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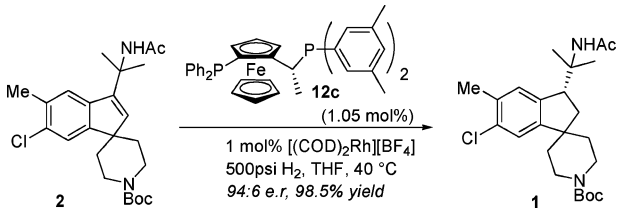
Synthesis of a Tertiary Carbinamide via a Novel Rh-Catalyzed Asymmetric Hydrogenation

John Limanto,* C. Scott Shultz, Benjamin Dorner, Richard A. Desmond, Paul N. Devine, and Shane W. Krska

Department of Process Research, Merck Research Laboratories, Merck & Co., Inc., Rahway, New Jersey 07065

john_limanto@merck.com

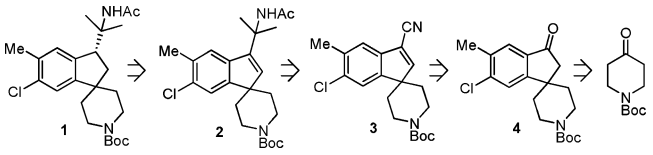
Received November 12, 2007



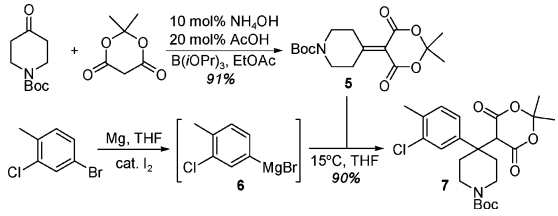
Asymmetric hydrogenation of allylic dimethylcarbinamide **2** with 1 mol % of cationic Rh(I)−Josiphos complex in THF under 500 psi of H_2 generated the corresponding tertiary carbinamide **1** in 98.5% assay yield and a 94:6 enantiomeric ratio. Upon crystallization, the product was isolated in 91% isolated yield and 95:5 enantiomeric ratio.

Compounds containing spiropiperidine backbones have been greatly utilized in pharmaceutical research due to their significant biological properties.[1] We recently required an efficient and scalable enantioselective approach to a structurally complex tertiary carbinamide **1**, which could potentially be prepared via an asymmetric hydrogenation of unsaturated tertiary carbinamide **2** (Scheme 1). While homogeneous catalytic asymmetric hydrogenation of olefins has been a very active area of research and has found abundant application in both academic and industrial arena,[2] hydrogenation involving α,α-disubstituted allylic amines or amides, such as **2**, has not yet been explored. On the other hand, enantioselective hydrogenation of β-substituted allylic amides or phthalimides[3] and a primary allylic carbinamine[4] has previously been reported. Due to the inherent steric congestion at a tertiary allylic carbinamine, catalytic asymmetric hydrogenation of this type of compound represents a challenging task. Herein we report an efficient catalytic enantioselective hydrogenation approach to **1**, which is amenable to preparative scale.

SCHEME 1. Retrosynthetic Analysis of Carbinamide 1



SCHEME 2. Preparation of Intermediate 7



The requisite hydrogenation precursor **2** could be constructed from the vinyl nitrile intermediate **3**, which, in turn, would be readily accessible from commercial *N*-Boc-4-piperidone. Hence, ammonium acetate catalyzed Knövenagel condensation between Meldrum's acid and *N*-Boc-4-piperidone in EtOAc afforded compound **5**, which was crystallized directly from the reaction mixture in 91% isolated yield (Scheme 2). Subsequent conjugate addition was performed using Grignard reagent **6**, in the absence of any copper salts,[5] in THF to afford compound **7** in 90% isolated yield.

Initial attempts to generate indanone **4a** from **7** under lanthanide-catalyzed intramolecular Friedel−Crafts cyclization[6] resulted only in the removal of the Boc group and decomposition of the starting material. On the other hand, heating compound **7** either in a 2:1 mixture of pyridine/H_2O at 90 °C or in wet toluene (5−10% v/v H_2O) in the presence of pyridine (2 molar equiv) at 85−100 °C resulted in sequential hydrolysis and decarboxylation to cleanly generate acid **8** in 90% yield (Scheme 3). While the product can be isolated as a pyridine complex, the crude material was used directly in the next step.[7] Conversion of the acid to the corresponding acid chloride **9**, followed by treatment with $AlCl_3$ (2−3 molar equiv) in either CH_2Cl_2 or

(1) For examples, see: (a) Lu, Z.; Tata, J. R.; Cheng, K.; Wei, L.; Chan, W. W.-S.; Butler, B.; Schleim, K. D.; Jacks, T. M.; Hickey, G.; Patchett, A. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3657. (b) Jia, L.; Zou, J.; So, S.-S.; Sun, H. *J. Chem. Inf. Mod.* **2007**, *47*, 1545. (c) Bakshi, R. K.; Dellurefício, J. P.; Dobbelaar, P. H.; Guo, L.; He, S.; Hong, Q.; Nargund, R. P.; Ye, Z. PCT Int. Appl. 2007, 132. (d) Allerton, C. M. N.; Owen, D. R.; Ryckmans, T.; Stammen, B. L. C. PCT Int. Appl. 2007, 197. (e) Ito, F.; Koike, H.; Sudo, M.; Yamagishi, T.; Ando, K. PCT Int. Appl. 2003, 196. (f) Tata, J. R.; Lu, Z.; Jacks, T. M.; Schleim, K. D.; Cheng, K.; Wei, L.; Chan, W. W.-S.; Butler, B.; Tsou, N.; Leung, K.; Chiu, S.-H. L.; Hickey, G.; Smith, R. G.; Patchett, A. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2319.

(2) For reviews on metal-catalyzed asymmetric hydrogenations, see: (a) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272. (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (c) Blaser, H. U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (d) Ojima, I. *Catalytic Asymmteric Synthesis*; Wiley-VCH: New York, 2000. (e) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. For examples of industrial applications, see: (f) Lennon, I. C.; Moran, P. H. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 855. (g) Genet, J.-P. *Acc. Chem. Res.* **2003**, *36*, 908.

(3) (a) Wang, C.-J.; Sun, X.; Zhang, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 4933. (b) Saylik, D.; Campi, E. M.; Donohue, A. C.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2001**, *12*, 657. (c) Brown, J. M; Parker, D. *J. Org. Chem.* **1982**, *47*, 2722. For an example of diastereoselective reduction of chiral cyclic allylic amide under heterogeneous conditions, see: Hu, X. E.; Kim, N. K.; Ledoussal, B. *Org. Lett.* **2002**, *4*, 4499.

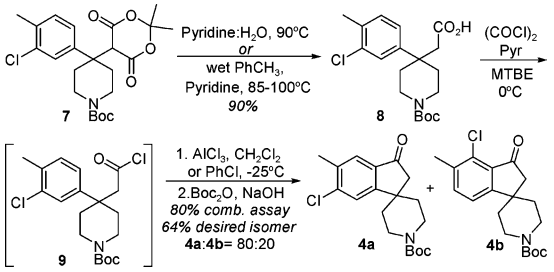
(4) For example, see: Yamano, T.; Yamashita, M.; Adachi, M.; Tanaka, M.; Matsumoto, K.; Kawada, M.; Uchikawa, O.; Fukatsu, K.; Ohkawa, S. *Tetrahedron: Asymmetry* **2006**, *17*, 184.

(5) For examples of copper-salt-mediated conjugated additions to Meldrum's alkylidenes, see: (a) Vogt, P. F.; Molino, B. F.; Robichaud, A. J. *Synth. Commun.* **2001**, *31*, 679. (b) Davies, A. P.; Egan, T. J.; Orchard, M. G.; Cunningham, D.; McArdle, P. *Tetrahedron* **1992**, *48*, 8725. (c) Huang, X.; Chan, C.-C.; Wu, Q.-L. *Tetrahedron Lett.* **1982**, *23*, 75.

(6) Fillion, E.; Fishlock, D. *Org. Lett.* **2003**, *5*, 4653.

10.1021/jo702429u CCC: $40.75
Published on Web 01/11/2008

SCHEME 3. Preparation of Indanone 4a



PhCl at −25 °C, effected the Friedel−Crafts reaction to yield an 80:20 regioisomeric mixture of indanones with concomitant removal of the Boc group. For compatibility purposes in the downstream chemistry, the crude amine was reprotected with Boc_2O to give regioisomeric products **4** in 80% combined assay yield or 64% yield of the desired indanone **4a**.

With indanone **4a** in hand, generation of the vinyl nitrile intermediate **3** was accomplished in a two-step one-pot process, involving cyanophosphorylation, followed by Lewis acid induced dehydrophosphorylation. Specifically, treatment of the crude mixture of indanones **4a**,**b** with diethyl cyanophosphate[8] in the presence of 20 mol % of LiOEt[9] or LiOMe in either MTBE, THF, or toluene at rt afforded intermediates **10a** and **10b**, which upon subsequent exposure to BF_3•Et_2O[13a] (0.5 molar equiv) at 0 °C → rt resulted in the chemoselective formation of the desired vinyl nitrile **3a**. Due to the slower elimination rate observed for the undesired regioisomer **10b** ($k_1 > k_2$),[10] the current protocol allowed for an efficient regioselectivity upgrade to solely generate compound **3** in 81% isolated yield after crystallization (Scheme 4). Subsequent incorporation of the *gem*-dimethyl group was accomplished via a $CeCl_3$-promoted double addition of MeLi under non-cryogenic conditions[11] to give carbinamine **11**, which upon acetylation in EtOAc generated the desired carbinamide **2** in 83% isolated yield.[12]

SCHEME 4. Synthesis of Vinyl Nitrile 3

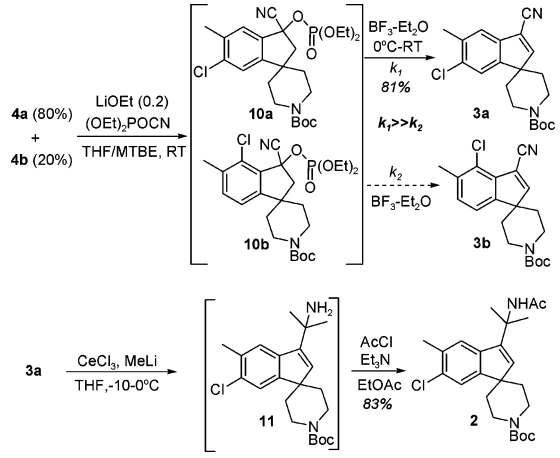
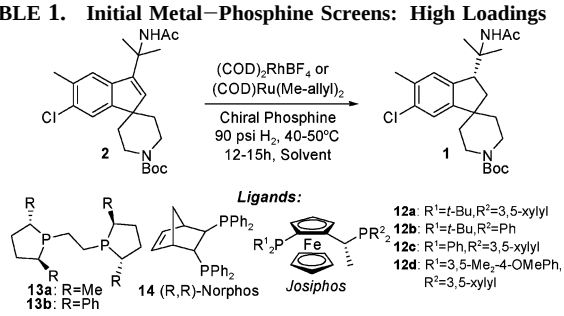


TABLE 1. Initial Metal−Phosphine Screens: High Loadings



entry	metal[a]	ligand	solvent[b]	S/C[c]	[SM][d]	% conv[e]	product[f] (LCAP)	% ee[g]
1	Ru	**12a**	MeOH	12	20	10	5	64
2	Ru	**12b**	MeOH	12	20	34	27	74
3	Ru	**12b**	TFE	12	20	94	64	40
4	Ru	**12b**	EtOAc	12	20	97	62	53
5	Ru	**12b**	THF	12	20	100	77	59
6	Ru	**12b**	THF	20	40	100	83	44
7	Rh	**14**	MeOH	12	20	90	78	49
8	Rh	**13a**	MeOH	12	10	100	84	21
9	Rh	**13b**	MeOH	12	20	83	75	67
10	Rh	**12d**	MeOH	12	20	36	28	86
11	Rh	**12d**	TFE	20	20	93	83	78
12	Rh	**12d**	EtOAc	20	20	91	71	82
13	**Rh**	**12d**	**THF**	**20**	**20**	**97**	**86**	**81**

[a] The Rh catalysts were formed by combining the metal precursor and the ligands at rt for 1 h in MeOH or, in the case of Ru−methallyl precursor, in DCE/MeOH along with 2 equiv of HBF_4•Et_2O for metal activation. [b] Dry solvents were used for the studies (KF < 100 ppm). [c] Substrate to catalyst ratio. [d] Concentration of starting olefin in g/L. [e] Uncorrected: [product A%/SM A%] × 100%. [f] HPLC area percent, uncorrected for absorption factor. [g] Determined by chiral HPLC analysis (Chiralcel OD-H). Absolute configuration was obtained by X-ray single-crystal structure (see Supporting Information).

With the requisite hydrogenation substrate **2a** in hand, the hydrogenation studies were initiated by screening a library of chiral phosphine ligands in combination with Ru or Rh metal precursors under high catalyst loading conditions (S/C = 12−20). From the initial screen, metal complexes of Josiphos-type (**12**),[13] BPE (**13**), and Norphos ligands (**14**) were found to exhibit significant reactivities toward the olefin at 45−50 °C and 90 psi of H_2 in the solvents presented in Table 1. Under Ru catalysis, Josiphos-type ligands **12a**,**b** offered modest enantioselectivities and low conversions in MeOH (entries 1 and 2), while the same transformations gave the highest conversions,

(7) Attempts to perform Friedel−Crafts acylation directly from **8** using various Brønsted acid or lanthanide triflates only resulted in Boc removal and/or poor conversions. For MsOH-promoted process, see: (a) Premasagar, V.; Palaniswamy, V. A.; Eisenbrau, E. J. *J. Org. Chem.* **1981**, *46*, 2974. For PPA, see: (b) Guy, A.; Guette, J.-P. *Synthesis* **1980**, *3*, 222. For TfOH, see: (c) Orita, A.; Yaruva, J.; Otera, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2267. (d) Quallich, G. J.; Woodall, T. M. *Tetrahedron* **1992**, *48*, 10239. For $ClSO_3H$, see: (e) Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 30. For lanthanide-promoted processes, see: (f) Cui, D.-M.; Kawamura, M.; Shimada, S.; Hayashi, T.; Tanaka, M. *Tetrahedron Lett.* **2003**, *44*, 4007 and references cited therein.

(8) Commercially available or generated in situ from $ClPO(OEt)_2$: Shi, E.; Xiao, J.; Pei, C. *Phosphorous, Sulfur Silicon Relat. Phenom.* **2004**, *179*, 1361.

(9) Treatment of $(EtO)_2POCN$ with LiOEt appears to generate LiCN and $(EtO)_3PO$ as suggested by comparing the ^{31}P NMR spectrum of the latter to that of the authentic sample. For LiCN-induced cyanophosphorylation, see: (a) Harusawa, S.; Yoneda, R.; Kurihara, T.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **25**, *4*, 427. For similar LDA-induced process, see: (b) Harusawa, S.; Yoneda, R.; Kurihara, T.; Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1983**, *31*, 2932.

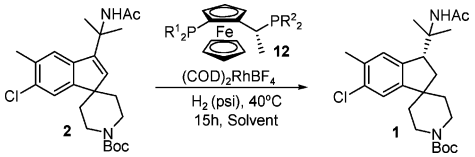
(10) The conversions were monitored periodically by both NMR and HPLC. After 18 h at rt, a full conversion of **10a** to **3a** was typically obtained, while ∼90% of **10b** remained unreacted under these conditions.

(11) Limanto, J.; Dorner, B.; Devine, P. N. *Synthesis* **2006**, *24*, 4143 and references cited therein.

(12) It is important to note that other protecting groups for the *piperidine nitrogen* such as benzamide, acetamide, CBz, or ethyl carbamate are not compatible with the organocerium chemistry, hence, justifying the necessity to reincorporate the Boc protecting group in the piperidine ring after Friedel−Crafts acylation.

(13) (a) McGarrity, J.; Spindler, F.; Fuchs, R.; Eyer, M. (LONZA-AG), EP-A 624587 A2, 1995. (b) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062.

TABLE 2. Catalyst Loading and Pressure Screens



entry	ligand[a]	solvent	H_2 (psi)	S/C[b]	[SM][c]	% conv[d]	product[e] (LCAP)	% ee[f]
1	**12d**	EtOAc	90	20	20	91	71	82
2	**12c**	EtOAc	90	40	25	29	23	79
3	**12c**	EtOAc	90	100	50	21	19	82
4	**12c**	EtOAc	500	100	70	87	74	87
5	**12c**	EtOAc	500	130	70	30	27	84
6	**12d**	EtOAc	500	100	70	99	85	87
7	**12d**	THF	500	100	70	100	93	89
8	**12c**	**THF**	**500**	**100**	**70**	**100**	**91 (98)[g]**	**88**

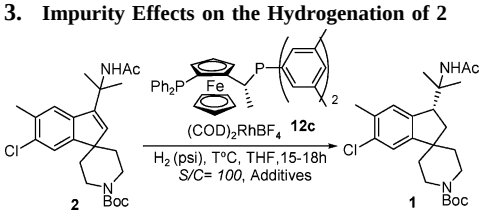
[a] Catalyst was formed by mixing the ligand and precursor in the solvent at rt for 1 h. [b] Substrate to catalyst ratio. [c] Concentration of starting material in g/L. [d] Uncorrected: [product A%/SM A%] × 100%. [e] Uncorrected HPLC area percent. [f] Determined by chiral SFC spectroscopy (Chiralcel OD-H). [g] Number in parentheses represents HPLC assay yield.

but lower selectivities in non-alcoholic solvents or TFE (entries 3−6). On the other hand, Rh complexes of BPE and Norphos ligands exhibited high reactivities, promoting the hydrogenation in high conversions, albeit in moderate enantioselectivities (entries 7−9). Alternatively, Rh−Josiphos complex **12d** catalyzed the desired transformation in high conversions (91−97%) and enantioselectivity (81%) when performed in non-alcoholic solvents, such as THF or EtOAc (entries 10−13). Encouraged by these promising results, further reaction optimization was performed using this and other Rh−Josiphos catalyst systems.

Subsequent studies showed that, with ligand **12c**, the reaction conversions were attenuated significantly when the catalyst loadings were reduced by more than 2-fold in EtOAc (entries 2 and 3, Table 2). However, with 1 mol % catalyst loading, the high reactivity can be restored upon performing the reaction at higher pressure (i.e., 500 psi), without sacrificing the enantioselectivity (entry 4). With less than 1 mol % of Rh−**12c** at 500 psi H_2, the reaction proceeded to give low conversion (entry 5), but still with high enantioselectivity. While other Josiphos ligands (i.e., **12d**) also effected the reaction efficiently at 1 mol % loading (entries 6 and 7), due to its bulk availability and lower cost, ligand **12c** was selected for large scale productions. Hence, *subjection of **2** to 1 mol % of Rh−**12c**(BF$_4$) in 10−14 mL/g THF at 40 °C under 500 psi of H_2 afforded the saturated product **1** in a 94:6 enantiomeric ratio and 98% assay yield*. Isolation by crystallization from MeCN afforded the desired compound **1** in 91% isolated yield and in a satisfactory 95:5 enantiomeric ratio (90% ee).

Although Rh−**12c** proves to be an active catalyst, its catalytic activity appears to be attenuated by the presence of impurities in the starting material (Table 3). For example, under optimized reaction conditions, a small amount of NaOAc (5−10 mol %) strongly inhibited the catalyst, resulting in only negligible conversions (entries 2 and 3). Such unfavorable reaction outcomes, however, were not observed when 5 mol % of Na_2CO_3 was present at the beginning of the reaction (entry 4). On the other hand, Et_3N, Et_3N•HCl salt, and Ac_2O were all potent inhibitors for the Rh−Josiphos catalyst system, even in very small amounts (entries 5−7). In addition, performing the hydrogenation in wet THF solution (i.e., 3 mol % of H_2O) resulted in much lower conversion and slightly reduced enantioselectivity (entry 8). For optimum results (entry 1), dry THF (KF < 100 ppm) was routinely used and the solution was first filtered through a 1 μm inline filter to remove any insoluble salts or particulates prior to hydrogenation.

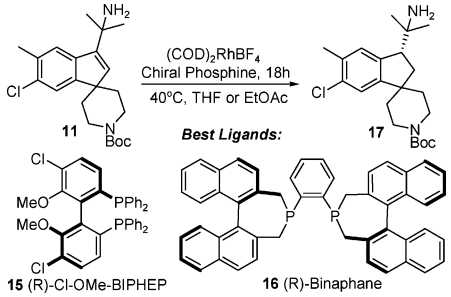
TABLE 3. Impurity Effects on the Hydrogenation of 2



entry	additives	mol %[a]	H_2 (psi)	T (°C)	[SM][b]	% conv[c]	% ee[d]
1	none	n/a	500	40	100	100	86
2	NaOAc	10	90	25	50	1	nd
3	NaOAc	5	500	40	100	8	nd
4	Na_2CO_3	5	500	40	100	90	81
5	Et_3N	1	500	40	100	7	58
6	Et_3NHCl	1	500	40	100	1	nd
7	Ac_2O	5	500	25	50	1	nd
8	H_2O	3	500	40	100	33	77

[a] With respect to starting olefin. [b] Concentration of starting olefin in g/L. [c] Uncorrected: [product A%/SM A%] × 100%. [d] Determined by chiral SFC analysis.

TABLE 4. Hydrogenation of Amine 11



entry	ligand[a]	H_2 (psi)	S/C[b]	[SM][c]	% conv[d]	% ee[e]
1	**15**	90	6	4	100	87
2	**15**	90	30	100	72	46
3	**15**	90	100	100	4	0
4	**15**	500	100	100	5	0
5	**16**	90	6	10	98	93
6	**16**	90	12	20	98	90
7	**16**	90	30	100	64	53
8	**16**	500	65	100	2	0

[a] The catalysts were typically preformed by heating the metal precursors and the ligands at 20−50 °C in DCE/EtOH or THF for 1 h. [b] Substrate to catalyst ratio. [c] Concentration of starting olefin in g/L. [d] Uncorrected: [product A%/SM A%] × 100%. [e] Determined by chiral SFC analysis.

Virtually all of the catalyst poisons in Table 3 were used or generated during the acetylation of **11** with AcCl or Ac_2O with Et_3N and/or during reaction workup with Na_2CO_3. In order to completely avoid these potential contamination issues, asymmetric hydrogenation of the free amine **11** was also investigated using our phosphine library. In this regard, a combination of $(COD)_2RhBF_4$ and either (*R*)-Cl−OMe−Biphep **15** or (*R*)-binaphane **16** was found to effect the desired transformation to generate amine **17** in good yields and enantioselectivities (Table 4). Unfortunately, the best results could only be obtained under high catalyst loadings (≥10 mol %, entries 1, 5, and 6). Both the conversion and enantioselectivity decreased significantly as the amount of catalyst was reduced to as low as 1 mol % (entries 4 and 8). On the basis of these observations, asymmetric

hydrogenation of carbinamide **2** with 1 mol % of Rh−**12c** Josiphos system is a more feasible process for large-scale productions provided that none of the aforementioned catalyst inhibitors are present in the starting material.

In summary, we have developed a practical, enantioselective approach to a pharmaceutically useful spiropiperidineindane-containing tertiary carbinamide **1**. The current route involves a seven longest linear step, four isolation steps, and 30% overall yield. The key transformation features a novel, unprecedented Rh−Josiphos-catalyzed asymmetric hydrogenation of a sterically hindered tertiary allylic carbinamide **2**, which is easily accessible from commercially available *N*-Boc-4-piperidone. Specifically, subjection of **2** to 1 mol % of Rh−**12c**(BF_4) in 10−14 mL/g THF at 40 °C under 500 psi of H_2 affords the corresponding saturated carbinamide **1** in a 94:6 enantioselectivity, and upon crystallization from MeCN, the desired product can be isolated in a 95:5 enantioselectivity and 91% yield.

Experimental Section

Rh−Josiphos (12c)-Catalyzed Asymmetric Hydrogenation of 2: In a nitrogen-filled glovebox (typically <10 ppm O_2), ligand **12c** (26.8 g, 0.042 mol, 0.011 equiv) was combined with $(COD)_2RhBF_4$ (16.3 g, 0.040 mol, 0.01 equiv) in a round-bottom flask. Dry THF (400 mL, N_2 degassed) was added, and the slurry was stirred for 60 min to give a homogeneous red-brown solution. The catalyst solution was then poured into a hydrogenation autoclave, containing a solution of the unsaturated carbinamide **1** (1.73 kg, 3.99 mol, 1 equiv) in THF (KF < 100 ppm). The resulting mixture was then placed under H_2 (500 psig), vented three times for degassing, and pressurized to 500 psi of H_2. The reaction temperature was increased to 40 °C while maintaining a H_2 pressure of 500 psig. The mixture was agitated at this temperature for 18 h, at which point no more starting material was observed by HPLC analysis. The reaction solution was cooled to rt, vented, and then assayed by HPLC to afford the crude product in 98% assay yield and 88% ee. Crystallization of the product from MeCN afforded (*R*)-**1** in 91% isolated yield with a 95:5 enantiomeric ratio. While chiral SFC analyses were performed for ee determination during screens, chiral HPLC was utilized routinely during larger scale runs. HPLC conditions: Chiralcel OD-RH, 150 × 4.6 mm i.d., isocratic 1:1 MeCN/0.1% H_3PO_4 in H_2O, 1 mL/min, 20 °C, retention times: 10.90 min for desired and 11.78 min for undesired enantiomer. The absolute configuration was assigned from the X-ray single-crystal structure (see Supporting Information): $[\alpha]^{25}_D$ = 33.8 (*c* 0.4, MeOH); mp 213−214 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (1H, s), 7.06 (1H, s), 5.72 (1H, br s), 4.31−3.87 (3H, m), 2.87 (2H, m), 2.32 (1H, m), 2.31 (3H, s), 2.00 (3H, s), 1.95 (1H, dt, J = 13.1, 4.4 Hz), 1.47 (9H, s), 1.52−1.37 (4H, m), 1.39 (3H, s), 1.24 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 155.0, 151.6, 141.4, 134.3, 133.1, 127.5, 123.5, 79.7, 56.3, 48.0, 44.4, 41.4, 37.7, 37.0, 28.6, 25.8, 24.8, 24.4, 20.6; IR (NaCl, cm^{-1}) 3429, 3313 (br), 3056, 2976, 2931, 2865, 1652, 1548, 1429, 1366, 1276, 1171, 1094, 1045, 1003, 958, 870, 770, 737, 704, 614. Anal. Calcd for $C_{24}H_{35}ClN_2O_3$: C, 66.27; H, 8.11; N, 6.44. Found: C, 66.06; H, 8.28; N, 6.35.

Acknowledgment. We greatly acknowledge Mr. Bob Reamer and Lisa DiMichelle for their assistance with NMR interpretation and structural assignments, and Ms. Mirlinda Biba for development of chiral assay. We also acknowledge Enrique Vazquez, Jason Kowal, Joe Payack, Wenji Li, and Shawn Springfield for their contributions to the racemic synthesis of the molecule, and Jennifer Foley for her assistance with crystallographic data.

Supporting Information Available: Additional experimental procedures, characterization data (PDF), and crystallographic data for **1** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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