

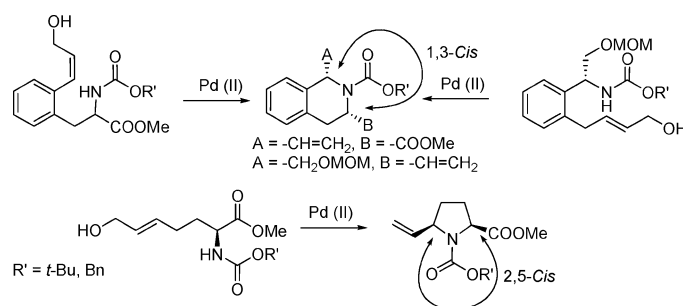
## Controlled Synthesis of Cis or Trans Isomers of 1,3-Disubstituted Tetrahydroisoquinolines and 2,5-Disubstituted Pyrrolidines

Jacques Eustache,<sup>\*,†</sup> Pierre Van de Weghe,<sup>†</sup> Didier Le Nouen,<sup>†</sup> Hiroshi Uyehara,<sup>‡</sup>  
Chizuko Kabuto,<sup>‡</sup> and Yoshinori Yamamoto<sup>\*,‡</sup>

Laboratoire de Chimie Organique et Bioorganique associé au CNRS, Université de Haute-Alsace, Ecole Nationale Supérieure de Chimie de Mulhouse, 3, rue Alfred Werner, F-68093 Mulhouse Cedex, France, and Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

*jacques.eustache@uha.fr*

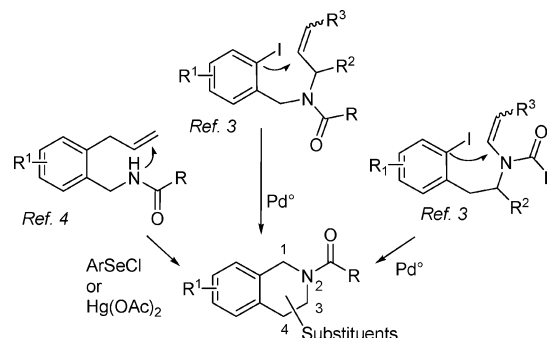
Received January 25, 2005



The stereoselective outcome of Pd(II)- or Ag(I)-catalyzed intramolecular *N*-alkylation to afford 1,3-disubstituted 1,2,3,4-tetrahydroisoquinolines was examined. In the absence of additional substituents, Pd(II) allows a facile access to the cis isomers, while Ag(I) favors formation of the trans isomers. The same observation was made for the synthesis of 2,5-disubstituted pyrrolidines. Possible reasons for the observed stereoselectivities are discussed.

### Introduction

The 1,2,3,4-tetrahydroisoquinoline moiety is commonly found in biologically active molecules of either natural<sup>1</sup> or synthetic origin. Although several well-established synthetic procedures (Pomeranz–Fritsch, Bischler–Napieralsky, and Pictet–Spengler) have long been available for preparing this heterocyclic system,<sup>2</sup> these traditional methods involve an electrophilic aromatic substitution as a key step and really work well only with electron-rich systems. Owing to the importance of the 1,2,3,4-tetrahydroisoquinoline moiety, other methods have been developed that do not rely on the electronic characteristics of the aromatic ring. For example, the intramolecular Heck reaction has successfully been used



**FIGURE 1.** “Nonclassical” syntheses of 1,2,3,4-tetrahydroisoquinolines.

to assemble the tetrahydroisoquinoline skeleton in complex alkaloids (Figure 1).<sup>3</sup> Electrophile-induced cycliza-

\* Corresponding author. Tel: +33 3 89 33 6858. Fax: +33 3 89 33 6860.

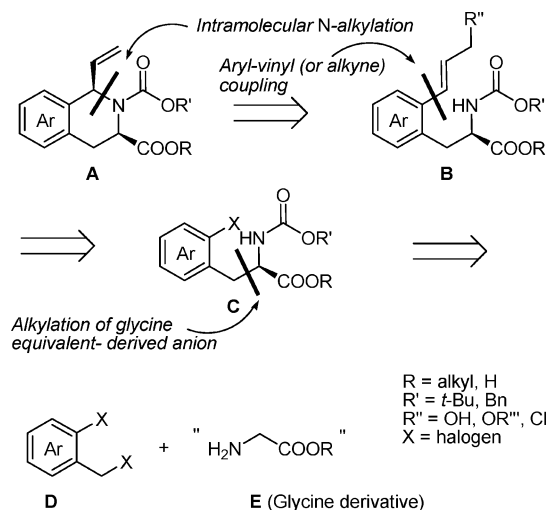
<sup>†</sup> Université de Haute-Alsace.

<sup>‡</sup> Tohoku University.

(1) For a recent review on tetrahydroisoquinoline antibiotics, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.

(2) For recent reviews on the synthesis of tetrahydroisoquinolines, see: (a) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341–3370. (b) Bracca, A. B. J.; Kaufman, T. S. *Tetrahedron* **2004**, *60*, 10575–10610. (c) Felpin, F. X.; Lebreton, J. *Curr. Org. Synth.* **2004**, *1*, 83–109. (d) Kirsch, G.; Hess, S.; Comel, A. *Curr. Org. Synth.* **2004**, *1*, 47–63. (e) Kaufman, T. S. *Synthesis* **2005**, 339–360.

(3) (a) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552–6554. For earlier examples of use of the intramolecular Heck reaction for the synthesis of tetrahydroisoquinolines see: (b) Burns, B.; Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron* **1992**, *48*, 7297–7320 and references therein. (c) Tietze, L. F.; Burkhardt, O. *Synthesis* **1994**, 1331–1336. (d) Tietze, L. F.; Burkhardt, O.; Henrich, M. *Liebigs Ann. Chem.* **1997**, 1407–1414.



**FIGURE 2.** Synthesis of 1,3-disubstituted 1,2,3,4-tetrahydroisoquinolines by intramolecular *N*-alkylation.

tion of *o*-allylbenzylamides has also been employed (Figure 1).<sup>4</sup> The number of recent reviews devoted to 1,2,3,4-tetrahydroisoquinolines<sup>1,2</sup> provides evidence for the considerable interest this class of compounds continues to attract from synthetic and medicinal chemists and highlights the need for efficient and selective synthetic approaches to this heterocyclic system.

For a project underway in our laboratories, we became interested in 1,3-disubstituted-1,2,3,4-tetrahydroisoquinolines, an important subclass of 1,2,3,4-tetrahydroisoquinolines commonly found in natural products. A key issue in the synthesis of these molecules is the control of the relative and absolute stereochemistries at C-1 and C-3 (see Figure 1 for numbering). Although some elegant answers to this problem have been reported,<sup>5</sup> to the best of our knowledge, a generally applicable synthesis of 1,3-disubstituted-1,2,3,4-tetrahydroisoquinolines does not exist at present. In the present study, we needed a convenient access to (3-substituted 1-vinyl)- and (1-substituted 3-vinyl)tetrahydroisoquinolines that fulfilled the following requirements: (1) The synthesis should be applicable to a wide range of aromatic substitutions. (2) It should afford 1,3-*cis*-1,2,3,4-tetrahydroisoquinolines preferentially. (3) An asymmetric version of the synthesis should be easy to develop.

Our first synthetic target was *cis*-3-carboxy-1-vinyl-tetrahydroisoquinolines (**A**, Figure 2). Inspection of the literature pertaining to 1,2,3,4-tetrahydroisoquinoline synthesis did not reveal a simple answer to our problem. Hence, we developed the approach shown in Figure 2, which fulfills requirements 2 and 3 listed above and should fulfill requirement 1 with the possible exception of cases where the aromatic ring substituents in **B** are strongly electron-withdrawing groups. An asymmetric version of the coupling **D** + **E** → **C** should be no problem to develop.

(4) (a) De Koning, C. B.; van Otterlo, W. A. L.; Michael, J. P. *Tetrahedron* **2003**, *59*, 8337–8345 and references therein. (b) Clive, D. L. J.; Farina, V.; Singh, A.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Org. Chem.* **1980**, *45*, 2120–2126.

(5) See, for example, ref 3a and: Magnus, P.; Matthews, K. S.; Lynch, V. *Org. Lett.* **2003**, *5*, 2181–2184.

The key reaction in this sequence is the intramolecular *N*-alkylation which establishes the relative stereochemistry between the substituents at positions 1 and 3 in a racemic synthesis and the absolute configuration at C-1 in an asymmetric synthesis. There were few reports of this particular cyclization prior to our work,<sup>6</sup> and the only example somewhat related to ours is the recently reported Hg(II)-promoted cyclization of 1-(2-allylphenyl)-ethylamines to afford 1,3-disubstituted tetrahydroisoquinolines.<sup>4a</sup> In that case, the *trans* isomer was the major product of the reaction. In contrast to tetrahydroisoquinolines, intramolecular *N*-alkylation has been used in several instances for the preparation of 2,6-disubstituted piperidines. Various agents can trigger the cyclization including Pd(0)<sup>7</sup> or Pd(II)<sup>8–10</sup> complexes and Ag(I) salts.<sup>8</sup> In the representative examples shown in Figure 3 the factors which determine the stereoselectivity are not obvious.

The conditions used for the cyclization and the substitution patterns of the substrates are different in each experiment, which renders comparisons difficult, but certain trends are apparent. In experiments c and d, the Pd(II)-induced cyclization leads to *trans* isomers, whereas a *cis* isomer is formed preferentially when using a NaH/Ag(I) or NaH/Pd(0) system. Comparing a and b gives opposite results. It is well-known that A<sup>1,3</sup>-pseudoallylic strain effects<sup>11</sup> largely determine the outcome of these cyclizations. However, other steric effects clearly play a role in the transition state (compare for example cyclization a when R = H or OBn). In our case, the situation is again different because the presence of an aromatic ring prevents a chairlike transition state generally used to explain the observed stereoselectivities (see the Discussion and refs 7–10). Therefore, before embarking on the synthesis of complex 1,2,3,4-tetrahydroisoquinolines, we considered it necessary to conduct careful cyclization studies using simpler models. Our first synthetic study toward (1-carboxy-3-vinyl)tetrahydroisoquinolines is depicted in Scheme 1.

## Results and Discussion

The synthesis commences with the alkylation of the enolate derived from *N*-[bis(methylthio)methylene]glycine methyl ester<sup>12</sup> by 2-iodobenzyl bromide to provide the 2-iodophenylalanine derivative (**2**). This was converted in two steps into *rac*-*N*-(benzyloxycarbonyl)-2-iodophenylalanine methyl ester (**4**). Sonogashira reaction

(6) While this work was in progress, the preparation of chiral C-1-substituted tetrahydroisoquinolines using Pd(0)-catalyzed intramolecular asymmetric amination of substituted phenethylamines was described. Conceivably, a nonenantioselective version of this method could be applied to the synthesis of 1,3-disubstituted tetrahydroisoquinolines: Ito, K.; Akashi, S.; Saito, B.; Katsuki, T. *Synlett*, **2003**, 1809–1812.

(7) Takao, K.-I.; Nigawara, Y.; Nishino, E.; Takagi, I.; Koji, M.; Tadano, K.-I.; Ogawa, S. *Tetrahedron* **1994**, *50*, 5681–5704.

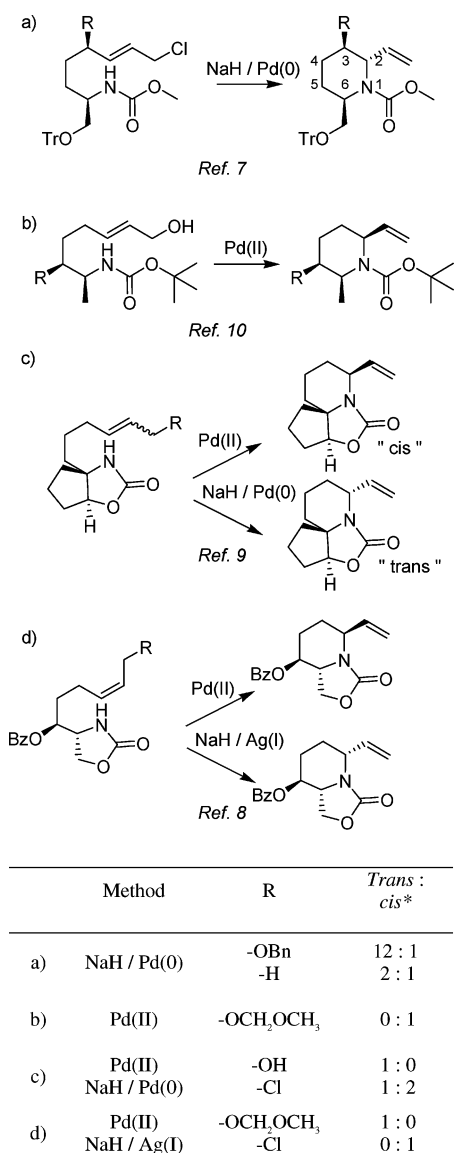
(8) Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776–777.

(9) Yokota, W.; Shindo, M.; Shishido, K. *Heterocycles* **2001**, *54*, 871–885.

(10) Makabe, H.; Kong, L. K.; Hirota, M. *Org. Lett.* **2003**, *5*, 27–29.

(11) (a) Johnson, R. A. *J. Org. Chem.* **1968**, *33*, 3627–3632. (b) Harding, K. E.; Marman, T. H. *J. Org. Chem.* **1984**, *49*, 2838–2840.

(12) Hoppe, D.; Beckmann, L. *Liebigs Ann. Chem.* **1979**, 2066–2075.



**FIGURE 3.** Literature examples of formation of 2,6-disubstituted piperidines by intramolecular *N*-alkylation. \*In c, *cis* and *trans* are defined arbitrarily to facilitate comparison with experiment d.

with propargyl alcohol<sup>13</sup> was followed by treatment with Lindlar catalyst to yield the *cis*-allylic alcohol **6**. Each step in the sequence proceeded with good yields. Based upon the literature precedents shown in Figure 3 (entries c and d), we first focused on the NaH/AgOTf combination for inducing the cyclization to the desired 1,3-*cis*-disubstituted tetrahydroisoquinoline **11**. Conversion of alcohol **6** to the allylic chloride **7** was effected in high yield by treatment with triphenylphosphine and *N*-chlorosuccinimide<sup>14</sup> (the alternative conversion involving mesylate

formation and treatment with LiCl afforded a much lower yield of **7**). We found the best conditions for cyclization to require low-temperature deprotonation of **7** by BuLi, followed by addition of an excess of freshly recrystallized AgOTf. Under these conditions, cyclization proceeded smoothly to afford a 1:3 mixture of **8** and **9**.<sup>15</sup> The isomers could be separated by chromatography and converted to the corresponding carboxylic acids by careful hydrolysis of the esters (solid LiOH, THF/MeOH/water). Using these optimized conditions, *cis/trans* isomerization could be minimized but not completely avoided. Establishing the relative stereochemistry between substituents on C-1 and C-3 in the newly formed ring proved unexpectedly challenging, and detailed NMR experiments failed to provide the answer. The stereochemistries were established as follows:

(a) The minor component of the tetrahydroisoquinoline mixture obtained after cyclization was converted to alcohol **13**, whose NMR data were compared with that of the known authentic *trans* isomer **14**<sup>16</sup> and found to be different (Scheme 2).

(b) The stereochemistry of **8** was subsequently confirmed from an X-ray structure of the ammonium salt **12** (Figure 4), clearly showing the *cis* relationship of the C-1 and C-3 substituents (Figure 4).

Thus, in our case, AgOTf-induced cyclization afforded mainly the *trans* instead of the desired *cis* isomer. We next examined whether the course of the cyclization could be modified by switching to the Pd(II) method as shown earlier by Hirai in his studies on piperidines.<sup>8</sup> We were pleased to observe that treatment of **6** with PdCl<sub>2</sub>(PhCN)<sub>2</sub> in THF at room temperature proceeded smoothly to afford almost exclusively the *cis* isomer **8**. The course of the reaction deserves some comments: upon addition of the catalyst **6** is rapidly converted to a slightly more polar compound. Thin layer chromatography (TLC) monitoring of the reaction indicates that after 2 h the new compound (assumed to be the *trans*-allylic alcohol **6'**) had considerably increased at the expense of **6**.

In the meantime, a less polar weakly UV active spot, corresponding to the cyclization product, appeared. Completion of the reaction required 24 h. Although we cannot exclude that a small amount of tetrahydroisoquinoline is formed directly from **6**, this appears to be a minor process as compared to the isomerization **6** → **6'** followed by cyclization of the latter.

Thus, in our case, the results are opposite to that observed in refs 8 and 9 (Figure 3c,d) and agree with those reported in refs 7 and 10 (Figure 3a,b). A tentative explanation is proposed in Figure 5.

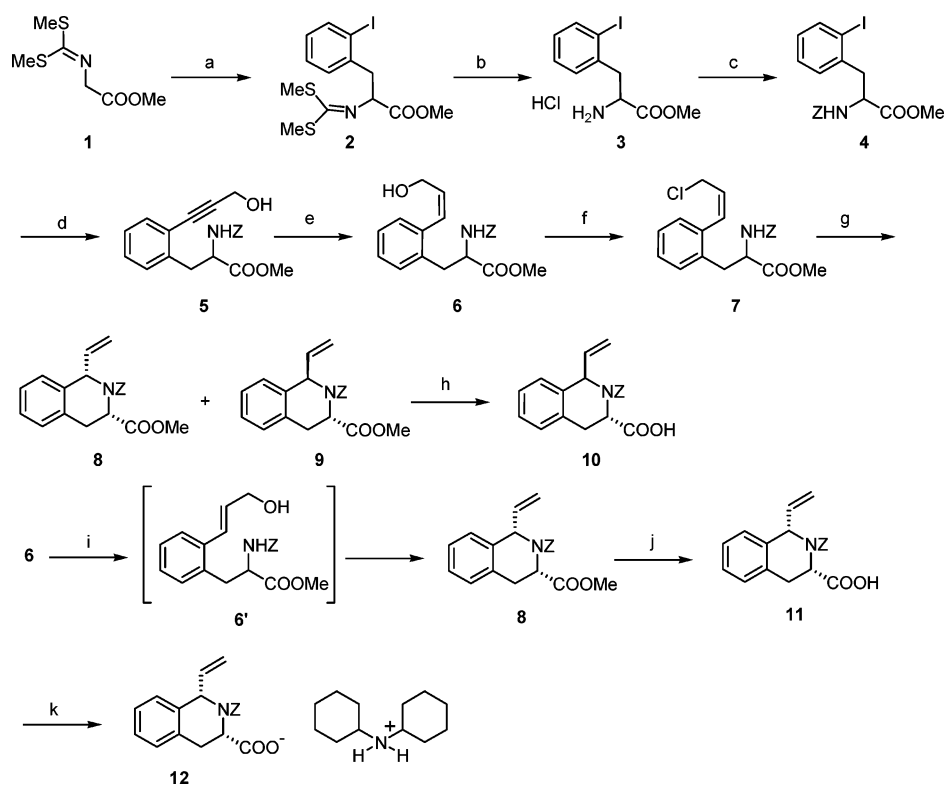
Several similar chairlike transition-state models have been proposed to explain the stereoselective outcome of intramolecular *N*-alkylation reactions to afford piperidines (**TsA**, **TsB**, **TsC**, and **TsD** in Figure 5). Transition state **TsB** in which A<sup>1,3</sup>-pseudoallylic strain is minimal leads to a *cis* isomer. In transition state **TsA**, repulsion between the trityloxymethyl and  $\pi$ -allyl pal-

(13) During the Sonogashira reaction, highly colored impurities are formed whose polarity is close to that of propargylic alcohol **5**. It is important to use a long enough silica gel column for removing these impurities. Failure to do so will render the next (reduction) step very sluggish. If this is the case, the inactivated Lindlar catalyst should be filtered off and replaced by a fresh one until hydrogen adsorption proceeds at a fast rate. Otherwise, slow reaction and over reduction may result.

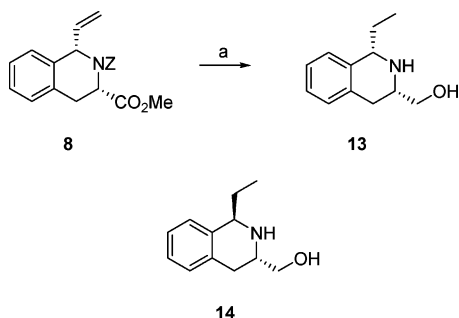
(14) Sakaitani, M.; Ohfuné, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150–1158.

(15) Similar results in terms of stereoselectivity were obtained using NaH (–20 °C to rt) or *N*-diisopropylethylamine (48 h, rt) as bases. Yields were lower, however and varied from experiment to experiment. On TLC (SiO<sub>2</sub>, ether/hexane, 1:2), **8** and **9** are weakly UV active. **8** is slightly less polar than **9**.

(16) Monsees, A.; Laschat, S.; Dix, I.; Jones, P. G. *J. Org. Chem.* **1998**, *63*, 10018–10021.

SCHEME 1<sup>a</sup>

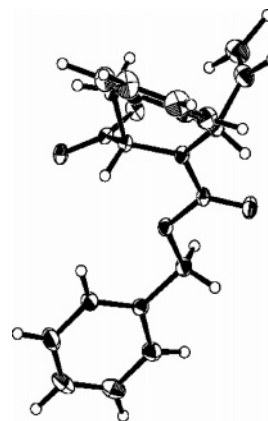
<sup>a</sup> Reagents and conditions: (a) *t*-BuOK (1 equiv), THF,  $-78\text{ }^{\circ}\text{C}$ , 1 h then 2-iodobenzyl bromide (1 equiv),  $-78\text{ }^{\circ}\text{C}$  to rt, 2 h; (b) HCl, THF/H<sub>2</sub>O, rt, 16 h, 71% (two steps); (c) ZCl (1.2 equiv), NEt<sub>3</sub> (2.4 equiv),  $-20\text{ }^{\circ}\text{C}$  to rt, 1 h, 81%; (d) propargyl alcohol (1 equiv), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5 mol %), CuI (5 mol %), NEt<sub>3</sub> (excess), THF, rt, 4 h, 68%; (e) H<sub>2</sub> (1 atm), Lindlar catalyst, MeOH, 83%; (f) PPh<sub>3</sub> (2 equiv), NCS (1.7 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0  $^{\circ}\text{C}$ , 15 min, 90%; (g) BuLi, (1 equiv),  $-78\text{ }^{\circ}\text{C}$ , 15 min then AgOTf (excess), THF, 6.5 h, 18% (**8**) and 53% (**9**); (h) LiOH·H<sub>2</sub>O (excess), THF/water, 60  $^{\circ}\text{C}$ , 8 h, 100% (11% *cis* isomer), (i) PdCl<sub>2</sub>(PhCN)<sub>2</sub> (19 mol %), THF, rt, 24 h, 75%; (j) LiOH·H<sub>2</sub>O (excess), THF/MeOH/water, 60  $^{\circ}\text{C}$ , 16 h, 98% (11% *trans* isomer), (k) dicyclohexylamine (1.1 equiv), ether, rt.

SCHEME 2<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) (i) H<sub>2</sub> (1 atm), Pd/C, MeOH, rt, 2.5 h; (ii) LiAlH<sub>4</sub>, THF, rt, 16 h, 62%, two steps).

ladium groups is apparently able to overcome minimization of A<sup>1,3</sup>-pseudoallylic strain resulting in the preferential formation of the *trans* isomer. In transition states **TsC** and **TsD**, the rigid cyclic carbamate can only occupy the equatorial position while the allyl alcohol or allylic chloride occupies an axial or equatorial position respectively due to differing complexation modes with Pd(II) or Ag(I).

Thus, besides the use of Pd(II) or Ag(I), a crucial factor for controlling the formation of 2,6-*trans*- or 2,6-*cis*-piperidines by intramolecular cyclizing *N*-alkylation appears to be the nature of the starting carbamate (cyclic or acyclic).<sup>17</sup> In our case, by analogy to the above models, the transition states in the Pd(II)- or Ag(I)-induced



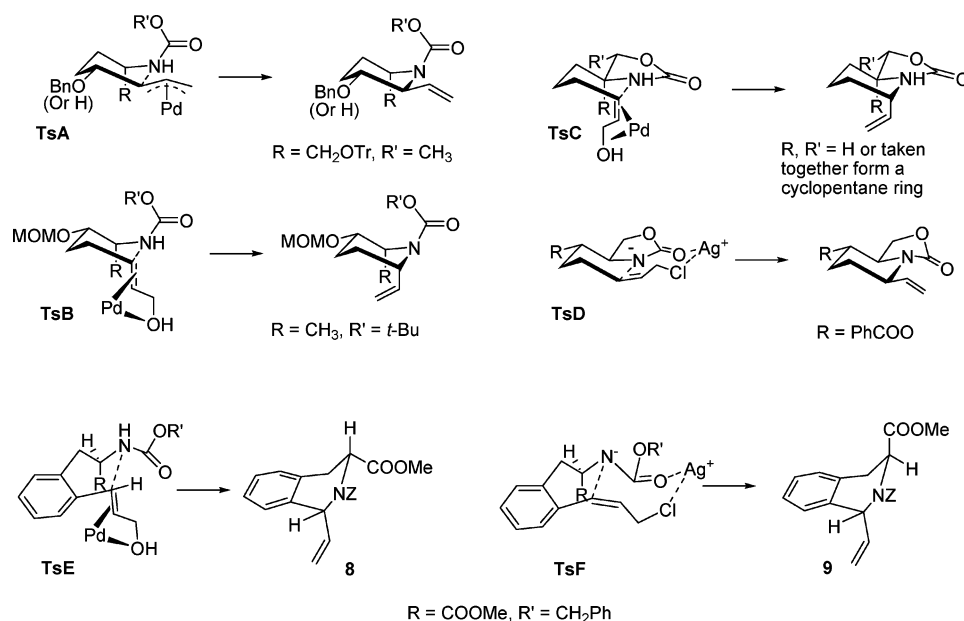
**FIGURE 4.** Crystal structure of **12** (dicyclohexylamine moiety omitted for clarity).

cyclization, which could explain our findings may be represented as shown in Figure 5 (**TsE** and **TsF**, respectively).

It should also be noted that an enantioselective version of these syntheses can be easily derived from the present results because our key intermediate **3** can easily be prepared in an optically active form.

(17) We thank one of the reviewers for pointing out the importance of the nature of the starting carbamate in establishing the stereoselectivity of the cyclization.



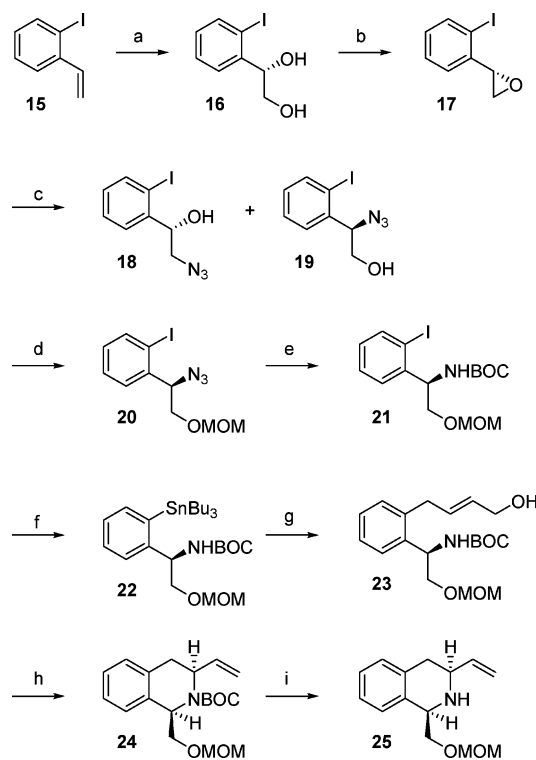


**FIGURE 5.** Possible transition-state models for intramolecular cyclizing *N*-alkylation leading to piperidines or tetrahydroisoquinolines. Chairlike transition states: A and B, acyclic carbamates;<sup>7,10</sup> C and D, cyclic carbamates;<sup>8,9</sup> E and F, this work.

We next examined the applicability of the method to the enantioselective preparation of our second series of target molecules, 1-substituted 3-vinyl-1,2,3,4-tetrahydroisoquinolines (Scheme 3).

Iodostyrene **15**<sup>18</sup> was converted in high yield to the diol derivative **16** (ee > 98%) by Sharpless asymmetric dihydroxylation using AD-mix- $\alpha$ .<sup>19</sup> Conversion to epoxide **17**,<sup>20</sup> and lithium perchlorate-assisted opening of the latter with NaN<sub>3</sub> provided a mixture of two  $\alpha$ -azido alcohols in which the desired regioisomer (**19**) predominated. Protection of the primary alcohol in **19** as a MOM ether, reduction of the azide,<sup>21</sup> and protection of the resulting amine as the corresponding BOC derivative afforded the protected amino alcohol **21**. Direct conversion of **21** to the required allylic alcohol **23** proved not to be possible: Stille coupling with tributyl(*Z*)-4-methoxymethoxybut-2-enyl)stannane was unsuccessful, and palladium acetate-catalyzed coupling with 2-vinylloxirane proceeded in low yield and without stereoselectivity.<sup>22</sup> The problem was solved by first converting **21** to the stannyl derivative **22**. Coupling with 2-vinylloxirane then proceeded smoothly in DMF, using the weakly liganded palladium complex (CH<sub>3</sub>CN)<sub>2</sub>PdCl<sub>2</sub> to afford allylic alcohol **23** in excellent yield as the pure (*E*)-isomer (within NMR detection limits).<sup>23</sup> Allylic alcohol **23** was submitted to the cyclization conditions shown earlier to favor the formation of 1,3-*cis*-tetrahydroisoquinolines. The reaction proceeded rapidly to provide **24** in very good yield and with very high stereoselectivity (*cis/trans* > 95/5). NMR studies of the free amine **25** revealed an NOE between

### SCHEME 3<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) AD-mix- $\alpha$ , *t*-BuOH/H<sub>2</sub>O, 0 °C, 5 h, 91%; (b) MeC(OEt)<sub>3</sub>, TMSCl, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h then K<sub>2</sub>CO<sub>3</sub>, MeOH, rt, 2 h, 92%; (c) NaN<sub>3</sub>, LiClO<sub>4</sub>, CH<sub>3</sub>CN, 60 °C, 5 h, 29% (**18**) and 67% (**19**); (d) MOMCl, <sup>i</sup>Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, rt, 3 h, 94%; (e) (i) SnCl<sub>2</sub>, PhSH, NEt<sub>3</sub>, THF, rt, 30 min; (ii) BOC<sub>2</sub>O, NEt<sub>3</sub>, rt, 3 h, 85%; (f) Bu<sub>3</sub>SnSnBu<sub>3</sub>, Pd(tBu<sub>3</sub>P)<sub>2</sub> (10 mol %), DMF, 100 °C, 20 h, 60%; (g) 2-vinylloxirane, PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> (10 mol %), DMF/H<sub>2</sub>O, rt, 10 h, 83%; (h) PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> (10 mol %), THF, rt, 2 h; (i) TFA/H<sub>2</sub>O (1:1), CH<sub>3</sub>CN, rt, 48 h, 78% (two steps).

(18) Acheson, R. M.; Lee, G. C. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2321–2332.

(19) Swindell, C. S.; Fan, W. *J. Org. Chem.* **1996**, *61*, 1109–1118.

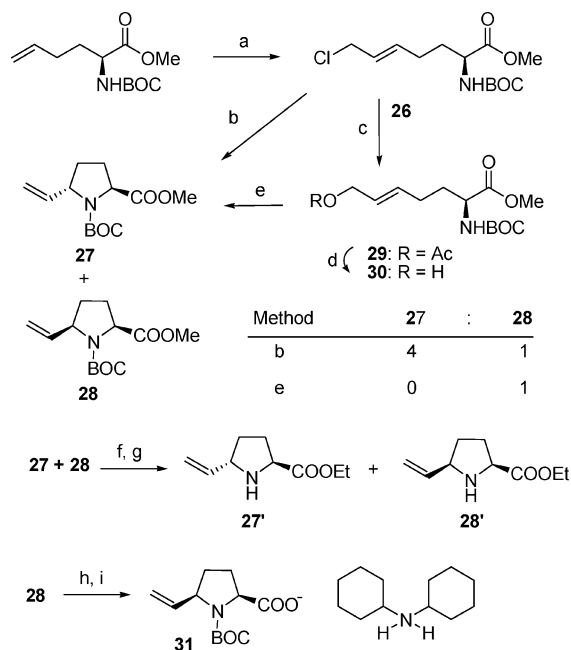
(20) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515–10530.

(21) Barta, M.; Romea, P.; Urpi, F.; Vilarrassa, J. *Tetrahedron* **1990**, *46*, 587–594.

(22) Larock, R. C.; Ding, S. *J. Org. Chem.* **1993**, *58*, 804–806.

(23) (a) Tueting, D. R.; Echavarren, A. M.; Stille, J. K. *Tetrahedron* **1989**, *45*, 979–992. (b) Echavarren, A. M.; Tueting, D. R.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 4039–4041.

the protons located at positions 1 and 3, thus establishing the *cis* relationship of the vinyl group and the protected

SCHEME 4<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a)  $\text{CH}_2=\text{CHCH}_2\text{Cl}$  (3.5 equiv), Grubbs II (10 mol %),  $\text{CH}_2\text{Cl}_2$ , 40 °C, 14 h, 67%; (b) BuLi, (1 equiv), -78 °C, 15 min then AgOTf (1.7 equiv), THF, rt, 2.5 h, 77% (**27**/**28** = 4:1); (c) NaOAc (10 equiv), DMF, 100 °C, 26 h, 70%; (d) NaOMe (0.1 M), MeOH, rt, 2.5 h, 90%; (e)  $\text{PdCl}_2(\text{CH}_3\text{CN})_2$  (15 mol %), THF, rt, 12 h, 77%; (f) NaOEt (0.04M), EtOH, rt; (g) HCl (4 M in dioxane), 0 °C, 1 h, 58% (two steps); (h)  $\text{LiOH}\cdot\text{H}_2\text{O}$  (7 equiv), THF/ $\text{H}_2\text{O}$ , 60 °C, 5 h, 100%; (i) dicyclohexylamine (1 equiv), ether, rt.

hydroxymethyl side chain. Here again, the model shown in Figure 5 can be used to explain the observed result.

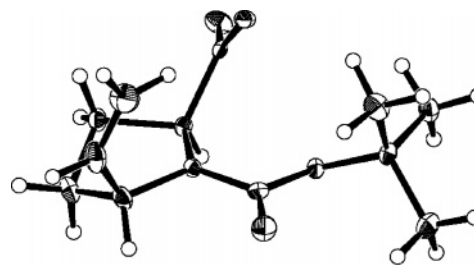
Our project also required the preparation of *cis*-2-carboxy-5-vinylpyrrolidines. The few reported syntheses of *cis*-2-carboxy-5-vinylpyrrolidines are poorly stereoselective.<sup>24</sup> Considering the favorable results we had obtained in the tetrahydroisoquinoline series, we decided to examine whether the methodology could be applied to the preparation of pyrrolidines. Here again, despite literature precedents, we could not find examples that would allow us to predict with certainty the stereoselective outcome of the cyclization.<sup>25</sup>

We developed the short route shown in Scheme 4. (*S*)-2-*tert*-Butoxycarbonylamino-hex-5-enoic acid methyl ester was prepared from BOC-iodoalanine methyl ester and allyl chloride.<sup>26</sup> Cross-metathesis using excess allyl chloride and [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)(tricyclohexyl-

(24) (a) Beal, L. M.; Liu, B.; Chu, W.; Moeller, K. D. *Tetrahedron* **2000**, *56*, 10113–10125. (b) Beal, L. M.; Moeller, K. D. *Tetrahedron Lett.* **1998**, *39*, 4639–4642. (c) Campbell, J. A.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6313–6325. (d) Manfré, F.; Kern, J.-M.; Biellmann, J.-F. *J. Org. Chem.* **1992**, *57*, 2060–2065.

(25) See, for example: Hirai, Y.; Terada, T.; Amemiya, Y.; Momose, T. *Tetrahedron Lett.* **1992**, *33*, 7893–7894. To the best of our knowledge, this is the only reported example of 2,5-disubstituted pyrrolidine synthesis via Pd(II)-induced cyclization of 4-(*Z*)-1-benzoyloxy-5-methoxymethoxy-pent-3-enyl-oxazolidin-2-one, and only the 2,5-*trans* isomer was formed. However, in this case, the benzoyloxy group may play a key role in determining the stereoselectivity of the reaction as observed for piperidines (ref 8). Ag(I)-induced cyclization was not studied in that case.

(26) Rodriguez, A.; Miller, D. D.; Jackson, R. F. W. *Org. Biomol. Chem.* **2003**, *1*, 973–977.



**FIGURE 6.** Crystal structure of **31** (dicyclohexylamine moiety omitted for clarity).

phosphine)ruthenium] (Grubbs II catalyst), according to Roy,<sup>27</sup> proceeded well to afford precursor **26** which was submitted to the Ag(I) cyclization conditions described previously (BuLi, AgOTf) to give a 4:1 mixture of pyrrolidines **27** and **28**. The 2,5-*trans* configuration in **27** was ascertained by conversion of the mixture **27**–**28** to the mixture of ethyl esters **27'**–**28'**. NMR data of the major isomer corresponded to that of the authentic material.<sup>28</sup> The Pd(II)-induced cyclization was examined next. To this effect, the allylic chloride **26** was converted in two steps to the allylic alcohol **30** which was treated with  $\text{PdCl}_2(\text{CH}_3\text{CN})_2$  in THF at room temperature to afford pyrrolidine **28** as a single isomer. To further support our stereochemical assignments, **28** was converted in two steps to the crystalline dicyclohexylamine salt **31** from which an X-ray structure was obtained showing the *cis* relationship between the 2 and 5 substituents (Figure 6).

## Conclusion

In conclusion, the Pd(II) and Ag(I) intramolecular *N*-alkylation initially developed by Hirai for the synthesis of piperidines and (in one instance) pyrrolidines has been applied to the preparation of 1,3-disubstituted 1,2,3,4-tetrahydroisoquinolines. In the absence of additional substituents, the Ag(I)/base conditions affords 1,3-*cis* isomers, whereas the Pd(II)-catalyzed reaction leads to the formation of *trans* isomers. This latter observation is in line with the results reported by Makabe<sup>10</sup> and contrasts with the findings of Hirai in the piperidine series. A tentative half-chair transition-state model was proposed for the reaction pathway giving rise to tetrahydroisoquinolines. The same observation (i.e., Pd-induced intramolecular *N*-alkylation leads to *cis* isomers) was made for 2,5-disubstituted pyrrolidines.

Both *cis* and *trans* isomers of chiral 1,3-disubstituted-1,2,3,4-tetrahydroisoquinolines are found in naturally occurring, biologically active alkaloids; therefore, the development of highly stereoselective and enantioselective methods to each isomer is important. The present work proposes a simple solution to this problem, and the new synthetic approaches compare favorably with previous ones in terms of efficacy and potential scope.

## Experimental Section

**General Methods.** <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded at 500 or 400 MHz and 125.6 and 100 MHz,

(27) Liu, B. Das, S. K.; Roy, R. *Org. Lett.* **2002**, *4*, 2723–2726.

(28) Collado, I.; Ezquerro, J.; Pedregal, C. *J. Org. Chem.* **1995**, *60*, 5011–5015.

respectively. Melting points are not corrected. When required, reactions were carried out under argon atmosphere with standard techniques for the exclusion of air and moisture. All solvents were dried before use. TLC was performed using fluorescent 60F<sub>254</sub> coated plates.

**Methyl 2-Amino-3-(2-iodophenyl)propionate Hydrochloride (3).** To a cold (−78 °C) solution of *N*-[bis(methylthio)methylene]glycine methyl ester **1** (11.40 g, 59.0 mmol) in THF (120 mL) was added under argon atmosphere powdered *t*-BuOK (6.62 g, 59.0 mmol). The mixture was stirred until *t*-BuOK was dissolved (ca. 1 h). 1-Bromomethyl-2-iodobenzene was then added (17.54 g, 59.0 mmol), and the reaction was stirred for 10 min at −78 °C and then 1 h at rt. The resulting brown-red solution was diluted with ethyl acetate and extracted with 1 N HCl and then saturated aqueous NaHCO<sub>3</sub>. The organic solution was dried over MgSO<sub>4</sub>, and the solvents were removed under reduced pressure. Polar, colored impurities and unreacted 1-bromomethyl-2-iodobenzene were removed by chromatography over a short silica gel column to afford 21.0 g of crude **2**. This was dissolved in THF (120 mL), and 2 N HCl (60 mL) was added. The turbid mixture was stirred at rt for 16 h at which time a clear solution was obtained. The THF was evaporated under reduced pressure, and the aqueous solution was extracted three times with ether and concentrated to ca. 20 mL at which time an abundant crystalline precipitate had formed. Ether (100 mL) was added, and the crystals were recovered by filtration. The crystalline residue was dissolved in hot chloroform (500 mL), and the solution was dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to ca. 50 mL. Compound **3** crystallized during the evaporation. Ether (200 mL) was added, and the crystals were filtered and dried to afford pure **3** (14.32 g, 71%): mp 183–186 °C; <sup>1</sup>H NMR (methanol-*d*<sub>4</sub>, 400 MHz) δ (ppm) 3.26 (1 H, dd, *J* = 14, 8 Hz), 3.42 (1 H, dd, *J* = 14, 8 Hz), 3.74 (3 H, s), 4.32 (1 H, t, *J* = 8 Hz), 7.05 (1 H, td, *J* = 7.5, 1.5 Hz), 7.31 (1 H, dd, *J* = 8, 1.5 Hz), 7.39 (1 H, td, *J* = 7.5, 1 Hz), 7.91 (1 H, dd, *J* = 8, 1 Hz). Anal. Calcd for C<sub>10</sub>H<sub>13</sub>ClINO<sub>2</sub> (M = 341.5): C, 35.16; H, 3.84; N, 4.10. Found: C, 35.21; H, 3.85; N, 4.10.

**2-Benzyloxycarbonylamino-3-(2-iodophenyl)propionic Acid Methyl Ester (4).** To a suspension of **3** (14.32 g, 41.9 mmol) in THF (200 mL) was added triethylamine (14.0 mL, 2.4 equiv). The mixture was cooled to −20 °C, and *Z*-chloride (7.18 mL, 1.2 equiv) was added. The mixture was stirred for 10 min at −20 °C and 1 h at rt. The solvents were evaporated, and the residue was taken up in ether. The precipitate (amine salts) was filtered off and the residue chromatographed over silica gel (hexane/ether, 2:1) to afford pure **4** (14.78 g, 81%) as a thick syrup which slowly solidified upon standing: mp 64–67 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ (ppm) 3.12 (1 H, dd, *J* = 14, 8 Hz), 3.29 (1 H, dd, *J* = 14, 6 Hz), 3.71 (3 H, s), 4.69 (1 H, m), 5.28 (1 H, br d, *J* = 8 Hz), 6.90 (1 H, t, *J* = 7 Hz), 7.16–7.40 (9 H, m); <sup>13</sup>C NMR (toluene-*d*<sub>8</sub>, 125.6 MHz) δ (ppm) 43.0, 51.8, 54.5, 66.9, 101.3, 128.1, 128.3, 128.4, 128.5, 128.7, 130.6, 139.9, 140.0, 155.7, 171.8; HRMS (ESI, positive mode) calcd for C<sub>18</sub>H<sub>18</sub>INO<sub>4</sub> + Na<sup>+</sup> 462.0178, found 462.0173.

**2-Benzyloxycarbonylamino-3-[2-(3-hydroxyprop-1-ynyl)phenyl]propionic Acid Methyl Ester (5).** The protected amino acid **4** (4.39 g, 10 mmol) was dissolved in THF (40 mL). The solution was degassed and placed under argon atmosphere. PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.350 g, 0.5 mmol), CuI (95 mg, 0.5 mmol), and triethylamine (20 mL) were added. The solution was degassed again and placed under argon atmosphere, and propargyl alcohol (0.60 mL, 1 equiv) was added under stirring. The mixture was stirred for 4 h and partitioned between ether and 2 N aqueous HCl. The organic layer was washed with 2 N aqueous HCl and saturated NaHCO<sub>3</sub>, dried, and evaporated to dryness. The residue was chromatographed over silica gel (hexane/ethyl acetate, 2:1), on a long column, to provide pure **5** as a light yellow syrup (2.495 g, 68%): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ (ppm) 3.09 (1 H, dd, *J* = 13, 8 Hz), 3.35 (1 H, dd, *J* = 13, 6 Hz), 3.42 (1 H, t, *J* = 6 Hz), 3.58 (3 H, s), 4.43 (1 H, dd, *J* = 16, 6 Hz), 4.48 (1 H, dd, *J* = 16, 6 Hz), 4.83 (1 H, dt, *J* =

8, 6 Hz), 5.07 (1 H, d, *J* = 12 Hz), 5.11 (1 H, d, *J* = 12 Hz), 5.49 (1 H, br d, *J* = 8 Hz), 7.03 (1 H, m), 7.19 (2 H, m), 7.28–7.40 (6 H, m); <sup>13</sup>C NMR (toluene-*d*<sub>8</sub>, 125.6 MHz) δ (ppm) 30.5, 38.8, 51.35, 51.5, 54.6, 67.3, 83.4, 94.1, 124.0, 127.2, 128.5, 128.6, 129.9, 132.0, 136.8, 138.9, 156, 172.2; HRMS (ESI, positive mode) calcd for C<sub>21</sub>H<sub>21</sub>NO<sub>5</sub> + Na<sup>+</sup> 390.1317, found 390.1312.

**2-Benzyloxycarbonylamino-3-[2-((*Z*)-3-hydroxyprop-1-enyl)phenyl]propionic Acid Methyl Ester (6).** The propargyl alcohol **5** (6.45 g, 17.5 mmol) was dissolved in methanol (150 mL). Lindlar catalyst (1 g) was added, and the adsorption of hydrogen was measured. Vigorous stirring was maintained until the expected amount of hydrogen had been adsorbed. Completion of the reaction requires about 30 min and can be checked by TLC on silica gel (hexane/ether, 1:3). The catalyst was filtered off, the solvents were evaporated, and the residue was chromatographed over silica gel (hexane/ether, 1:3) to afford pure **6** (5.41 g, 83%): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ (ppm) 2.45 (1 H, t, *J* = 6 Hz), 2.84 (1 H, dd, *J* = 14, 9 Hz), 3.24 (1 H, dd, *J* = 14, 5 Hz), 3.71 (3 H, s), 4.08 (1 H, m), 4.20 (1 H, m), 4.72 (1 H, td, *J* = 9, 5.5 Hz), 4.93 (1 H, d, *J* = 12 Hz), 4.99 (1 H, d, *J* = 12 Hz), 5.19 (1 H, d, *J* = 9 Hz), 6.00 (1 H, ddd, *J* = 11.5, 5.5, 4 Hz), 6.67 (1 H, d, *J* = 11.5 Hz), 6.9–7.4 (9 H, m); <sup>13</sup>C NMR (toluene-*d*<sub>8</sub>, 125.6 MHz) δ (ppm) 37.0, 51.8, 54.0, 58.9, 67.0, 126.9, 127.5, 128.0, 128.3, 128.5, 128.7, 30.7, 130.8, 134.4, 134.7, 136.6, 136.9, 156.1, 172.3; HRMS (ESI, positive mode) calcd for C<sub>21</sub>H<sub>23</sub>NO<sub>5</sub> + Na<sup>+</sup> 392.1474, found 392.1468.

**2-Benzyloxycarbonylamino-3-[2-((*Z*)-3-chloroprop-1-enyl)phenyl]propionic Acid Methyl Ester (7).** The allylic alcohol **6** (1.787 g, 4.87 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (70 mL) under argon at 0 °C. Triphenylphosphine (2.52 g, 2 equiv) and *N*-chlorosuccinimide (1.12 g, 1.7 equiv) were added. The reaction mixture was stirred at 0 °C for 15 min, the solvents were evaporated, and the residue was purified by chromatography over silica gel (toluene/ethyl acetate, 19:1). Compound **7** (1.685 g, 90%) was obtained as a colorless oil which slowly solidified upon standing: mp 61–62.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ (ppm) 2.97 (1 H, dd, *J* = 14, 7.5 Hz), 3.24 (1 H, dd, *J* = 14, 6 Hz), 3.67 (3 H, s), 4.04 (2 H, d, *J* = 8 Hz), 4.58 (1 H, td, 8, 6.5 Hz), 4.96–5.05 (2 H, m), 5.15 (1 H, d, *J* = 8.5 Hz), 5.95 (1 H, dt, *J* = 11, 7.5 Hz), 6.72 (1 H, d, *J* = 11 Hz), 7.10 (1 H, d, *J* = 7 Hz), 7.2–7.35 (8 H, m); <sup>13</sup>C NMR (toluene-*d*<sub>8</sub>, 125.6 MHz) δ (ppm) 36.4, 40.8, 51.6, 54.5, 66.9, 127.2, 128.1, 128.15, 128.4, 128.6, 129, 129.6, 130.65, 131.9, 135.2, 135.6, 137.1, 155.5, 172; HRMS (ESI, positive mode) calcd for C<sub>21</sub>H<sub>22</sub>ClNO<sub>4</sub> + Na<sup>+</sup> 410.1135, found 410.1130.

**1,3-cis-2-Benzyloxycarbonyl-1-vinyl-3,4-dihydro-1*H*-isoquinoline-3-carboxylic Acid Methyl Ester (8) and 1,3-trans-2-Benzyloxycarbonyl-1-vinyl-3,4-dihydro-1*H*-isoquinoline-3-carboxylic Acid Methyl Ester (9).** (a) **Silver Triflate Method.** To a cold (−78 °C) solution of allylic chloride **7** (1.469 g, 3.79 mmol) in THF (15 mL) was added dropwise, under argon, a solution of BuLi (1.6 M in hexane, 2.37 mL, 1 equiv). After 15 min, silver triflate (1.3 g, freshly recrystallized from toluene) was added. The light-brown, clear solution was allowed to warm to rt over the course of 2 h. The now dark brown suspension was stirred at rt for 2 h. At this point, TLC showed ca. 80% conversion of the starting material. More AgOTf (0.4 g) was added, and the reaction was completed in 30 min. TLC (silica gel, hexane/ether, 3:1, two migrations) showed the formation of two weakly UV-active, faster migrating spots. The reaction mixture was diluted with ether, washed with 2 N aqueous HCl and saturated NaHCO<sub>3</sub>, dried, and evaporated to dryness. The residue was chromatographed over silica gel (hexane/ether, 2:1) to give successively **8** (0.248 g, 18%) and then **9** (0.698 g, 53%).

**8** (colorless oil): <sup>1</sup>H NMR (toluene-*d*<sub>8</sub>, 500 MHz, 100 °C) δ (ppm) 2.78 (1 H, dd, *J* = 15, 6 Hz), 3.01 (1 H, dd, *J* = 15, 10 Hz), 3.36 (3 H, s), 4.57 (1 H, br s), 4.99 (1 H, dt, *J* = 10, 1 Hz), 5.04 (1 H, br d, *J* = 12 Hz), 5.12 (1 H, d, *J* = 12 Hz), 5.17 (1 H, dt, *J* = 17, 1 Hz), 5.80 (1 H, br s), 6.14 (1 H, ddd, *J* = 17,



10, 4.5 Hz), 6.88–7.21 (9 H, m);  $^{13}\text{C}$  NMR (toluene- $d_8$ , 125.6 MHz)  $\delta$  (ppm) 30.8, 30.9, 51.6, 55.9, 56.1, 58.5, 58.6, 67.4, 67.7, 115.4, 115.7, 127.0, 127.2, 127.3, 127.4, 127.6, 127.7, 127.8, 128.0, 128.1, 128.2, 128.25, 128.35, 128.5, 128.6, 133.3, 133.4, 135.9, 136.9, 137.0, 137.3, 138.9, 155.4, 155.7, 172.2, 172.6; HRMS (ESI, positive mode) calcd for  $\text{C}_{21}\text{H}_{21}\text{NO}_4 + \text{Na}^+$  374.1368, found 374.1361.

**9** (colorless oil which solidifies upon standing):  $^1\text{H}$  NMR (toluene- $d_8$ , 500 MHz, 100 °C)  $\delta$  (ppm) 2.93 (1 H, dd,  $J = 15$ , 2 Hz), 3.00 (1 H, dd,  $J = 15$ , 6 Hz), 3.14 (3 H, s), 4.85 (1 H, d,  $J = 10$  Hz), 4.90 (1 H, d,  $J = 17$  Hz), 4.92 (1 H, br s), 5.06 (1 H, d,  $J = 12.5$  Hz), 5.20 (1 H, d,  $J = 12.5$  Hz), 5.74 (1 H, br s), 5.84 (1 H, m), 6.25–7.25 (9 H, m);  $^{13}\text{C}$  NMR (toluene- $d_8$ , 125.6 MHz)  $\delta$  (ppm) 31.3, 31.5, 51.5, 51.6, 56.0, 56.1, 58.9, 59.1, 67.4, 67.6, 113.4, 113.8, 127.4, 127.5, 127.55, 127.7, 127.75, 128.0, 128.05, 128.1, 128.25, 128.3, 128.5, 132.5, 132.6, 136.3, 136.4, 137.3, 139.2, 139.7, 155.5, 156, 171.5, 171.9; HRMS (ESI, positive mode) calcd for  $\text{C}_{21}\text{H}_{21}\text{NO}_4 + \text{Na}^+$  374.1368, found 374.1362.

**(b) Pd(II) Method.** The allylic alcohol **6** (5.41 g, 14.6 mmol) was dissolved in dry THF (50 mL) under argon.  $\text{PdCl}_2(\text{PhCN})_2$  (843 mg, 15 mol %) was added, and the reaction mixture was stirred at rt for 8 h. More catalyst (230 mg) was added, and stirring was continued for 16 h. The mixture was partitioned between ether and saturated  $\text{NaHCO}_3$ , the organic layer was dried, and the solvents were evaporated. TLC indicated formation of **8** as a major isomer. The proportion of **8** and **9** in the mixture of isomers was established by measuring the relative intensities of the olefinic protons and found to be 10:1. Careful chromatography as above (hexane/ether, 2:1) afforded pure **8** (3.88 g, 75%).

**1,3-trans-2-Benzoyloxycarbonyl-1-vinyl-3,4-dihydro-1H-isoquinoline-3-carboxylic Acid (10).** The pure *trans*-methyl ester **9** (0.717 g, 2.04 mmol) was dissolved in a mixture of THF (15 mL), methanol (1 mL), and water (0.5 mL). Powdered  $\text{LiOH}\cdot\text{H}_2\text{O}$  (630 mg) was added, and the suspension was stirred at 60 °C under argon for 12 h and partitioned between ether and 2 N aqueous HCl. The organic layer was washed with water until the aqueous extracts were neutral (litmus paper), dried, and evaporated under reduced pressure to afford **10** containing 11% of the *cis* isomer **11** (0.685 g, quantitative), which crystallized upon standing. A small amount was recrystallized (ether/pentane) to afford an analytical sample (<3% **11**):  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz, 100 °C)  $\delta$  (ppm) 3.03 (1 H, dd,  $J = 15$ , 2 Hz), 3.21 (1 H, dd,  $J = 15$ , 6 Hz), 4.85 (1 H, dd,  $J = 6$ , 2 Hz), 4.96–5.01 (2 H, m), 5.15 (2 H, s), 5.56 (1 H, d,  $J = 5$  Hz), 5.89 (1 H, ddd,  $J = 17$ , 10, 5 Hz), 6.9–7.5 (9 H, m), 12.0 (1 H, br s);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 100 MHz, 100 °C)  $\delta$  (ppm) 30.2, 54.5, 57.7, 66.1, 112.9, 126.4, 126.45, 126.7, 126.8, 127.15, 127.2, 127.7, 131.75, 135.4, 136.3, 138.7, 154.6, 171.7; HRMS (ESI, positive mode) calcd for  $\text{C}_{20}\text{H}_{19}\text{NO}_4 + \text{Na}^+$  360.1212, found 360.1206.

**1,3-cis-2-Benzoyloxycarbonyl-1-vinyl-3,4-dihydro-1H-isoquinoline-3-carboxylic Acid (11).** The pure *cis*-methyl ester **8** (3.88 g, 11.0 mmol) was treated as **9** to afford the corresponding carboxylic acid **11** containing 11% of the *trans* isomer **10** (3.649 g, 98%):  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz, 100 °C)  $\delta$  (ppm) 3.02 (1 H, dd,  $J = 15$ , 10 Hz), 3.15 (1 H, dd,  $J = 15$ , 6 Hz), 4.46 (1 H, dd,  $J = 10$ , 6 Hz), 4.97 (1 H, dt,  $J = 10$ , 1.5 Hz), 5.01 (1 H, d,  $J = 13$  Hz), 5.06 (1 H, d,  $J = 13$  Hz), 5.07 (1 H, dt,  $J = 17$ , 1.5 Hz), 5.67 (1 H, dt,  $J = 5$ , 1.5 Hz), 6.07 (1H, ddd,  $J = 17$ , 10, 5 Hz), 7.2–7.5 (9 H, m), 12.0 (1 H, br s);  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 100 MHz, 100 °C)  $\delta$  (ppm) 29.5, 54.5, 57.4, 66.2, 114.7, 126.0, 126.7, 126.8, 127.0, 127.15, 127.6, 132.3, 135.3, 136.1, 137.8, 154.5, 172.0; HRMS (ESI, positive mode) calcd for  $\text{C}_{20}\text{H}_{19}\text{NO}_4 + \text{Na}^+$  360.1212, found 360.1206.

**1,3-cis-2-Benzoyloxycarbonyl-1-vinyl-3,4-dihydro-1H-isoquinoline-3-carboxylic Acid Dicyclohexylamine Salt (12).** The carboxylic acid **11** (47 mg, 0.139 mmol, containing 11% of the *trans* isomer **10**) was dissolved in ether (0.15 mL). Dicyclohexylamine (27 mg) dissolved in ether (0.1 mL) was added, and the clear solution was allowed to stand at rt for 48

h upon which time the dicyclohexylamine salt **12** had crystallized (0.49 g): mp 139–140 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ , 100 MHz, 100 °C)  $\delta$  (ppm) 1.05–1.30 (8 H, m), 1.55 (2 H, m), 1.67 (4 H, m), 1.80 (4 H, m), 2.63 (2H, m), 3.02 (1H, dd,  $J = 15$ , 9 Hz), 3.12 (1 H, dd,  $J = 15$ , 6 Hz), 4.42 (1 H, dd,  $J = 10$ , 6 Hz), 5.05 (1 H, dt,  $J = 10$ , 1.5 Hz), 5.10 (1 H, d,  $J = 13$  Hz), 5.15 (1 H, d,  $J = 13$  Hz), 5.19 (1 H, dt,  $J = 17$ , 1.5 Hz), 5.63 (1 H, dt,  $J = 5$ , 1.5 Hz), 6.14 (1H, ddd,  $J = 17$ , 10, 5 Hz), 7.2–7.5 (9 H, m),  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 100 MHz, 100 °C)  $\delta$  (ppm) 23.7, 25.0, 29.8, 32.2, 52.1, 54.9, 57.5, 66.0, 114.4, 125.8, 126.0, 126.55, 126.6, 127.0, 127.15, 127.5, 132.9, 135.5, 136.3, 138.2, 154.6, 172.2; HRMS (ESI, positive mode).

**(1R,3R)-3-Ethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methanol (13).** A mixture of **8** (30 mg, 0.085 mmol) and Pd/C (30 mg) in MeOH (2 mL) was vigorously stirred at rt for 2.5 h under  $\text{H}_2$  atmosphere. The mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was dissolved in THF (2 mL), and  $\text{LiAlH}_4$  (30 mg, 0.8 mmol) was added. The mixture was stirred overnight at rt, water was added, and the product was extracted with  $\text{Et}_2\text{O}$  (three times). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and concentrated. The crude product was purified by chromatography on silica gel (chloroform/2-propanol, 10:1), and **13** was isolated as a pale yellow oil (10 mg, 62%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 0.97 (3 H, t,  $J = 7.4$  Hz), 1.74 (1 H, m), 2.12 (1 H, m), 2.65 (2 H, m), 3.07 (1 H, m), 3.54 (1 H, dd,  $J = 7.8$ , 10.6 Hz), 3.82 (1 H, dd,  $J = 3.7$ , 10.6 Hz), 4.04 (1 H, m), 7.15 (4 H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 9.71, 28.65, 32.25, 54.78, 57.32, 66.03, 125.37, 126.07, 126.12, 129.27, 134.79, 138.63. HRMS calcd for  $\text{C}_{12}\text{H}_{17}\text{NO} + \text{Na}^+$  214.1208, found 214.1237 (*trans* isomer<sup>14</sup>).

**(S)-1-(2-Iodophenyl)ethane-1,2-diol (16).** A mixture of *tert*-butyl alcohol (150 mL), water (150 mL) and AD-mix- $\alpha$  (30 g), was stirred at 0 °C until two clear phases were produced, and then a solution of **15** (4.0 g, 17.3 mmol) in *tert*-butyl alcohol (10 mL) and water (10 mL) was added. After 5 h at 0 °C, the reaction mixture was treated with  $\text{Na}_2\text{SO}_3$  (35 g) with stirring at rt for 30 min. The aqueous layer was extracted twice with  $\text{CH}_2\text{Cl}_2$ , and the combined organic layers were dried over  $\text{MgSO}_4$  and concentrated. After flash chromatography on silica gel (cyclohexane/ethyl acetate, 1:1), a white solid was obtained (4.2 g, 91% yield, > 98% ee): mp 65–66 °C;  $[\alpha]_D^{20} +57.1$  (c 1.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 3.24 (2 H, br s), 3.50 (1 H, dd,  $J = 11.4$ , 8.2 Hz), 3.87 (1 H, dd,  $J = 11.4$ , 2.8 Hz), 5.02 (1 H, dd,  $J = 8.2$ , 2.8 Hz), 6.98 (1 H, br t,  $J = 8.0$  Hz), 7.35 (1 H, br t,  $J = 8.0$  Hz), 7.51 (1 H, br d,  $J = 8.0$  Hz), 7.80 (1 H, br d,  $J = 8.0$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 66.44, 77.98, 97.50, 127.61, 128.57, 129.67, 139.39, 142.28. Anal. Calcd for  $\text{C}_8\text{H}_9\text{IO}_2$  (M = 164): C, 36.39; H, 3.44. Found: C, 36.32; H, 3.51.

**(S)-2-(2-Iodophenyl)oxirane (17).** To a solution of diol **16** (2.10 g, 7.9 mmol) and triethyl orthoacetate (1.8 mL, 9.54 mmol, 1.2 equiv) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at 0 °C was added trimethylsilyl chloride (1.2 mL, 9.54 mmol, 1.2 equiv). The reaction mixture was stirred for 2 h and evaporated under reduced pressure. The residue was dissolved in methanol (12 mL), and  $\text{K}_2\text{CO}_3$  (2.8 g, 20 mmol, 2.5 equiv) was added. The suspension was stirred at rt for 2 h, and the solid was filtered and washed with  $\text{CH}_2\text{Cl}_2$ . The combined filtrates were evaporated, and the crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 8:2) to yield pure **17** as a colorless oil (1.80 g, 92% yield):  $[\alpha]_D^{20} +62.1$  (c 1.4,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 2.62 (1 H, dd,  $J = 5.6$ , 2.6 Hz), 3.18 (1 H, dd,  $J = 5.6$ , 4.4 Hz), 3.99 (1 H, m), 7.01 (1 H, br t,  $J = 7.6$  Hz), 7.20 (1 H, br d,  $J = 7.6$  Hz), 7.33 (1 H, br t,  $J = 7.6$  Hz), 7.82 (1 H, br d,  $J = 7.6$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 50.88, 56.55, 96.65, 125.96, 128.41, 129.53, 138.71, 140.03; HRMS (EI, positive mode) calcd for  $\text{C}_8\text{H}_7\text{IO}$  245.9542, found 245.9536.

**(S)-2-Azido-1-(2-iodophenyl)ethanol (18) and (R)-2-Azido-2-(2-iodophenyl)ethanol (19).** Epoxide **17** (0.5 g, 2.03 mmol) was dissolved in acetonitrile (10 mL).  $\text{NaN}_3$  (0.8 g, 12.2



mmol, 6 equiv) and LiClO<sub>4</sub> (3.9 g, 36.5 mmol, 18 equiv) were added, and the mixture was stirred for 5 h at 60 °C. After the mixture was cooled to rt, the solids were removed by filtration through a pad of Celite and the filtrate was concentrated. The residue was partitioned between water and ether. The aqueous layer was extracted three times with ether, and the combined organic layers were washed with NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub>, and concentrated. After flash chromatography on silica gel (cyclohexane/ethyl acetate 4:1), the two regioisomers were isolated as colorless oils (**19**: 394 mg, 67% and **18**: 170 mg, 29%).

**19**: [α]<sub>D</sub><sup>20</sup> -47.7 (*c* 0.7, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm) 2.05 (1 H, br s), 3.62 (1 H, dd, *J* = 11.6, 8.3 Hz), 3.84 (1 H, dd, *J* = 11.6, 3.8 Hz), 5.05 (1 H, dd, *J* = 8.3, 3.8 Hz), 7.03 (1 H, d, *J* = 7.8 Hz), 7.41 (2 H, m), 7.85 (1 H, d, *J* = 7.8 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 65.67, 71.12, 98.89, 128.09, 128.84, 130.22, 138.71, 139.89. Anal. Calcd for C<sub>8</sub>H<sub>8</sub>IN<sub>3</sub>O (M = 289): C, 33.24; H, 2.79; N, 14.54. Found: C, 33.90; H, 2.80; N, 13.78.

**18**: [α]<sub>D</sub><sup>20</sup> +111.6 (*c* 1.15, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm) 2.67 (1 H, br s), 3.30 (1 H, dd, *J* = 12.6, 8.3 Hz), 3.56 (1 H, dd, *J* = 12.6, 2.8 Hz), 5.10 (1 H, dd, *J* = 8.3, 2.8 Hz), 7.01 (1 H, br t, *J* = 7.8 Hz), 7.42 (1 H, br t, *J* = 7.8 Hz), 7.58 (1 H, br d, *J* = 7.8 Hz), 7.80 (1 H, br d, *J* = 7.8 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm) 56.41, 76.73, 97.11, 127.40, 128.72, 130.00, 139.44, 142.14. Anal. Calcd for C<sub>8</sub>H<sub>8</sub>IN<sub>3</sub>O (M = 289): C, 33.24; H, 2.79; N, 14.54. Found: C, 33.35; H, 2.84; N, 14.02.

**1-((R)-1-Azido-2-methoxymethoxyethyl)-2-iodobenzene (20)**. To a solution of **19** (390 mg, 1.35 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were successively added <sup>1</sup>Pr<sub>2</sub>NEt (290 μL, 1.2 equiv, 1.62 mmol) and MOMCl (125 μL, 1.2 equiv, 1.62 mmol) at rt, and the reaction mixture was stirred for 6 h. The mixture was diluted with water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (three times), the combined organic layers were dried over MgSO<sub>4</sub>, and concentrated. After flash chromatography on silica gel (cyclohexane/ethyl acetate 4:1) **20** was isolated as a colorless oil (426 mg, 94%): [α]<sub>D</sub><sup>20</sup> -43.7 (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm) 3.40 (3 H, s), 3.58 (1 H, dd, *J* = 10.8, 8.6 Hz), 3.82 (1 H, dd, *J* = 10.8, 3.2 Hz), 4.70 (2 H, Abq, *J* = 6.8 Hz), 5.09 (1 H, dd, *J* = 8.6, 3.2 Hz), 7.02 (1 H, br t, *J* = 7.8 Hz), 7.41 (2 H, m), 7.86 (1 H, br d, *J* = 7.8 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm) 55.49, 68.76, 70.33, 96.50, 98.83, 128.08, 128.75, 130.10, 138.89, 139.75; HRMS (ESI, positive mode) calcd for C<sub>10</sub>H<sub>12</sub>IN<sub>3</sub>O<sub>2</sub> + Na<sup>+</sup> 355.9872, found 355.9866.

**[(R)-1-(2-Iodophenyl)-2-methoxymethoxyethyl]carbamic Acid *tert*-Butyl Ester (21)**. At rt, PhSH (930 μL, 9 mmol, 6.0 equiv) and NEt<sub>3</sub> (940 μL, 6.75 mmol, 4.5 equiv) were added to a suspension of SnCl<sub>2</sub> (425 mg, 2.25 mmol, 1.5 equiv) in THF (5 mL). The azide **20** (0.5 g, 1.5 mmol, 1.0 equiv) dissolved in THF (5 mL) was then added, and the resulting mixture was stirred for 30 min at rt. NaOH (2 M, 25 mL) and CH<sub>2</sub>Cl<sub>2</sub> (25 mL) were added, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (three times), and the combined organic layers were dried (MgSO<sub>4</sub>) and concentrated. The resulting colorless oil was dissolved in THF (10 mL), and NEt<sub>3</sub> (1.1 mL, 7.5 mmol, 5.0 equiv) and BOC<sub>2</sub>O (440 mg, 1.3 equiv, 2 mmol) were added. The reaction mixture was stirred at rt overnight, hydrolyzed, and extracted with ethyl acetate (3 times). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated. After chromatography on silica gel (cyclohexane/ethyl acetate 9:1), **21** was isolated as a white solid (520 mg, 85%): mp 81–82 °C; [α]<sub>D</sub><sup>20</sup> +22.1 (*c* 1.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 50 °C) δ (ppm) 1.39 (9 H, br s), 3.28 (3 H, s), 3.62 (1 H, m), 3.82 (1 H, dd, *J* = 10.4, 4.1 Hz), 4.55 (1 H, d, *J* = 6.5 Hz), 4.62 (1 H, d, *J* = 6.5 Hz), 5.06 (1 H, m), 5.36 (1 H, br s), 6.93 (1 H, br t, *J* = 7.3 Hz), 7.29 (2 H, m), 7.84 (1 H, br d, *J* = 7.6 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm) 28.41, 55.45, 59.07, 69.45, 79.83, 96.82, 98.64, 127.68, 128.22, 129.10, 139.84, 142.87, 155.20. Anal. Calcd for C<sub>15</sub>H<sub>22</sub>INO<sub>4</sub> (M = 407): C, 44.24; H, 5.45; N, 3.44. Found: C, 44.81; H, 5.56; N, 3.45.

**[(R)-2-Methoxymethoxy-1-(2-tributylstannanylphenyl)ethyl]carbamic Acid *tert*-Butyl Ester (22)**. A solution of **21** (410 mg, 1 mmol), Pd(P-*t*-Bu)<sub>3</sub><sub>2</sub> (50 mg, 0.1 mmol, 10 mol %) and Bu<sub>3</sub>SnSnBu<sub>3</sub> (760 μL, 1.3 mmol, 1.3 equiv) in DMF (1 mL) was stirred overnight at 100 °C under argon atmosphere. After being cooled to rt, the reaction mixture was diluted with water and extracted with ether (three times). The combined organic layers were dried over MgSO<sub>4</sub>, filtered through a pad of Celite, and concentrated. After purification by chromatography on silica gel (cyclohexane/ethyl acetate 9:1), the product **22** was isolated as a pale yellow oil (350 mg, 60%): [α]<sub>D</sub><sup>20</sup> -8.7 (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm) 0.85 (9 H, t, *J* = 7.3 Hz), 1.10 (6 H, m), 1.30 (6 H, m), 1.40 (9 H, br s), 1.55 (6 H, m), 3.25 (3 H, s), 3.70 (2 H, m), 4.57 (2 H, s), 4.63 (1 H, br s), 5.00 (1 H, br s), 7.20 (1 H, br t, *J* = 7.1 Hz), 7.29 (1 H, br t, *J* = 7.1 Hz), 7.40 (2 H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm) 10.57, 13.71, 27.46, 28.37, 29.31, 55.33, 57.51, 70.78, 79.47, 96.54, 125.56, 127.03, 128.48, 137.18, 146.74, 154.93 (C<sub>quat</sub>-Sn failed); HRMS (ESI, positive mode) calcd for C<sub>27</sub>H<sub>49</sub>-NO<sub>4</sub>Sn + Na<sup>+</sup> 594.2581, found 594.2576.

**{(R)-1-[2-((E)-4-Hydroxybut-2-enyl)phenyl]-2-methoxymethoxyethyl}carbamic Acid *tert*-Butyl Ester (23)**. A mixture of stannyl derivative **22** (350 mg, 0.61 mmol), butadiene monoxide (250 μL, 3.1 mmol, 5 equiv), PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> (15 mg), and H<sub>2</sub>O (550 μL, 50 equiv) in DMF (2 mL) was stirred at 0 °C and slowly allowed to reach rt overnight. Water was added, and the mixture was extracted with Et<sub>2</sub>O (twice). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated. The residue was purified by PLC (cyclohexane/ethyl acetate, 3:2) to furnish alcohol **23**, a colorless oil (178 mg, 83% yield): [α]<sub>D</sub><sup>20</sup> -17.4 (*c* 0.7, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm) 1.40 (9 H, br s), 2.65 (1 H, br s), 3.25 (3 H, s), 3.57 (2 H, br s), 3.70 (2 H, m), 4.05 (2 H, br d, *J* = 6.0 Hz), 4.60 (2 H, m), 5.20 (2 H, m), 5.60 (1 H, td, *J* = 15.4, 6.0 Hz), 5.85 (1 H, td, *J* = 15.4, 5.8 Hz), 7.20 (4 H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm) 28.39, 36.10, 51.00, 55.38, 63.74, 70.32, 79.86, 96.17, 126.28, 126.83, 127.64, 130.52, 131.04, 131.42, 136.98, 138.59, 155.36; HRMS (ESI, positive mode) calcd for C<sub>19</sub>H<sub>29</sub>NO<sub>5</sub> + Na<sup>+</sup> 374.1943, found 374.1938.

**(1R,3S)-1-Methoxymethoxymethyl-3-vinyl-3,4-dihydro-1H-isoquinoline-2-carboxylic Acid *tert*-Butyl Ester (24)**. A solution of allylic alcohol **23** (12 mg, 0.034 mmol) and PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> (1 mg) in THF (0.5 mL) was stirred at rt for 2 h under argon atmosphere. The solvent was evaporated, and the crude product was purified by PLC (cyclohexane/ethyl acetate, 1:1) to give **24** as a colorless oil (10 mg, 90%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm) 1.43 (9 H, br s), 2.95 (2 H, m), 3.27 (3 H, br s), 3.75 (2 H, m), 4.60 (3 H, m), 5.10 (2 H, m), 5.32 (1 H, br s), 5.90 (1 H, m), 7.24 (4 H, m); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>, 90 °C) δ (ppm) 27.50, 31.96, 45.57, 51.68, 54.08, 69.93, 78.82, 95.39, 113.64, 125.41, 126.25, 126.47, 127.34, 132.66, 134.99, 139.99, 153.85. HRMS calcd for C<sub>19</sub>H<sub>27</sub>NO<sub>4</sub> + Na<sup>+</sup> 356.1838, found 356.1861.

**(1R,3S)-1-Methoxymethoxymethyl-3-vinyl-1,2,3,4-tetrahydroisoquinoline (25)**. A solution of TFA (50% in H<sub>2</sub>O, 50 μL), was added to a solution of **24** (8 mg, 0.024 mmol) in CH<sub>3</sub>CN (1 mL), and the reaction mixture was stirred at rt for 48 h. After addition of NaOH (2 M, 0.5 mL), the mixture was extracted with ethyl acetate (twice), and the combined organic extracts were dried over MgSO<sub>4</sub>, and concentrated. The crude product was purified by PLC (cyclohexane/ethyl acetate, 1:1) to furnish **25**, a colorless oil (5 mg, 78% from **23**): [α]<sub>D</sub><sup>20</sup> -61.0 (*c* 0.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm) 2.37 (1 H, br s), 2.80 (2 H, m), 3.20 (3 H, s), 3.55 (1 H, br q, *J* = 8.0 Hz), 3.75 (1 H, dd, *J* = 9.6, 8.0 Hz), 4.15 (1 H, dd, *J* = 9.6, 3.2 Hz), 4.36 (1 H, m), 4.70 (2 H, m), 5.30 (2 H, m), 6.00 (1 H, m), 7.17 (4 H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm) 35.89, 55.44, 55.73, 56.39, 71.43, 96.81, 115.58, 124.83, 125.93, 126.12, 129.39, 134.62, 135.31, 140.17; HRMS (ESI, positive mode) calcd for C<sub>14</sub>H<sub>19</sub>NO<sub>2</sub> + H<sup>+</sup> 234.1494, found 234.1489.

**(E)-(S)-2-*tert*-Butoxycarbonyloxy-7-chlorohept-5-enoic Acid Methyl Ester (26)**. To a solution of (*S*)-2-*tert*-

butoxycarbonyloxyhex-5-enoic acid methyl ester (325 mg, 1.34 mmol) and allyl chloride (430  $\mu$ L, 4 equiv) in  $\text{CH}_2\text{Cl}_2$  (22 mL) was added Grubbs catalyst second generation (114 mg, 0.13 mmol). The reaction mixture was refluxed for 14 h, the solvents were evaporated under reduced pressure, and the residue was chromatographed on silica gel (hexane/ethyl acetate 10:1) to afford **26** (261 mg, 67%) as a 86:14 mixture of trans and cis isomers and recovered starting material (70 mg, 21%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.44 (9 H, s), 1.66–1.77 (1 H, m), 1.96 (1 H, m), 2.09–2.20 (2 H, m), 3.74 (3 H, s), 4.02 (2 H, d,  $J = 6.6$  Hz), 4.26–4.35 (1 H, m), 4.96–5.08 (1 H, m), 5.65 (1H, dt,  $J = 15.1, 6.6$  Hz), 5.75 (1H, dt,  $J = 15.1, 6.6$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 27.9, 28.4, 32.1, 45.1, 52.4, 53.0, 80.0, 127.2, 133.8, 161.6, 173.0; HRMS (ESI, positive mode) calcd for  $\text{C}_{13}\text{H}_{22}\text{ClNO}_4 + \text{Na}$  314.1135, found 314.1130.

**(2S,5S)-N-tert-Butoxycarbonyl-5-vinylpyrrolidine-2-carboxylic Acid Methyl Ester (27) and (2S,5R)-N-tert-Butoxycarbonyl-5-vinylpyrrolidine-2-carboxylic Acid Methyl Ester (28).** (a) **Silver Triflate Method.** Under Ar atmosphere, the protected amino acid **26** (62 mg, 0.21 mmol) was dissolved in THF (0.8 mL) and the solution was cooled to  $-78^\circ\text{C}$ . A solution of BuLi (1.6 M in hexanes, 130  $\mu$ L, 1 equiv) was added dropwise, and the mixture was stirred at  $-78^\circ\text{C}$  for 15 min. AgOTf (87 mg, 1.6 equiv) was added, and the light brown solution was allowed to warm to rt over the course of 1.5 h and then stirred for a further 1 h. The heterogeneous reaction mixture was diluted with ether, washed successively with 2 N HCl, saturated  $\text{NaHCO}_3$ , and brine, dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate 2:1) afforded a 87:13 mixture of **27** and **28** (41 mg, 77%) which could not be separated:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_2-\text{CDCl}_2$ ,  $120^\circ\text{C}$ )  $\delta$  (ppm) 1.39 (9 H, s), 1.65–1.68 (1 H, m), 1.82–1.90 (1 H, m), 2.10–2.20 (2 H, m), 3.68 (3 H, s), 4.45 (2 H, br), 5.04 (1 H, dd,  $J = 10.5, 1.2$  Hz), 5.05 (1 H, dd,  $J = 17.1, 1.2$  Hz), 5.76 (1H, ddd,  $J = 17.1, 10.5, 5.4$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 27.4, 27.7, 28.3, 28.35, 29.3, 30.0, 52.0, 52.3, 59.7, 65.8, 79.9, 80.0, 113.8, 114.0, 137.8, 138.3, 153.3, 154.2, 173.1, 173.4; HRMS calcd for  $\text{C}_{13}\text{H}_{21}\text{NO}_4\text{Na}$   $m/z$  278.1368, found  $m/z$  278.1363.

(b) **Pd(II) Method.** Under Ar atmosphere, a solution of **30** (230 mg, 0.84 mmol) and  $\text{PdCl}_2(\text{CH}_3\text{CN})_2$  (33 mg, 15 mol %) in THF (17 mL) was stirred at rt for 12 h. The mixture was partitioned between ethyl acetate and water, and the organic layer was washed with brine, dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (hexane/ethyl acetate 4:1) to afford pure **28** (165 mg, 77%):  $[\alpha]_{\text{D}}^{23} -14.45$  ( $c$  1.460,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_2-\text{CDCl}_2$ ,  $120^\circ\text{C}$ )  $\delta$  (ppm) 1.40 (9 H, s), 1.76 (1 H, dt,  $J = 10.7, 5.0$  Hz), 1.90–2.14 (3 H, m), 3.69 (3 H, s), 4.26–4.32 (2 H, m), 5.05 (1 H, d,  $J = 10.2$  Hz), 5.25 (1 H, d,  $J = 17.3$  Hz), 5.88 (1H, ddd,  $J = 17.3, 10.2, 6.1$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 28.1, 28.3, 28.8, 30.9, 31.6, 51.9, 52.0, 59.6, 59.8, 60.2, 60.6, 80.0, 114.7, 115.0, 138.0, 138.8, 153.4, 154.2, 173.3, 173.4; HRMS (ESI, positive mode) calcd for  $\text{C}_{13}\text{H}_{21}\text{NO}_4 + \text{Na}$  278.1368, found 278.1363.

**Mixture of (2S,5S)-5-Vinylpyrrolidine-2-carboxylic Acid Ethyl Ester (27') and (2S,5R)-5-Vinylpyrrolidine-2-carboxylic Acid Ethyl Ester (28').** A portion of the mixture of isomers **27** and **28** (67 mg, 0.26 mmol) prepared by the silver triflate method was dissolved in a 0.04 M solution of NaOEt in ethanol (6.6 mL). The solution was stirred for 16 h at rt, at which time TLC showed a single spot just above that of the starting material. The solvents were evaporated, and the residue was partitioned between ether and 1 N HCl. The organic layer was washed with  $\text{H}_2\text{O}$  and brine and dried, and the solvents were evaporated under reduced pressure. The residue was dissolved in dioxane (0.8 mL), and anhydrous HCl (4 M in dioxane) was added. The mixture was stirred for 1 h, the solution was concentrated in vacuo and dissolved in 1 N aqueous HCl, and the aqueous layer was washed with ether. NaOH (1 N) was added, and the aqueous layer was extracted with ether. The organic extract was dried and evaporated to

afford a mixture of **27'** and **28'** (25 mg, 58%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) (major isomer)  $\delta$  (ppm) 1.26 (3 H, t,  $J = 7.1$  Hz), 1.51–1.59 (1 H, m), 2.08–2.26 (2 H, m), 3.85 (1 H, dd,  $J = 8.5, 5.6$  Hz), 4.16 (2 H, d,  $J = 7.1$  Hz), 5.00 (1 H, d,  $J = 10.1$  Hz), 5.15 (1 H, ddd,  $J = 17.1, 1.6, 1.1$  Hz), 5.77 (1 H, ddd,  $J = 17.1, 10.1, 6.9$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 35.89, 55.44, 55.73, 56.39, 71.43, 96.81, 115.58, 124.83, 125.93, 126.12, 129.39, 134.62, 135.31, 140.17; HRMS (ESI, positive mode) calcd for  $\text{C}_9\text{H}_{15}\text{NO}_2 + \text{H}$  170.1181, found 170.1199.

**(E)-(S)-7-Acetoxy-2-tert-butoxycarbonyloxyhept-5-enoic Acid Methyl Ester (29).** A mixture of protected amino acid **26** (1.0 g, 3.43 mmol) and NaOAc (280 mg, 10 equiv) in DMF (20 mL), was heated at  $100^\circ\text{C}$  for 23 h. More NaOAc (100 mg) was added, and stirring was continued for 3 h. The reaction mixture was cooled to rt, diluted with ether, and washed with saturated  $\text{NH}_4\text{Cl}$ . The organic layer was dried and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (hexane/ethyl acetate 4:1) to afford pure **29** (726 mg, 70%) and recovered starting material (131 mg, 13%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.43 (9 H, s), 1.66–1.77 (1 H, m), 1.86–1.97 (1 H, m), 2.06 (3 H, m), 2.08–2.23 (2 H, m), 3.74 (3 H, s), 4.25–4.36 (1 H, m), 4.50 (2 H, d,  $J = 6.3$  Hz), 4.99–5.10 (1 H, m), 5.55–5.69 (1 H, m), 5.74 (1H, dt,  $J = 15.3, 6.6$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 21.2, 28.1, 28.4, 32.1, 52.3 53.0, 64.9, 80.0, 125.1, 134.0, 155.2, 170.6, 172.9; HRMS (ESI, positive mode) calcd for  $\text{C}_{15}\text{H}_{25}\text{NO}_6 + \text{Na}$  338.1580, found 338.1574.

**(E)-(S)-2-tert-Butoxycarbonyloxy-7-hydroxyhept-5-enoic Acid Methyl Ester (30).** The protected amino acid **29** (512 mg, 1.62 mmol) was dissolved in a solution of NaOMe in MeOH (0.1 M, 16 mL). The mixture was stirred for 2.5 h, and 1 N aqueous HCl (5 mL) was added, followed by ether. The organic layer was washed with  $\text{H}_2\text{O}$  and brine and then dried, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography to afford allylic alcohol **30** (400 mg, 90%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 1.45 (9 H, s), 1.65–1.77 (1 H, m), 1.85–1.97 (1 H, m), 2.09–2.19 (2 H, m), 3.74 (3 H, s), 4.08 (2 H, t,  $J = 4.1$  Hz), 4.27–4.37 (1 H, m), 4.95–5.03 (1 H, m), 5.72–5.60 (2 H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 28.0, 28.4, 32.1, 52.3, 52.8, 63.4, 80.0, 130.5, 130.7, 155.2, 173.2; HRMS (ESI, positive mode) calcd for  $\text{C}_{13}\text{H}_{23}\text{NO}_5 + \text{Na}$  296.1474, found 296.1468.

**(2S,5R)-N-tert-Butoxycarbonyl-5-vinylpyrrolidine-2-carboxylic Acid Dicyclohexylamine Salt (31).** To stirred solution of ester **28** (81 mg, 0.32 mmol) in THF (2 mL) containing  $\text{H}_2\text{O}$  (60  $\mu$ L) and toluene was added  $\text{LiOH}\cdot\text{H}_2\text{O}$  (93 mg, 2.2 mmol). The reaction mixture was stirred at  $60^\circ\text{C}$  for 5 h. The mixture was cooled to  $20^\circ\text{C}$  and extracted with ether, and the organic layer was washed twice with 10% HCl, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated to give the corresponding acid (quantitative). A portion of the acid (32 mg, 0.132 mmol) was dissolved in ether (100  $\mu$ L). A solution of dicyclohexylamine (24 mg, 1 equiv) in ether (100  $\mu$ L) was added. The mixture was allowed to stand at rt for 16 h. The crystals were isolated by filtration (40 mg): HRMS (ESI, negative mode) calcd for  $\text{C}_{12}\text{H}_{18}\text{NO}_4$   $m/z = 240.1236$ , found  $m/z = 240.1241$ .

**X-ray Crystallographic Studies.** Crystal data for compound **12**: MF =  $\text{C}_{34}\text{H}_{42}\text{N}_2\text{O}_{4.5}$ ; MW = 550.72, triclinic,  $P-1$  (#2);  $a = 10.417(2)$  Å,  $b = 11.773(3)$  Å,  $c = 14.433(4)$  Å,  $\alpha = 77.35(2)^\circ$ ,  $\beta = 81.38(2)^\circ$ ,  $\gamma = 69.06(1)^\circ$ ,  $V = 1608.0(7)$  Å $^3$ ;  $Z = 2$ ,  $D(\text{calcd}) = 1.137$  g/cm $^3$ , a colorless crystal (size =  $0.20 \times 0.15 \times 0.15$  mm), Mo  $K\alpha$  radiation ( $\lambda = 0.71069$  Å), a total of 28641 ( $2\theta$  max =  $55^\circ$ ) measured, 7352 unique ( $R_{\text{int}} = 0.065$ ), final  $R_1$  is 0.055 for reflections of  $I_o > 2\sigma(I_o)$  and  $wR_2$  is 0.158 for all reflections, GOF = 0.922. Crystal data for compound **31**: MF =  $\text{C}_{24}\text{H}_{42}\text{N}_2\text{O}_4$ ; MW = 422.61, monoclinic,  $P2_1$ ;  $a = 12.992(3)$  Å,  $b = 10.203(3)$  Å,  $c = 18.760(5)$  Å,  $\beta = 100.5181(11)^\circ$ ,  $V = 2445.0(11)$  Å $^3$ ;  $Z = 4$ ,  $D(\text{calcd}) = 1.148$  g/cm $^3$ , a colorless crystal (size =  $0.25 \times 0.2 \times 0.15$  mm), Mo  $K\alpha$  radiation ( $\lambda = 0.71069$  Å), a total of 35818 ( $2\theta$  max =  $55^\circ$ ) measured, 11161 unique ( $R_{\text{int}} = 0.069$ ), final  $R_1$  is 0.041 for

reflections of  $I_o > 2\sigma(I_o)$  and  $wR_2$  is 0.057 for all reflections, GOF = 1.01.

**Acknowledgment.** This project is supported in France by the Ministère de l'Éducation Nationale, de l'Enseignement Supérieur et de la Recherche, and the Centre National de la Recherche Scientifique (CNRS). J.E. gratefully acknowledges the Japan Society for the

Promotion of Science (JSPS) for a Long Term Invitation Fellowship.

**Supporting Information Available:** X-ray crystallographic data (CIF) and ORTEP drawings. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO0501543