

Desymmetrization of *meso*-2,5-Diallylpyrrolidiny 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.^[1] 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

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-allylpyrrolidine-1-carboxamide derivatives **5** (Scheme 1).^[8] 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).^[9]

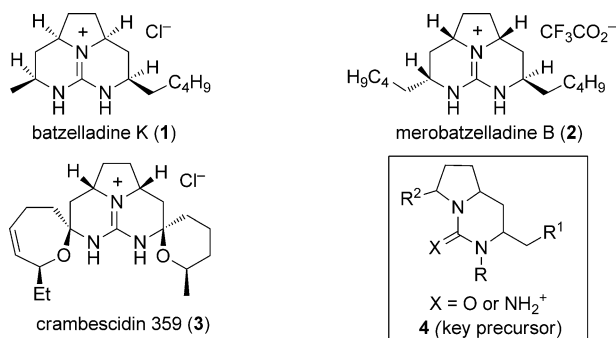
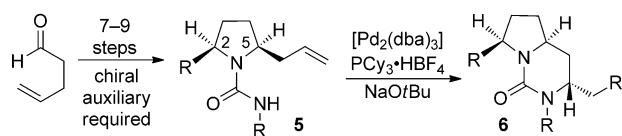


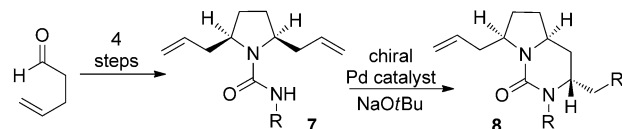
Figure 1. Bioactive guanidine alkaloids prepared from bicyclic urea precursors.

products,^[2] including the batzelladine alkaloids^[3] (e.g., batzelladine K, **1**),^[3c] the merobatzelladine alkaloids (e.g., merobatzelladine B, **2**),^[4] and the crambescidin alkaloids^[5] (e.g., crambescidin 359, **3**).^[5b] 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.^[6–8] As such,

Prior approach - substrate-controlled cyclization



This work - catalytic asymmetric desymmetrization



Scheme 1. Synthesis of bicyclic ureas through Pd-catalyzed asymmetric desymmetrization. Cy = cyclohexyl, dba = *trans,trans*-dibenzylideneacetone.

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-diallylpyrrolidiny urea **7**. This approach would allow for facile introduction of different R¹ 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 alkene carboamination reactions, and also the first examples of the formation of a six-membered ring in an asymmetric Pd-catalyzed alkene carboamination.^[10–12]

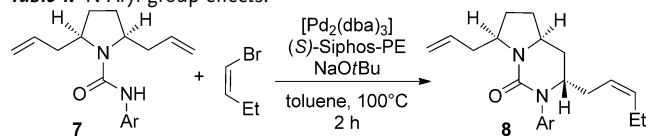
[*] N. R. Babij, Prof. J. P. Wolfe
 Department of Chemistry, University of Michigan
 930 N. University Ave, Ann Arbor, MI 48109-1055 (USA)
 E-mail: jpwolfe@umich.edu

[**] The authors acknowledge the NIH-NIGMS (GM 098314) and the University of Michigan Associate Prof. Support Fund for financial support of this work. Additional funding was provided by Glaxo-SmithKline and Amgen.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201302720>.

In initial experiments, we employed a catalyst composed of $[\text{Pd}_2(\text{dba})_3]/(\text{S})\text{-Siphos-PE}^{[13]}$ 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 Z-1-bromobutene^[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.^[a]



Entry	Ar	Yield [%] ^[b]	d.r. ^[c]	e.r.
1	4-MeO-C ₆ H ₄	65	7:1	86:14
2	3,4-(MeO) ₂ C ₆ H ₄	41	7:1	82:18
3	4-Cl-C ₆ H ₄	76	12:1 (20:1) ^[d]	95:5
4	4-Br-C ₆ H ₄	12 ^[e]	18:1	94:6
5	4-CN-C ₆ H ₄	40 ^[e]	17:1	95:5
6	4-NO ₂ -C ₆ H ₄	22 ^[f]	20:1	96:4

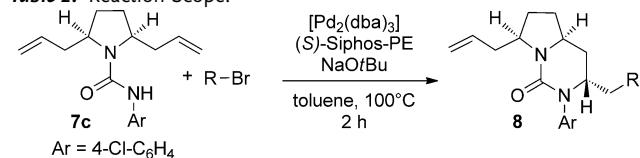
[a] Conditions: substrate (1.0 equiv), (Z)-1-bromobutene (1.5 equiv), NaOtBu (1.5 equiv), $[\text{Pd}_2(\text{dba})_3]$ (2 mol%), (S)-Siphos-PE (8 mol%), toluene (0.2 M), 100°C, 2 h. [b] Yield of isolated product (average of two or more runs). [c] Diastereomeric ratio of the isolated pure material. Diastereomeric ratios of the isolated materials were identical to those of the crude products except for entry 3. [d] The diastereomeric ratio of the crude material was 12:1. The product was isolated in 76% yield with 20:1 d.r. [e] This material contained a small amount of the corresponding aniline derivative. [f] 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*-chlorophenyl group was transformed to the desired product with both good chemical yield and stereoselectivity (Table 1, entry 3).^[17]

The asymmetric desymmetrization reactions of **7c** are effective with a number of different alkenyl and aryl bromide electrophiles (Table 2). The main side products generated in these reactions were *cis*-2,5-diallylpyrrolidine (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 **7c** 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 alkenyl bromides, electron-rich aryl bromides, or electron-neutral aryl bromides were employed as substrates. Diastereoselectivities were generally higher with the alkenyl electrophiles than with aryl electrophiles. Use of sterically

Table 2: Reaction Scope.^[a]

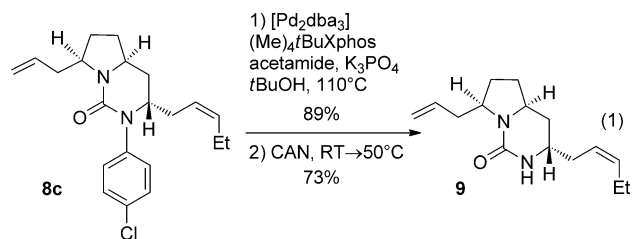


Entry	R	Product	Yield [%] ^[b]	d.r. ^[c]	e.r.
1	Z-butene	8c	76	> 20:1 ^[d]	95:5
2	<i>E</i> -hexene	8g	50 ^[f]	> 20:1 ^[d]	95:5
3	Z-hexene	8h	61	> 20:1 ^[d]	94:6
4	2-methyl propene	8i	48	10:1	94:6
5	2-propene	8j	55	20:1 ^[d]	88:12
6	4-Me-C ₆ H ₄	8k	84	8:1	92:8
7	4-MeO-C ₆ H ₄	8l	70	7:1	92:8
8	Ph	8m	83	6:1	90:10
9	4-F ₃ C-C ₆ H ₄	8n	74	5:1	85:15
10	4-F ₃ C-C ₆ H ₄	8n	55 ^[g]	11:1 ^[e]	90:10
11	4-F ₃ CO-C ₆ H ₄	8o	68	7:1	87:13
12	4-F ₃ CO-C ₆ H ₄	8o	51 ^[g]	18:1 ^[d]	92:8
13	3-MeO-C ₆ H ₄	8p	72	5:1	87:13
14	2-naphthyl	8q	75	7:1	88:12
15	2-Me-C ₆ H ₄	8r	81	5:1	71:29

[a] Conditions: substrate (1.0 equiv), R-Br (1.5 equiv), NaOtBu (1.5 equiv), $[\text{Pd}_2(\text{dba})_3]$ (2 mol%), (S)-Siphos-PE (8 mol%), toluene (0.2 M), 100°C, 2 h. [b] Yield of isolated product (average of two or more runs). [c] Diastereomeric ratio of the isolated pure material. Diastereomeric ratios of the isolated materials were identical to those of the crude products unless otherwise noted. [d] The diastereomeric ratio of the crude material was 10:1–12:1. [e] The diastereomeric ratio of the crude material was 6:1. [f] This material contained 15% of the analogous 2-hex-1-enyl regioisomer. [g] The reaction was conducted using NaOMe as base instead of NaOtBu.

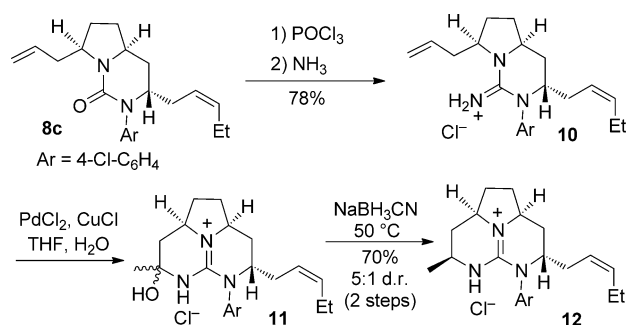
hindered aryl bromides (Table 2, entries 14 and 15) or electron-poor aryl bromides (entries 9, 11, and 13) led to lower diastereo- and enantioselectivities. Selectivities improved when NaOMe was used in place of NaOtBu in reactions of electron-poor aryl bromides (Table 2, entries 10 and 12), although yields decreased in these cases.

To further demonstrate the utility of the asymmetric desymmetrization reactions, we examined the deprotection of **8c** and the conversion of **8c** to tricyclic guanidine derivatives. 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.

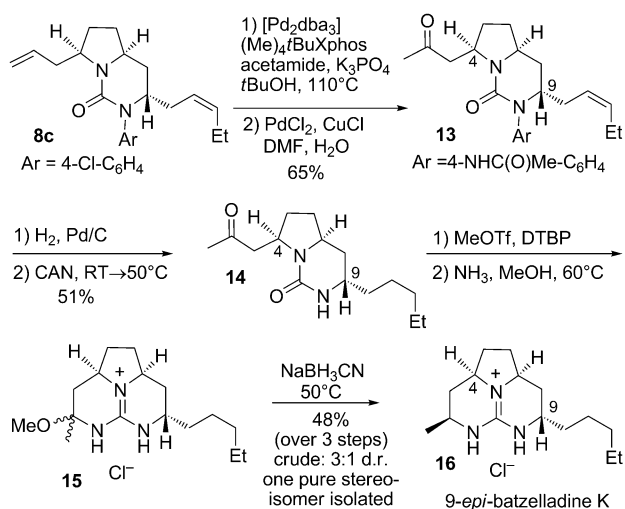
The conversion of **8c** to tricyclic guanidine **12** was carried out as shown in Scheme 2. Treatment of **8c** with POCl₃



Scheme 2. Conversion of **8c** to a tricyclic guanidine derivative.

followed by NH_3 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 NaBH_3CN .^[22] 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 epimeri-



Scheme 3. Conversion of **8c** to 9-*epi*-batzelladine K. DMF = *N,N*-dimethylformamide, DTBP = 2,6-di-*tert*-butylpyridine.

zation of the C4 stereocenter, the Pd-catalyzed *N*-arylation with acetamide was carried out prior to Wacker oxidation of the alkene. This two-step sequence provided **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.

Received: April 2, 2013

Published online: July 3, 2013

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

- [1] For reviews, see: a) A. Enríquez-García, E. P. Kündig, *Chem. Soc. Rev.* **2012**, *41*, 7803–7831; b) M. D. Díaz de Villegas, J. A. Galvez, P. Etayo, R. Badorrey, P. Lopez Ram de Viu, *Chem. Soc. Rev.* **2011**, *40*, 5564–5587; c) T. Rovis in *New Frontiers in Asymmetric Catalysis* (Eds.: K. Mikami, M. Lautens), Wiley, Hoboken, NJ, **2007**, p. 275–309; d) K. Mikami, A. Yoshida, *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 732–739; e) B. M. Trost, *Isr. J. Chem.* **1997**, *37*, 109–118.
- [2] a) R. G. S. Berlinck, A. E. Trindade-Silva, M. F. C. Santos, *Nat. Prod. Rep.* **2012**, *29*, 1382–1406; b) R. G. S. Berlinck, A. C. B. Burtoloso, A. E. Trindade-Silva, S. Romminger, R. P. Morais, K. Bandeira, C. M. Mizuno, *Nat. Prod. Rep.* **2010**, *27*, 1871–1907; c) R. G. S. Berlinck, A. C. B. Burtoloso, M. H. Kossuga, *Nat. Prod. Rep.* **2008**, *25*, 919–954; d) R. G. S. Berlinck, M. H. Kossuga, *Nat. Prod. Rep.* **2005**, *22*, 516–550; e) C. A. Bewley, S. Ray, F. Cohen, S. K. Collins, L. E. Overman, *J. Nat. Prod.* **2004**, *67*, 1319–1324.
- [3] a) R. Laville, O. P. Thomas, F. Berrue, D. Marquez, J. Vacelet, P. Amade, *J. Nat. Prod.* **2009**, *72*, 1589–1594; b) W. A. Gallimore, M. Kelly, P. J. Scheuer, *J. Nat. Prod.* **2005**, *68*, 1420–1423; c) H.-M. Hua, J. Peng, D. C. Dunbar, R. F. Schinazi, A. G. de Castro Andrews, C. Cuevas, L. F. Garcia-Fernandez, M. Kelly, M. T. Hamann, *Tetrahedron* **2007**, *63*, 11179–11188; d) A. D. Patil, N. V. Kumar, W. C. Kokke, M. F. Bean, A. J. Freyer, C. De Brosse, S. Mai, A. Truneh, D. J. Faulkner, B. Carte, A. L. Breen, R. P. Hertzberg, R. K. Johnson, J. W. Westley, B. C. M. Potts, *J. Org. Chem.* **1995**, *60*, 1182–1188.
- [4] a) S. Takishima, A. Ishiyama, M. Iwatsuki, K. Otoguro, H. Yamada, S. Omura, H. Kobayashi, R. W. M. van Soest, S. Matsunaga, *Org. Lett.* **2009**, *11*, 2655–2658; b) S. Takishima, A. Ishiyama, M. Iwatsuki, K. Otoguro, H. Yamada, S. Omura, H. Kobayashi, R. W. M. van Soest, S. Matsunaga, *Org. Lett.* **2010**, *12*, 896.
- [5] a) V. Martín, C. Vale, S. Bondu, O. P. Thomas, M. R. Vieytes, L. M. Botana, *Chem. Res. Toxicol.* **2013**, *26*, 169–178; b) J. C. Braekman, D. Daloz, R. Tavares, E. Hajdu, R. W. M. Van Soest, *J. Nat. Prod.* **2000**, *63*, 193–196; c) E. A. Jares-Erijman, R. Sakai, K. L. Rinehart, *J. Org. Chem.* **1991**, *56*, 5712–5715.
- [6] For examples of bicyclic ureas as intermediates in the synthesis of tricyclic guanidines, see: a) P. A. Evans, J. Qin, J. E. Robinson, B. Bazin, *Angew. Chem.* **2007**, *119*, 7561–7563; *Angew. Chem. Int. Ed.* **2007**, *46*, 7417–7419; b) Z. D. Aron, L. E. Overman, *J. Am. Chem. Soc.* **2005**, *127*, 3380–3390; c) A. V. Rama Rao, M. K. Gurjar, J. Vasudevan, *J. Chem. Soc. Chem. Commun.* **1995**,

- 1369–1370; d) L. E. Overman, M. H. Rabinowitz, P. A. Renhowe, *J. Am. Chem. Soc.* **1995**, *117*, 2657–2658.
- [7] For examples of bicyclic guanidines as intermediates in the synthesis of tricyclic guanidines, see: a) M. A. Arnold, K. A. Day, S. G. Duron, D. Y. Gin, *J. Am. Chem. Soc.* **2006**, *128*, 13255–13260; b) F. Cohen, L. E. Overman, *J. Am. Chem. Soc.* **2006**, *128*, 2604–2608; c) S. K. Collins, A. I. McDonald, L. E. Overman, Y. H. Rhee, *Org. Lett.* **2004**, *6*, 1253–1255; d) T. Ishiwata, T. Hino, H. Koshino, Y. Hashimoto, T. Nakata, K. Nagasawa, *Org. Lett.* **2002**, *4*, 2921–2924.
- [8] N. R. Babij, J. P. Wolfe, *Angew. Chem.* **2012**, *124*, 4204–4206; *Angew. Chem. Int. Ed.* **2012**, *51*, 4128–4130.
- [9] The substrate required for the preparation of (+)-merobatzelladine B contained a functionalized side chain bearing a stereocenter, 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.
- [10] A single report has described asymmetric desymmetrization reactions through Cu-catalyzed intramolecular carboaminations, which afford benzo-fused indolizidine products. See: L. Miao, I. Haque, M. R. Manzoni, W. S. Tham, S. R. Chemler, *Org. Lett.* **2010**, *12*, 4739–4741.
- [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.
- [12] For examples of asymmetric Pd-catalyzed desymmetrization reactions that afford enantiomerically enriched nitrogen heterocycles, see: a) R. H. Snell, M. J. Durbin, R. L. Woodward, M. C. Willis, *Chem. Eur. J.* **2012**, *18*, 16754–16764; b) R. H. Snell, R. L. Woodward, M. C. Willis, *Angew. Chem.* **2011**, *123*, 9282–9285; *Angew. Chem. Int. Ed.* **2011**, *50*, 9116–9119; c) B. D. Chapsal, I. Ojima, *Org. Lett.* **2006**, *8*, 1395–1398; d) B. M. Trost, D. E. Patterson, *Chem. Eur. J.* **1999**, *5*, 3279–3284; e) B. M. Trost, D. E. Patterson, *J. Org. Chem.* **1998**, *63*, 1339–1341.
- [13] (*S*)-Siphos-PE = (11a*S*)-(+)-10,11,12,13-tetrahydroindeno[7,1-*de*:1',7'*fg*]-[1,3,2]dioxaphosphocin-5-bis[(*R*)-1-phenylethyl]amine.
- [14] B. A. Hopkins, J. P. Wolfe, *Angew. Chem.* **2012**, *124*, 10024–10028; *Angew. Chem. Int. Ed.* **2012**, *51*, 9886–9890.
- [15] For asymmetric Pd-catalyzed alkene carboamination reactions that afford pyrrolidines, see: a) D. N. Mai, J. P. Wolfe, *J. Am. Chem. Soc.* **2010**, *132*, 12157–12159; b) D. N. Mai, B. R. Rosen, J. P. Wolfe, *Org. Lett.* **2011**, *13*, 2932–2935; for asymmetric Pd-catalyzed cascade oxidative cyclizations that proceed through *syn*-aminopalladation, see: c) W. He, K.-T. Yip, N.-Y. Zhu, D. Yang, *Org. Lett.* **2009**, *11*, 5626–5628; for asymmetric Cu-catalyzed alkene carboamination reactions, see: d) W. Zeng, S. R. Chemler, *J. Am. Chem. Soc.* **2007**, *129*, 12948–12949; e) T. W. Liwosz, S. R. Chemler, *J. Am. Chem. Soc.* **2012**, *134*, 2020–2023; for a discussion of the influence of alkene aminopalladation mechanism on asymmetric induction, see: f) A. B. Weinstein, S. S. Stahl, *Angew. Chem.* **2012**, *124*, 11673–11677; *Angew. Chem. Int. Ed.* **2012**, *51*, 11505–11509.
- [16] This electrophile was chosen for optimization studies as it had proven to be a satisfactory coupling partner in our synthesis of merobatzelladine 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.
- [19] This product results from competing β-hydride elimination/isomerization of the alkenylpalladium intermediate generated from oxidative addition of *E*-1-bromohexene. For further discussion of the origin of this side product, see: J. E. Ney, M. B. Hay, Q. Yang, J. P. Wolfe, *Adv. Synth. Catal.* **2005**, *347*, 1614–1620.
- [20] T. Ikawa, T. E. Barder, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 13001–13007.
- [21] (Me)₃tBuXPhos = 2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-tri-*iso*-propylbiphenyl.
- [22] B. B. Snider, J. Chen, *Tetrahedron Lett.* **1998**, *39*, 5697–5700.
- [23] For synthesis of bicyclic guanidines through Pd-catalyzed alkene diamination, see: C. H. Hövelmann, J. Streuff, L. Brelot, K. Muñoz, *Chem. Commun.* **2008**, 2334–2336.
- [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].
- [26] For syntheses of batzelladine K, see: a) M. Sekine, Y. Iijima, O. Iwamoto, K. Nagasawa, *Heterocycles* **2010**, *80*, 395–408; b) N. Ahmed, K. G. Brahmabhatt, I. P. Singh, K. K. Bhutani, *Synthesis* **2010**, 2567–2570; c) N. Ahmed, K. G. Brahmabhatt, S. I. Khan, M. Jacob, B. L. Tekwani, S. Sabde, D. Mitra, I. P. Singh, I. A. Kahn, K. K. Bhutani, *Chem. Biol. Drug Des.* **2013**, *81*, 491–498.
- [27] D. S. Coffey, A. I. McDonald, L. E. Overman, M. H. Rabinowitz, P. A. Renhowe, *J. Am. Chem. Soc.* **2000**, *122*, 4893–4903.