Desymmetrization of *meso*-2,5-Diallylpyrroldinyl Ureas through Asymmetric Palladium-Catalyzed Carboamination: Stereocontrolled Synthesis of Bicyclic Ureas**

Nicholas R. Babij and John P. Wolfe*

Catalytic asymmetric desymmetrization reactions are powerful and efficient tools for the synthesis of chiral molecules. These transformations convert simple achiral substrates into complex enantioenriched products through the differentiation of two enantiotopic groups, and can generate complex structures that bear multiple stereocenters in a highly controlled fashion. As such, the development of asymmetric desymmetrization reactions that allow for the construction of important structural motifs is of considerable utility.

Tricyclic guanidines are an interesting class of compounds that could potentially be accessed through catalytic asymmetric desymmetrization reactions (Figure 1). These scaffolds are present in a wide variety of biologically active natural products, including the batzelladine alkaloids (e.g., batzelladine K, 1), the merobatzelladine alkaloids (e.g., merobatzelladine B, 2), and the crambescidin alkaloids (e.g., crambescidin 359, 3). Many synthetic routes to these compounds involve the generation of a fused bicyclic urea or guanidine derivative (e.g., 4), which is then transformed to the tricyclic guanidine in subsequent steps. As such, development of a concise asymmetric synthesis of 4 could provide access to a broad array of interesting alkaloids.

We recently reported an asymmetric synthesis of the tricyclic guanidine natural product (+)-merobatzelladine B (2), which featured a new strategy for the construction of bicyclic ureas and polycyclic guanidines through Pd-catalyzed carboamination reactions of enantiomerically enriched 2-allylpyrroldin-1-carboxamide derivatives 5 (Scheme 1). These reactions provided bicyclic urea products 6 in good yield with excellent diastereoselectivity, but control of the absolute stereochemistry required the chiral-auxiliary-mediated introduction of the C2 stereocenter during the fairly lengthy asymmetric synthesis of 5 (7–9 steps).

A potentially more attractive route to enantiomerically enriched bicyclic ureas and related bi- and tricyclic guanidines would involve the asymmetric Pd-catalyzed desymmetrization of *meso*-2,5-diallylpyrroldinyl urea 7. This approach would allow for facile introduction of different R’ substituents, and the alkene present in product 8 provides a convenient handle for further elaboration to tricyclic guanidine products or more highly substituted urea derivatives. In addition, the meso substrate 7 can be prepared in only four steps. Our preliminary studies in this area are described herein. These transformations represent the first examples of asymmetric desymmetrizations of bis-alkene substrates in intermolecular Pd-catalyzed alkenic carboamination reactions, and also the first examples of the formation of a six-membered ring in an asymmetric Pd-catalyzed alkene carboamination. 

Figure 1. Bioactive guanidine alkaloids prepared from bicyclic urea precursors.

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In initial experiments, we employed a catalyst composed of [Pd(dba)$_3$]/(S)-Siphos-PE$^{[13]}$ for desymmetrization reactions of 7, as we previously illustrated that this complex provides good results in related asymmetric carboamination reactions of simple N-allyl urea derivatives.$^{[14,15]}$ We decided to first optimize the structure of the N-aryl group of the urea, as prior studies in our lab suggested that this group may have a significant influence on the level of asymmetric induction.$^{[14]}$ Thus, we explored the coupling of 1-1-bromohexene$^{[16]}$ with ureas 7, which bear different N-aryl substituents. The use of electron-poor p-cyanophenyl or p-nitrophenyl N-aryl groups resulted in the formation of products 8 with the highest levels of both diastereoselectivity and enantioselectivity (Table 1).

### Table 1: N-Aryl group effects.$^{[9]}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Yield [%]</th>
<th>d.r.$^{[6]}$</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MeO-C$_6$H$_4$</td>
<td>65</td>
<td>7:1</td>
<td>86:14</td>
</tr>
<tr>
<td>2</td>
<td>3,4-(MeO)$_2$C$_6$H$_4$</td>
<td>41</td>
<td>7:1</td>
<td>82:18</td>
</tr>
<tr>
<td>3</td>
<td>4-Cl-C$_6$H$_4$</td>
<td>76</td>
<td>12:1 (20:1)$^{[4]}$</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>4-Br-C$_6$H$_4$</td>
<td>12$^{[a]}$</td>
<td>18:1</td>
<td>94:6</td>
</tr>
<tr>
<td>5</td>
<td>4-CN-C$_6$H$_4$</td>
<td>40$^{[4]}$</td>
<td>17:1</td>
<td>95:5</td>
</tr>
<tr>
<td>6</td>
<td>4-NO$_2$-C$_6$H$_4$</td>
<td>22$^{[4]}$</td>
<td>20:1</td>
<td>96:4</td>
</tr>
</tbody>
</table>

[a] Conditions: substrate (1.0 equiv), (S)-Siphos-PE (2 mol %), toluene, 100°C, 2 h. [b] Yield of isolated product (average of two or more runs). [c] Diastereomeric ratio of the isolated pure material. [d] Diastereomeric ratios of the isolated materials were identical to those of the crude products except for entry 3. [e] The diastereomeric ratio of the crude material was 12:1. The product was isolated in 76% yield with 20:1 d.r. [f] This material contained a small amount of the corresponding aniline derivative. [g] The reaction was conducted at 120°C for 16 h. The isolated material contained ca. 8% of unreacted substrate.

However, these electron-poor substrates were transformed in modest chemical yield because of competing cleavage of the urea moiety (Table 1, entries 5 and 6). Use of the electron-rich p-methoxyphenyl group led to improved yields but with lower levels of stereocontrol. After some exploration, we found that a substrate bearing a p-bromophenyl group transformed into the desired product with both good chemical yield of both diastereoselectivity and enantioselectivity (Table 1).

The asymmetric desymmetrization reactions of 7 are effective with a number of different alkyl and aryl bromide electrophiles (Table 2). The main side products generated in these reactions were cis-2,5-diallylpyrroldine (resulting from competing urea cleavage) and an unsaturated bicyclic urea that is generated by competing β-hydride elimination of an intermediate alkylpalladium complex.$^{[18]}$ In the reaction of 7e with E-1-bromohexene, a regioisomeric side product that bears a 2-hex-1-enyl group was also generated.$^{[19]}$

The best enantioselectivities were obtained when either alkyl bromides, electron-rich aryl bromides, or electron-neutral aryl bromides were employed as substrates. Diastereoselectivities were generally higher with the alkyl electrophiles than with aryl electrophiles. Use of sterically hindered aryl bromides (Table 2, entries 14 and 15) or electron-poor aryl bromides (entries 9, 11, and 13) led to lower diastereo- and enantioselectivities. Selectivities improved when NaOMe was used in place of NaOH, as we previously illustrated that this complex provides good results in related asymmetric carboamination reactions of simple N-allyl urea derivatives.$^{[14,15]}$

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As shown in Equation (1), cleavage of the N-p-chlorophenyl group can be accomplished through Pd-catalyzed N-arylation with acetamide$^{[20,21]}$ followed by oxidation of the resulting N-aryl amide with ceric ammonium nitrate (CAN). This sequence afforded 9 in 65% yield over two steps.

The conversion of 8e to tricyclic guanidine 12 was carried out as shown in Scheme 2. Treatment of 8e with POCl$_3$...
followed by NH₃ provided bicyclic guanidine 10 in 78% yield. Wacker oxidation of 10 afforded hemiaminal 11, which was then transformed to tricyclic product 12 in 70% yield with 5:1 d.r. through reductive amination with NaBH₄CN.[25] Overall, the synthesis of 12, which is structurally related to the batzelladine and merobatzelladine alkaloids, was accomplished in five steps and 41% yield from meso-2,5-diallylpyrrolidinyl urea 7c. In addition, this is the first example of a Wacker oxidation/ring-closure sequence to generate a tricyclic guanidine.[23,24]

Finally, 8c was converted to tricyclic guanidine 16 (Scheme 3), which is an unnatural stereoisomer of batzelladine K.[25-26] To avoid problems with base-mediated epimerization of the C4 stereocenter, the Pd-catalyzed N-arylation was carried out prior to Wacker oxidation of the alkene. This two-step sequence provided urea 13 in 65% yield. Reduction of the alkene followed by CAN deprotection generated urea 14, which was converted to guanidine aminal 15 through O-methylation and treatment with ammonia.[27] The reduction of 15 proceeded with modest diastereoselectivity (3:1 d.r.), but upon purification 9-epi-batzelladine K was isolated as a single stereoisomer in 48% yield over three steps from 14.

In conclusion, we have developed a concise route to enantiomerically enriched bicyclic ureas through Pd-catalyzed desymmetrizing carboamination reactions of meso-diallylpyrrolidinyl ureas. These transformations effect formation of both a C–N and a C–C bond, and provide products that bear three stereocenters with good levels of diastereoselectivity and enantioselectivity. These reactions illustrate the potential utility of asymmetric Pd-catalyzed alkene carboamination for desymmetrization processes and provide synthetically valuable products in a straightforward manner. Further exploration of enantioselective Pd-catalyzed alkene difunctionalization reactions are currently under way.

Keywords: alkaloids · asymmetric catalysis · desymmetrization · heterocycles · palladium

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[9] The substrate required for the preparation of (+)-merobatelladine B contained a functionalized side chain bearing a stereo-center, and the synthesis of this substrate required nine steps. Synthesis of an enantiopure substrate 5 (R = CH₂CH = C(H)TMS) required seven steps. See the Supporting information for details on the preparation of this latter compound, which was used to assign absolute stereochemistry of products 8 generated in catalytic reactions.


[11] Although there is an intramolecular component to the reactions described herein, the aryl/alkenyl halide and urea substrate are separate components coupled in an intermolecular process. This contrasts with the prior work cited in reference [10], in which all components involved in C–C or C–N bond formation are tethered together.


[13] (S)-Siphos-PE = (11aS)-(4)-10,11,12,13-tetrahydrodieno[7,1-de:1',7',1'g]-[1,3,2]dioxaphosphocin-5-bis(1-phenylethyl)amine.


[16] This electrophile was chosen for optimization studies as it had proven to be a satisfactory coupling partner in our synthesis of merobatelladine B; see reference [8].

[17] The reaction of the analogous p-bromophenyl derivative proceeded in low yield because of competing oligomerization of the substrate (Table 1, entry 4).

[18] In some instances (Table 2, entries 2, 3, and 5), modest yields were due to product losses during the chromatographic separation of diastereomers.


[21] For the isolation of batzelladine K, see Ref. [3c].

[22] Efforts to cleave the N-aryl group from Batzelladine K, see Ref. [3c]. For the isolation of batzelladine K, see Ref. [3c].


[24] Efforts to cleave the N-aryl group from 12 have thus far been unsuccessful.

[25] For the isolation of batzelladine K, see Ref. [3c].
