

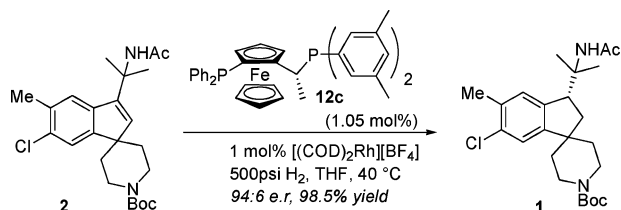
# Synthesis of a Tertiary Carbinamide via a Novel Rh-Catalyzed Asymmetric Hydrogenation

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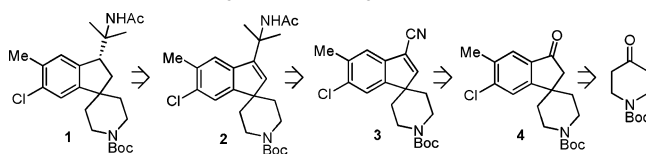
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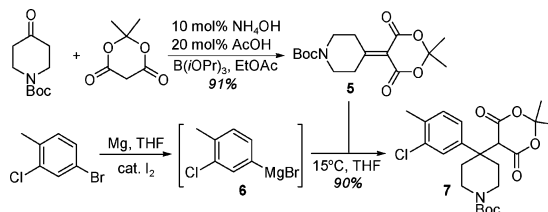
Asymmetric hydrogenation of allylic dimethylcarbinamide **2** with 1 mol % of cationic Rh(I)–Josiphos complex in THF under 500 psi of H<sub>2</sub> generated the corresponding tertiary carbinamide **1** in 98.5% assay yield and a 94:6 enantiomeric ratio. Upon crystallization, the product was isolated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

Compounds containing spiro-piperidine backbones have been greatly utilized in pharmaceutical research due to their significant biological properties.<sup>1</sup> 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,<sup>2</sup> hydrogenation involving  $\alpha,\alpha$ -disubstituted allylic amines or amides, such as **2**, has not yet been explored. On the other hand, enantioselective hydrogenation of  $\beta$ -sub-

## SCHEME 1. Retrosynthetic Analysis of Carbinamide 1



## SCHEME 2. Preparation of Intermediate 7



tuted allylic amides or phthalimides<sup>3</sup> and a primary allylic carbinamide<sup>4</sup> has previously been reported. Due to the inherent steric congestion at a tertiary allylic carbinamide, 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.

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,<sup>5</sup> 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<sup>6</sup> 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<sub>2</sub>O at 90 °C or in wet toluene (5–10% v/v H<sub>2</sub>O) 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.<sup>7</sup> Conversion of the acid to the corresponding acid chloride **9**, followed by treatment with AlCl<sub>3</sub> (2–3 molar equiv) in either CH<sub>2</sub>Cl<sub>2</sub> 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.; Dellureficio, 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 Asymmetric 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.

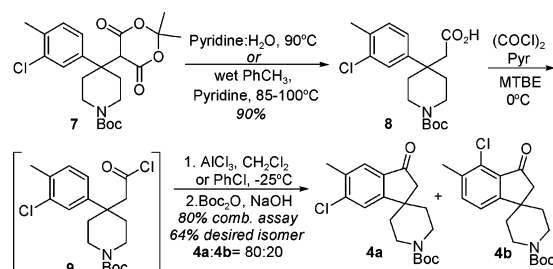
(3) (a) Wang, C.-J.; Sun, X.; Zhang, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 4933. (b) Saylik, D.; Campi, E. M.; Donohue, A. C.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2001**, *12*, 657. (c) Brown, J. M.; Parker, D. J. *Org. Chem.* **1982**, *47*, 2722. For an example of diastereoselective 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.

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## SCHEME 3. Preparation of Indanone 4a



PhCl at  $-25^{\circ}\text{C}$ , 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  $\text{Boc}_2\text{O}$  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<sup>8</sup> in the presence of 20 mol % of  $\text{LiOEt}$ <sup>9</sup> or  $\text{LiOMe}$  in either MTBE, THF, or toluene at rt afforded intermediates **10a** and **10b**, which upon subsequent exposure to  $\text{BF}_3\cdot\text{Et}_2\text{O}$ <sup>13a</sup> (0.5 molar equiv) at  $0^{\circ}\text{C} \rightarrow \text{rt}$  resulted in the chemoselective formation of the desired vinyl nitrile **3a**. Due to the slower elimination rate observed for the undesired regioisomer **10b** ( $k_1 > k_2$ ),<sup>10</sup> 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  $\text{CeCl}_3$ -promoted double addition of MeLi under non-cryogenic conditions<sup>11</sup> to give carbinamine **11**, which upon acetylation in EtOAc generated the desired carbinamide **2** in 83% isolated yield.<sup>12</sup>

(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  $\text{MsOH}$ -promoted process, see: (a) Premasagar, V.; Palaniswamy, V. A.; Eisenbraun, E. J. *J. Org. Chem.* **1981**, *46*, 2974. For PPA, see: (b) Guy, A.; Guette, J.-P. *Synthesis* **1980**, 3, 222. For  $\text{TfOH}$ , 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  $\text{ClSO}_3\text{H}$ , 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  $\text{ClPO}(\text{OEt})_2$ : Shi, E.; Xiao, J.; Pei, C. *Phosphorous, Sulfur Silicon Relat. Phenom.* **2004**, *179*, 1361.

(9) Treatment of  $(\text{EtO})_2\text{POCN}$  with  $\text{LiOEt}$  appears to generate  $\text{LiCN}$  and  $(\text{EtO})_3\text{PO}$  as suggested by comparing the  $^{31}\text{P}$  NMR spectrum of the latter to that of the authentic sample. For  $\text{LiCN}$ -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  $\sim 90\%$  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.

## SCHEME 4. Synthesis of Vinyl Nitrile 3

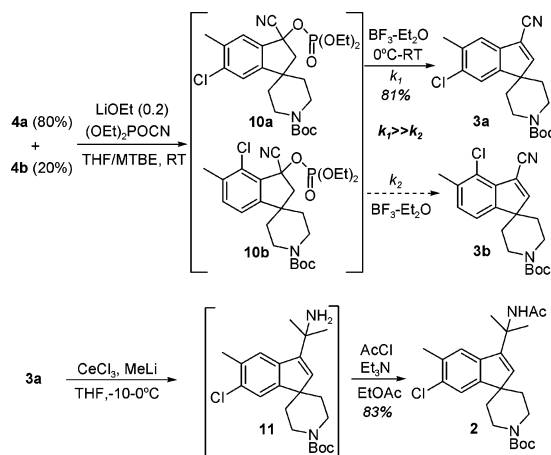


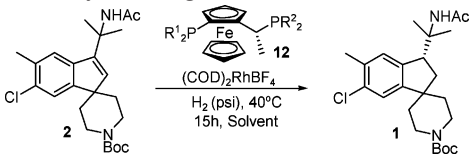
TABLE 1. Initial Metal–Phosphine Screens: High Loadings

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

<sup>a</sup> 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  $\text{HBF}_4\cdot\text{Et}_2\text{O}$  for metal activation. <sup>b</sup> Dry solvents were used for the studies ( $\text{KF} < 100 \text{ ppm}$ ). <sup>c</sup> Substrate to catalyst ratio. <sup>d</sup> Concentration of starting olefin in g/L. <sup>e</sup> Uncorrected:  $[\text{product A}/\text{SM A}] \times 100\%$ . <sup>f</sup> HPLC area percent, uncorrected for absorption factor. <sup>g</sup> 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 ( $\text{S/C} = 12\text{--}20$ ). From the initial screen, metal complexes of Josiphos-type (**12**),<sup>13</sup> BPE (**13**), and Norphos ligands (**14**) were found to exhibit significant reactivities toward the olefin at  $45\text{--}50^{\circ}\text{C}$  and 90 psi of  $\text{H}_2$  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,

TABLE 2. Catalyst Loading and Pressure Screens



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

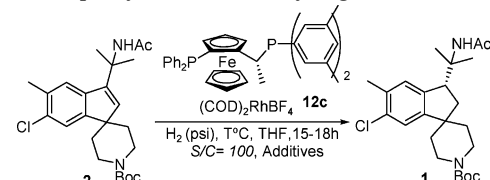
<sup>a</sup> Catalyst was formed by mixing the ligand and precursor in the solvent at rt for 1 h. <sup>b</sup> Substrate to catalyst ratio. <sup>c</sup> Concentration of starting material in g/L. <sup>d</sup> Uncorrected: [product A%/SM A%] × 100%. <sup>e</sup> Uncorrected HPLC area percent. <sup>f</sup> Determined by chiral SFC spectroscopy (Chiralcel OD-H). <sup>g</sup> 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<sub>2</sub>, 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<sub>4</sub>) in 10–14 mL/g THF at 40 °C under 500 psi of H<sub>2</sub> 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<sub>2</sub>CO<sub>3</sub> was present at the beginning of the reaction (entry 4). On the other hand, Et<sub>3</sub>N, Et<sub>3</sub>N•HCl salt, and Ac<sub>2</sub>O 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<sub>2</sub>O) resulted in much lower conversion and slightly reduced enan-

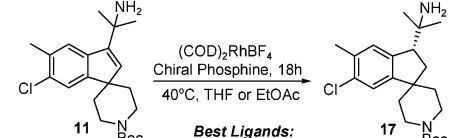
TABLE 3. Impurity Effects on the Hydrogenation of 2



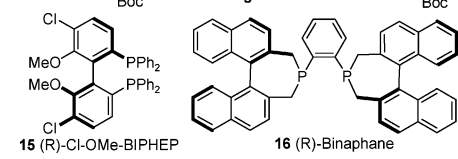
| entry | additives                       | mol % <sup>a</sup> | H <sub>2</sub> (psi) | T (°C) | [SM] <sup>b</sup> | % conv <sup>c</sup> | % ee <sup>d</sup> |
|-------|---------------------------------|--------------------|----------------------|--------|-------------------|---------------------|-------------------|
| 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 <sub>2</sub> CO <sub>3</sub> | 5                  | 500                  | 40     | 100               | 90                  | 81                |
| 5     | Et <sub>3</sub> N               | 1                  | 500                  | 40     | 100               | 7                   | 58                |
| 6     | Et <sub>3</sub> NHCl            | 1                  | 500                  | 40     | 100               | 1                   | nd                |
| 7     | Ac <sub>2</sub> O               | 5                  | 500                  | 25     | 50                | 1                   | nd                |
| 8     | H <sub>2</sub> O                | 3                  | 500                  | 40     | 100               | 33                  | 77                |

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

TABLE 4. Hydrogenation of Amine 11



**Best Ligands:**



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

<sup>a</sup> 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. <sup>b</sup> Substrate to catalyst ratio. <sup>c</sup> Concentration of starting olefin in g/L. <sup>d</sup> Uncorrected: [product A%/SM A%] × 100%. <sup>e</sup> Determined by chiral SFC analysis.

tioselectivity (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.

Virtually all of the catalyst poisons in Table 3 were used or generated during the acetylation of **11** with AcCl or Ac<sub>2</sub>O with Et<sub>3</sub>N and/or during reaction workup with Na<sub>2</sub>CO<sub>3</sub>. 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)<sub>2</sub>RhBF<sub>4</sub> 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 spiroperidineindane-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, subsection of **2** to 1 mol % of Rh–**12c**(BF<sub>4</sub>) in 10–14 mL/g THF at 40 °C under 500 psi of H<sub>2</sub> 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<sub>2</sub>), ligand **12c** (26.8 g, 0.042 mol, 0.011 equiv) was combined with (COD)<sub>2</sub>RhBF<sub>4</sub> (16.3 g, 0.040 mol, 0.01 equiv) in a round-bottom flask. Dry THF (400 mL, N<sub>2</sub> 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<sub>2</sub> (500 psig), vented three times for degassing, and pressurized to 500 psi of H<sub>2</sub>. The reaction temperature was increased to 40 °C while maintaining a H<sub>2</sub> 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<sub>3</sub>PO<sub>4</sub> in H<sub>2</sub>O, 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): [α]<sub>D</sub><sup>25</sup> = 33.8 (c 0.4, MeOH); mp 213–214 °C (dec); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 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<sup>−1</sup>) 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<sub>24</sub>H<sub>35</sub>ClN<sub>2</sub>O<sub>3</sub>: C, 66.27; H, 8.11; N, 6.44. Found: C, 66.06; H, 8.28; N, 6.35.

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**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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