display good reactivity with hindered olefins including those with poorly chelating functional groups,[5] we focused on a diverse library of catalysts generated in situ from chiral phosphines, $(COD)Ru(methallyl)_2$, and HBF_4. Cationic ruthenium catalysts with electron-rich ligands such as Et-DuPHOS (entry 3) or various Josiphos derivatives (entries 4 and 5) gave markedly higher reactivity with good to excellent enantioselectivity at the benzylic center. Catalysts derived from C_2-symmetric biaryl phosphines such as BINAP also gave moderate to high enantioselectivity at the benzylic carbon (Table 1, entries 6−9), although only electron-rich variants such as Xyl-BINAP (entry 7) and TMBTP (entry 9) showed useful activity toward the tandem reduction. Interestingly, absolute selectivity at the amino ester center (C1 in Table 1) was low to moderate across all the diverse cationic ruthenium catalysts tested.

Table 1. Catalyst Screening for the Asymmetric Hydrogenation of Diene **2**[a]



entry	metal[b]	ligand	solvent	S/C[c]	**2**:**3**:**4**[d]	er 1*S*:1*R*[e]	er 4*S*:4*R*[e]
1	Ir	**5**	DCM	5	85:11:4		
2	Rh	**6**	MeOH	1	0:65:35	>99:1	52:48
3	Ru	**7**	EtOH/DCM[f]	3	0:30:70	54:46	90:10
4	Ru	**8**	EtOH/DCM[f]	3	0:0:100	82:18	95:5
5	Ru	**9**	EtOH/DCM[f]	3	0:6:94	52:48	99:1
6	Ru	**10**	EtOH/DCM[f]	3	0:91:9	37:63	>99:1
7	Ru	**11**	EtOH/DCM[f]	3	0:0:100	74:26	97:3
8	Ru	**12**	EtOH/DCM[f]	3	0:63:37	59:41	86:14
9	Ru	**13**	EtOH/DCM[f]	3	0:0:100	87:13	<1:99

[a] See Supporting Information for experimental details. See Figure 1 for ligand structures. [b] Ir and Ru catalysts prepared in situ from chiral phosphine and $(COD)_2IrBF_4$ or $(COD)Ru(methallyl)_2/HBF_4$, respectively. Rh catalysts screened as isolated (ligand)Rh(COD)BF_4 complexes. [c] Substrate/catalyst ratio. [d] Determined by chiral HPLC. [e] Enantiomeric ratio at specified chiral center in product **4**. [f] 3:2 ratio, respectively.

Further optimization revealed that the cationic ruthenium catalyst derived from (−)-TMBTP gave the best combination of reactivity and selectivity, giving full conversion to **4** in 20 h using only 0.3 mol % catalyst at 65 °C and 70 psig H_2 in MeOH at multikilogram scale. Under these conditions the enantiomeric ratio at the benzylic stereocenter was 99.6:0.4, while the amino ester stereocenter was nearly racemic (55:45).[6] The hydrogenation of the allylic amine operates under catalyst control, as the same sense of induction at the benzylic center is obtained regardless of the configuration of the amino ester center.[7] Our efforts to control the geometry of the allylic amine were justified, since exposure of a Z-olefin derivative to the optimized reaction conditions afforded lower enantiomeric ratios (87:13).[8]

Advancing from hydrogenation product **4**, a straightforward process was developed to azapanone **1** involving deprotection, trifluoroethylation, and cyclization (Scheme 2).[9] The *trans* relationship between C1 and C4 was effectively established *via* thermodynamic epimerization of the amine center catalyzed by 5 mol % of 2-hydroxy-5-nitrobenzaldehyde in the presence of Et_3N,[10] and the synthesis of telcagepant was successfully completed by coupling with the pyridine heterocycle.[2]

(3) (a) Shultz, S. C.; Krska, S. K. *Acc. Chem. Res.* **2007**, *12*, 1320–1326. (b) Wang, C.-J.; Sun, X.; Zhang, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 4933–4935. (c) Deng, J.; Duan, Z.-C.; Huang, J.-D.; Hu, X.-P.; Wang, D.-Y.; Yu, S.-B.; Xu, X.-F.; Zheng, Z. *Org. Lett.* **2007**, *9*, 4825–4828. (d) Yamano, T.; Yamashita, M.; Adachi, M.; Tanaka, M.; Matsumoto, K.; Kawada, M.; Uchikawa, O.; Fukatsu, K.; Ohkawa, S. *Tetrahedron: Asymmetry* **2006**, *17*, 184–190. (e) Fahrang, R.; Sinou, D. *Bull. Soc. Chim. Belg.* **1989**, *98*, 387–393. (f) Saylik, D.; Campi, E. M.; Donohue, A. C.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2001**, *12*, 657–667. (g) Sun, X.; Zhou, L.; Li, W.; Zhang, X. *J. Org. Chem.* **2007**, *72*, 1002–1005. (h) Limanto, J.; Shultz, C. S.; Dorner, B.; Desmond, R. A.; Devine, P. N.; Krska, S. W. *J. Org. Chem.* **2008**, *73*, 1639–1642. (i) Brown, J. M.; Parker, D. *J. Org. Chem.* **1982**, *47*, 2722–2725. (j) Broene, R. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12569–12570. (k) Yamashita, M.; Yamano, T. *Chem. Lett.* **2009**, *38*, 100–101. (l) Burk, M. A.; Allen, J. G.; Kiesman, W. F. *J. Am. Chem. Soc.* **1998**, *120*, 657–663.

(4) For unsaturated ester preparation, see: (b) Baxter, J. M.; Steinhuebel, D. P.; Palucki, M.; Davies, I. W. *Org. Lett.* **2005**, *7*, 215–218.

(5) (a) Genet, J.-P. *Acc. Chem. Res.* **2003**, *36*, 908–918, and references therein. (b) Dobbs, D. A.; Vanhessche, K. P. M.; Brazi, E.; Rautenstrauch, V.; Lenoir, J.-V.; Genet, J.-P.; Wiles, J.; Bergens, S. H. *Angew. Chem., Int. Ed.* **2000**, *39*, *11*, 1992–1995. (c) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570.

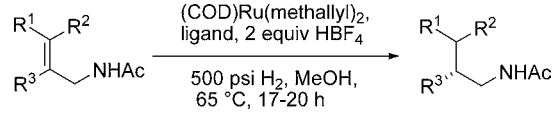
(6) Benincori, T.; Cesarotti, E.; Piccolo, O.; Sannicol, F. *J. Org. Chem.* **2000**, *65*, 2043–2047.

(7) Both enantiomers of (Me-DuPHOS)Rh(COD)BF_4 were used to prepare enantiomerically enriched samples of (*R*)- and (*S*)-**3**, which were then hydrogenated with $(COD)Ru(methallyl)_2/HBF_4$/(−)-TMBTP to afford **4** with identical enantioselectivity at the benzylic center.

(8) The monoreduced bis-Boc derivative was used. For similar results see: (a) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272–3296.

(9) See Supporting Information for experimental details.

Table 2. Scope of Asymmetric Hydrogenation of Allylic Amines[a]



entry	olefin	R^1	R^2	R^3	ligand	er[b]
1	**14**	H	H	Ph	**10**	95:5
2	**14**	H	H	Ph	**11**	96:4
3	**14**	H	H	Ph	**(−)-13**	90:10
4	**15**	Ph	H	Ph	**(−)-13**	94:6
5	**16**	Ph	H	p-i-PrO-C_6H_4	**(−)-13**	97:3
6	**17**	Ph	H	p-CF_3-C_6H_4	**(−)-13**	96:4
7	**18**	Ph	H	Me	**(−)-13**	92:8
8	**19**	$CH_2C(CO_2Et)_2NHAc$	H	Ph	**(−)-13**	95:5
9	**20**	H	$CH_2C(CO_2Et)_2NHAc$	Ph	**(−)-13**	91:9
10	**21**	$CH_2C(CO_2Et)_2NHAc$	H	Bn	**(−)-13**	96:4

[a] S/C = 50 for most reactions, see Supporting Information for experimental details. [b] Determined by chiral SFC.

Given the success of the asymmetric hydrogenation of diene **2**, we continued to define the scope with respect to variously substituted allylic amines. For this purpose, 1,1-disubstituted olefin **14** was screened against a similar set of catalysts as in Table 1. With this less hindered substrate, Rh, Ir, and Ru (neutral and cationic) catalysts all displayed good reactivity, although only cationic ruthenium catalysts with C_2-symmetric biaryl phosphine ligands gave high levels of enantioselectivity (Table 2, entries 1−3).[11]

The results shown in Table 2 illustrate the effect of olefin substitution on the reaction. Substrates with a 2,3-diaryl substitution give enantiomeric ratios of >94:6 or higher (entries 4−6). An alkyl substituent in the 2-position is also tolerated (entry 7). Substrate **19** (entry 8), structurally related to **3**, also provided good enantioselectivity, while hydrogenation of the corresponding Z-isomer afforded lower selectivity (entry 9). Lastly, a branched alkyl substituent at C2 was also a functional substrate (entry 10).

A mechanistic investigation of this reaction using olefin **14** revealed that the N−Ac allylic amine is converted to the enamide upon exposure to the cationic ruthenium complex in the absence of H_2.[12] Subsequent hydrogenation of the isolated enamide under standard reaction conditions exhibited lower selectivity (71:29). Taken together these observations suggest that under the standard reaction conditions olefin isomerization is competitive with hydrogenation, and the allylic amine isomer enables higher enantioselectivity compared with the enamide. Consistent with this hypothesis is the observation that the hydrogenation of **14** under a D_2 atmosphere in either CH_3OH or CD_3OD gives deuterium incorporation into the methyl, methylene, and benzylic positions.[13]

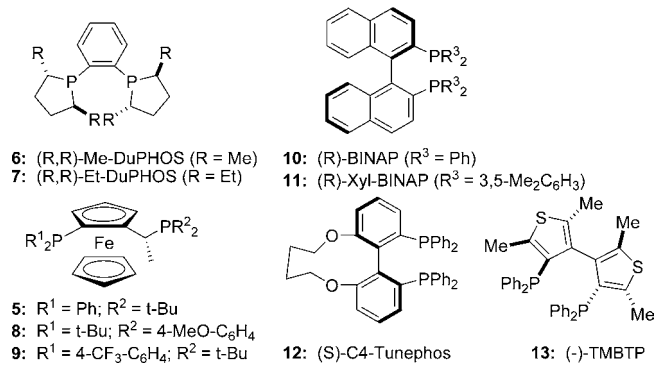


Figure 1. Chiral ligands used in optimization.

In summary, we have described a novel, asymmetric hydrogenation of allylic amines employing commercially available reagents. We have clearly exemplified the practical utility in the synthesis of the caprolactam of a contemporary active pharmaceutical ingredient. We expect widespread utilization of this novel method in academic and industrial laboratories that exploit innovative asymmetric hydrogenation methodologies.

Acknowledgment. The authors thank P. Rizos, M. Biba, Z. Pirzada, T. Brkovic of Process Research for chiral analysis and R. Reamer of Process Research for NMR analysis.

Supporting Information Available: Experimental procedures, compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) A 96:4 ratio of *trans*:*cis* diastereomers was obtained after heating at 55 °C. For use of salicylaldehyde derivatives in epimerization, see: (a) Reider, P. J.; Davis, P.; Hughes, D. L.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 955–957. (b) Armstrong, J. D.; Eng, K. K.; Keller, J. L.; Purick, R. M.; Hartner, F. W.; Choi, W. B.; Askin, D.; Volante, R. P. *Tetrahedron Lett.* **1994**, *35*, 3239–3242.

(11) Although the N-Boc analogue of **14** also performs in the reaction, the acetamide-protected gives higher reactivity and selectivity.

(12) The olefin geometry was confirmed by NOE studies.

(13) Under these conditions the enantiomeric ratio decreases from 96:4 to 83:17, consistent with a kinetic isotope effect favoring olefin isomerization over catalyst turnover via reductive elimination.