JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Exercising Regiocontrol in Palladium-Catalyzed Asymmetric Prenylations and Geranylation: Unifying Strategy toward Flustramines A and B

Barry M. Trost,* Sushant Malhotra, and Walter H. Chan

Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States

Supporting Information

ABSTRACT: Pd-catalyzed asymmetric prenylation of oxindoles to afford selectively either the prenyl or reverse-prenyl product has been demonstrated. Control of the regioselectivity in this transformation is governed by the choice of ligand, solvent, and halide additive. The resulting prenylated and reverse-prenylated products were transformed into *ent*-flustramides and *ent*-flustramines A and B. Additionally, control of the regio- and diastereoselectivity was obtained using π-geranylpalladium complexes.

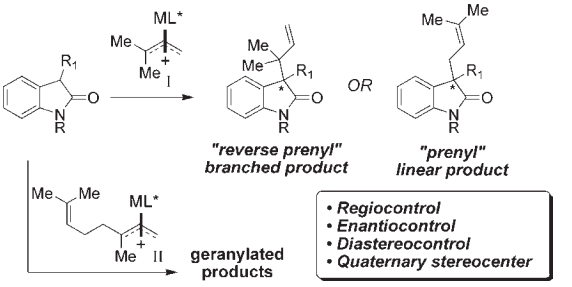


Figure 1. Regio- and stereoselective prenylation and geranylation of 3-alkyloxindoles.

Prenylated, reverse-prenylated, and geranylated hexahydropyrrolo[2,3-*b*]indole natural products exhibit a broad spectrum of biological activities.[1] Current methods for accessing such motifs include the organotin-mediated diastereo- and regioselective reverse prenylation of organoselenides derived from tryptophan,[2] the sigmatropic rearrangement of chiral 2-prenyloxyindoles,[3] the electrophilic prenylation of Witkop's indole,[4] and the enantioselective Friedel−Crafts alkylation of tryptamine and α,β-unsaturated aldehydes employing iminium catalysis.[5] We envisioned the direct incorporation of either the prenyl or reverse-prenyl group via catalytic asymmetric addition of oxindoles to π-prenyl organometallic species **I** (Figure 1). Additionally, in the nucleophilic attack using π-geranylmetal species **II**, we thought that simultaneous regio- and diastereocontrol could potentially selectively afford any of the four isomeric products. However, control of the regio-, enantio-, and diastereoselectivity in the generation of quaternary stereocenters, especially vicinal quaternary stereocenters, using such electrophilic species remains to be achieved.[6]

Danishefsky and co-workers[2] previously proposed a cationic prenyl species for accessing prenylated indole alkaloids, but the use of this synthon in the context of an enantioselective transformation has remained undeveloped.[7] We previously described Mo-catalyzed asymmetric allylic alkylation (AAA) to give 3,3′-disubstituted oxindoles in high ee,[8] but this process is not applicable to 1,1-disubstituted allylating agents such as prenyl. On the other hand, Pd-catalyzed processes work well with such allylating agents; however, the typical regioselectivity involves nucleophilic addition to the less substituted terminus.[9] Despite this, previous work on Pd-catalyzed AAA has demonstrated that with heteroatom and malonate nucleophiles and monosubstituted allyl electrophiles, this regioselectivity can be reversed to favor the branched products.[10,11] However, prenylation represents an extreme case, since attack at the more substituted terminus with carbon nucleophiles involves formation of a quaternary center.[12] This regioselectivity issue becomes magnified when the prochiral nucleophile is tertiary, since this would lead to the formation of adjacent quaternary centers, a truly sterically demanding event.

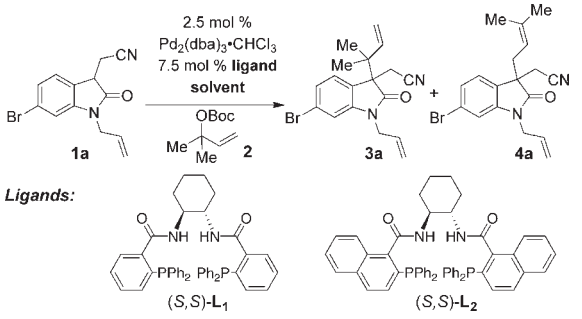
Beginning our investigation using ligands $\mathbf{L_1}$ and $\mathbf{L_2}$ in Pd-catalyzed AAA resulted in promising levels of enantiocontrol (85−97% ee). While ligand $\mathbf{L_2}$ favored attack at the more substituted terminus, biasing the regioselectivity toward product **3a**, $\mathbf{L_1}$ offered complementary regioselectivity toward product **4a** (Table 1, entries 1 and 2).[13] Previous work on Pd-catalyzed AAA demonstrated that the solvent and halide additive (by promoting $\pi-\sigma-\pi$ equilibration) can influence the regio- and enantioselectivity.[11] Indeed, evaluation of several solvents revealed that CH_2Cl_2 and 30 mol % tetrabutylammonium difluorotriphenylsilicate (TBAT) employing ligand $\mathbf{L_2}$ afforded the desired product **3a** in 88% yield with 87% ee and 18:1 regioselectivity for the branched product (entries 3−6). In contrast, the use of ligand $\mathbf{L_1}$ with toluene as the solvent favored the formation of the linear product **4a** in 66% yield with 96% ee and 3.2:1 selectivity favoring the linear isomer **4a** (entries 7−10). The regioselectivity differences afforded by $\mathbf{L_1}$ and $\mathbf{L_2}$ may be attributed to the greater steric demands of $\mathbf{L_2}$, which favor coordination of the Pd(0)−$\mathbf{L_2}$ complex to the less substituted alkene in the transition state of the nucleophilic attack and thus result in the branched product (as opposed to a Pd(0)−$\mathbf{L_2}$ complex with the trisubstituted alkene, which would lead to the linear product).

The scope of the regio- and enantioselective reverse prenylation was then evaluated (Table 2).[14a] Substrate selection was

Received: March 7, 2011
Published: April 26, 2011

dx.doi.org/10.1021/ja2020873 | *J. Am. Chem. Soc.* 2011, 133, 7328–7331

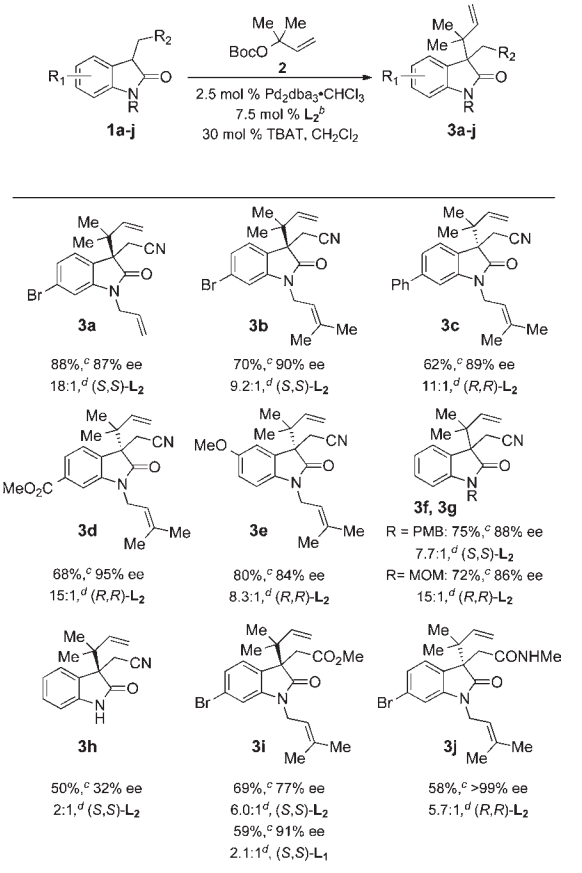
Table 1. Selected Optimization Studies



entry[a]	ligand	solvent	3a:4a[b]	% yield[c] 3a,4a	% ee[d] 3a,4a
1	L_1	THF	1:1.6	33,56	93,97
2	L_2	THF	2:1	59,29	85,95
		Tuning the Branched Selectivity			
3	L_2	dioxane	3.1:1	**3a**: 29	**3a**: 80
4	L_2	DCE	5.6:1	**3a**: 58	**3a**: 75
5	L_2	DCM	5.1:1	**3a**: 82	**3a**: 91
6	L_2	**DCM**	**18:1**[e]	**3a: 88**	**3a: 87**
		Tuning the Linear Selectivity			
7	L_1	cyclohexane	1:3.7	ND[f]	**4a**: 66
8	L_1	hexane	1:3.4	ND[f]	**4a**: 84
9	L_1	benzene	1:2.4	**4a**: 57	**4a**: 94
10	L_1	**toluene**	**1:3.2**	**4a: 66**	**4a: 96**

[a] Reactions were conducted on a 0.034 mmol scale using 1.5 equiv of carbonate and 1.0 equiv of nucleophile at 0.17 M. [b] Based on ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yields. [d] Determined by chiral HPLC. [e] 30 mol % TBAT was added. [f] ND = not determined.

Table 2. Regioselective Pd-Catalyzed Asymmetric Reverse Prenylation[a]



[a] Reactions were conducted on a 0.034 mmol scale using 1.5 equiv of carbonate and 1.0 equiv of nucleophile at 0.17 M. [b] Unless otherwise specified. [c] Isolated yield of major product only. [d] Regioselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.

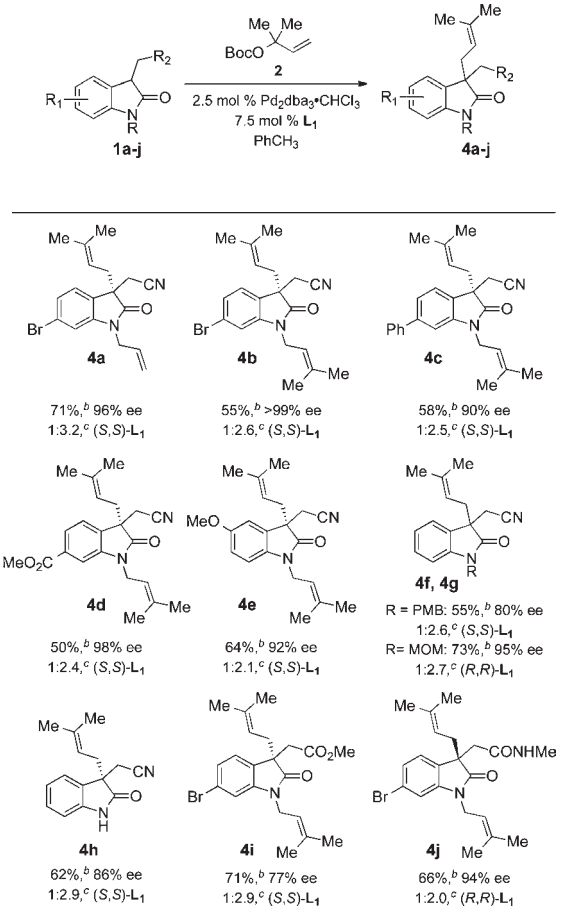
inspired by the development of a general strategy for accessing diverse prenylated hexahydropyrrolo[2,3-*b*]indoles for the broader investigation of the biological activity of such compounds in enantioenriched form.[15] Substitution at nitrogen was well-tolerated: *N*-allyl, *N*-prenyl, *N*-*p*-methoxybenzyl (*N*-PMB), and *N*-methoxymethyl (*N*-MOM) groups all afforded products with high regio- and enantiocontrol (**3a**−**c**). The non-N-substituted derivative **1h**, however, resulted in low selectivity. Incorporation of an electron-donating or -withdrawing group or a phenyl group on the oxindole carbocycle had minimal influence on the selectivity. From the standpoint of enantio- and regiocontrol, the nitrile-containing oxindole derivatives **1a**−**g** proved to be superior. Modification of this group by employing ester **1i** and secondary amide **1j** also afforded the desired products with high enantiocontrol but slightly lowered regiocontrol.

The prenylation of the same oxindoles was investigated with the aim of obtaining the linear regioisomers (Table 3). All of the N-protecting groups examined afforded linear prenylated products with high enantiocontrol, and non-N-substituted oxindole **1h** afforded the product **4h** in 62% yield with 86% ee. Substitution on the oxindole carbocycle and at the 3-position of the oxindole was well-tolerated. Although the regiocontrol in the formation of linear products **4a**−**i** was lower than that of reverse-prenylated compounds **3a**−**i**, the regioisomers were separable by silica gel chromatography in all cases.

Evaluation of π-geranylpalladium complex **II** (Figure 1, M = Pd) was motivated by the recent isolation of several geranylated hexahydropyrrolo-[2,3-*b*]indoles.[6] This electrophile poses the added challenge of diastereocontrol. Employing **1a** and racemic linalyl carbonate **5** (Scheme 1) afforded a 15:15:1 mixture of linalylated **6**, geranylated **8**, and nerylated **10** as products. Gratifyingly, **6** was formed as a single diastereomer with 90% ee, albeit in 46% yield.[14b] On the basis of this result, we hypothesized that the reaction with branched electrophile **5** partitions equally through slowly equilibrating syn and anti π-allyl complexes to afford equal amounts of products **6** and **8**.[16] To test this hypothesis, we investigated the use of geometrically defined linear carbonates **7** and **9**. The ionization of these more hindered carbonates was achieved by conducting the reaction at 40 °C and switching to the more reactive Pd(Cp)allyl precatalyst. Indeed, under these conditions, geranyl carbonate **7** exclusively afforded the geranylated product **8** in 76% yield with 91% ee. Furthermore, neryl 2,2,2-trichloroethyl (Troc) carbonate **9** in CH_2Cl_2 afforded the linalylated product **6** as a single diastereoisomer in 92% yield with 91% ee and 13:1 selectivity versus the neryl isomer.[17] Switching the solvent to dioxane afforded the neryl isomer **10** with 94% ee but in only 41% yield, a result of the modest regioselectivity (1.5:1 over the linalyl isomer, with a small amount of the geranyl isomer also being formed).

dx.doi.org/10.1021/ja2020873 |*J. Am. Chem. Soc.* 2011, 133, 7328–7331

Table 3. Regioselective Pd-Catalyzed Asymmetric Prenylation[a]

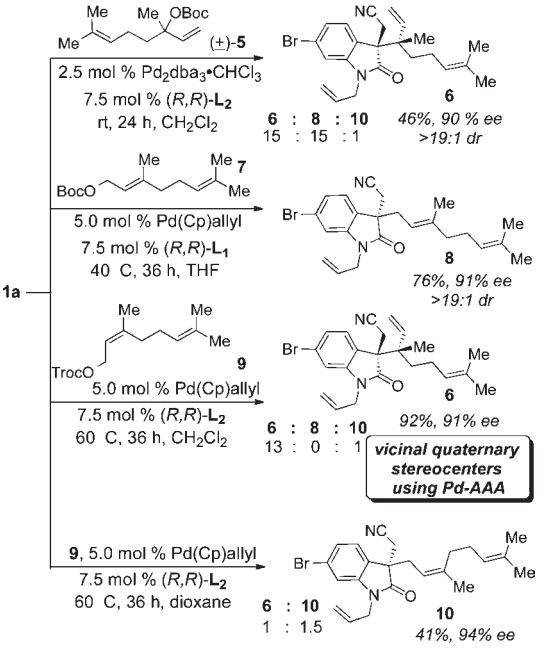


[a] Reactions were conducted on 0.034 mmol scale using 1.5 equiv of carbonate and 1.0 equiv of nucleophile at 0.17 M. [b] Isolated yield of major product only. [c] Regioselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.

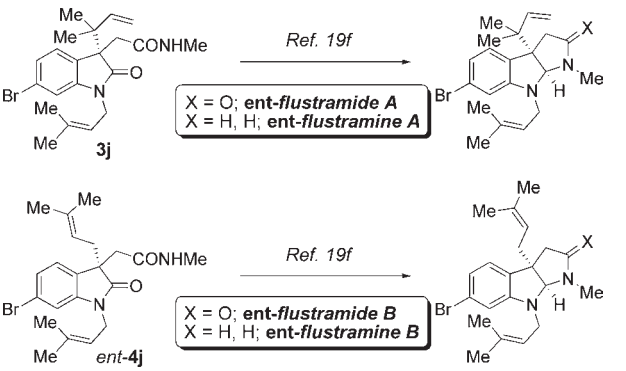
To demonstrate the synthetic utility of this methodology and assign the absolute configuration of the products, reverse-prenylated oxindole **3j** and the regioisomeric product **4j** were converted to *ent*-flustramide A {$[\alpha]_D^{25}$ +62.2 [90% ee from (*R*,*R*)-**L$_1$**, *c* 1.10, EtOH]; lit.[18] $[\alpha]_D^{18}$ −73.2, *c* 1.09, EtOH} and *ent*-flustramide B {$[\alpha]_D^{26}$ +73.7 [76% ee from (*S*,*S*)-**L$_1$**, *c* 1.78, EtOH]; lit. $[\alpha]_D^{25}$ −104.2, *c* 1.75, EtOH}, respectively, and to *ent*-flustramine A {$[\alpha]_D^{25}$ +126.9 [90% ee from (*R*,*R*)-**L$_1$**, *c* 0.73, EtOH]; lit. $[\alpha]_D^{18}$ −139.4, *c* 0.73, EtOH} and *ent*-flustramine B {$[\alpha]_D^{24}$ +74.2 [76% ee from (*S*,*S*)-**L$_1$**, *c* 1.50, EtOH]; lit. $[\alpha]_D^{23}$ −93.5 (*c* 1.5, EtOH)}, respectively, using literature procedures (Scheme 2).[19] Flustramines A and B possess skeletal and smooth muscle relaxant activity.[20] Flustramine A has also been shown to have voltage-gated channel blocking activity,[21] while (−)-debromoflustramine B possesses significant butyrylcholinesterase inhibitory activity when evaluated as a single enantiomer.

The syntheses of *ent*-flustramides A and B revealed that opposite enantiomers of the reverse-prenylated and prenylated species were formed when the same enantiomer of the ligand was used. This suggests that either face of the oxindole can approach the π-prenylpalladium complex (Figure 2). In the context of our working model, the depicted orientation of the oxindole

Scheme 1. Pd-Catalyzed AAA Using Carbonates (±)-5, 7, and 9



Scheme 2. Catalytic Asymmetric Synthesis of *ent*-Flustramides and *ent*-Flustramines A and B



minimizes the charge separation between the enolate and the allyl cation, thereby rationalizing the change in enantiotopic faces of the prochiral nucleophile when it approaches the two different termini of the bound allyl unit.[22,23]

In conclusion, regiocontrol in accessing prenylated and reverse-prenylated C-3a oxindoles in high optical purities has been achieved. These products are valuable building blocks leading toward the flustramine family of natural products. Results from the geranylation studies have presented for the first time the asymmetric synthesis of vicinal all-carbon quaternary centers for both reaction partners. The opposite regioselectivity observed using isomeric π-geranyl- and π-nerylpalladium complexes allows three of the four isomeric products to be accessed selectively. This work demonstrates that unusual ligand-dependent versatility can be observed in Pd-catalyzed AAA reactions and presents new opportunities for directing nucleophilic attack to the internal carbon more generally using π-allylpalladium complexes.

dx.doi.org/10.1021/ja2020873 |*J. Am. Chem. Soc.* 2011, 133, 7328–7331

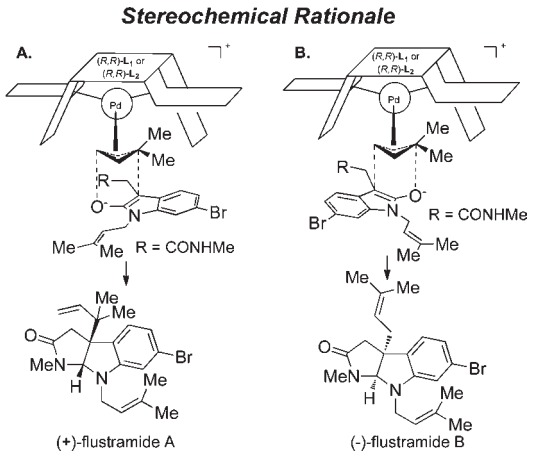


Figure 2. Rationalizing the divergent absolute stereochemistries of the prenylation reaction.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
bmtrost@stanford.edu

■ ACKNOWLEDGMENT

This work was supported by the National Institutes of Health (GM033049) and the National Science Foundation. S.M. acknowledges Stanford University for a graduate fellowship. Palladium salts were generously supplied by Johnson-Matthey.

■ REFERENCES

(1) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151 and references therein.

(2) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143.

(3) Kawasaki, T.; Shinada, M.; Ohzono, M.; Ogawa, A.; Terashima, R.; Sakamoto, M. *J. Org. Chem.* **2008**, *73*, 5959.

(4) Cardoso, A. S. P.; Marques, M. M. B.; Srinivasan, N.; Prabhakar, S.; Lobo, A. M. *Tetrahedron* **2007**, *63*, 10211.

(5) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482.

(6) Several geranylated hexahydropyrrolo[2,3-*b*]indole-containing natural products have recently been isolated. See: (a) Okada, M.; Sato, I.; Cho, S. J.; Dubnau, D.; Sakagami, Y. *Tetrahedron* **2006**, *62*, 8907. (b) Okada, M.; Yamaguchi, H.; Sato, I.; Tsuji, F.; Dubnau, D.; Sakagami, Y. *Biosci., Biotechnol., Biochem.* **2008**, *72*, 914. (c) Rochfort, S. J.; Moore, S.; Craft, C.; Martin, N. H.; Van Wagoner, R. M.; Wright, J. L. C. *J. Nat. Prod.* **2009**, *72*, 1773.

(7) For the use of π-prenyl species (**I**, M = Pd) in regioselective allylic alkylations, aminations, and etherifications leading to the formation of tetrasubstituted centers, see: Alkylation: (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730. (b) For highly enantioselective formation of linear isomers using azalactones, see: Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727. Amination:(c) Åkermark, B.; Vitagliano, A. *Organometallics* **1985**, *4*, 1275. (d) Åkermark, B.; Åkermark, G.; Hegedus, L. S.; Zetterberg, K. *J. Am. Chem. Soc.* **1981**, *103*, 3037. (e) Watson, I. D. G.; Styler, S. A.; Yudin, A. K. *J. Am. Chem. Soc.* **2004**, *126*, 5086. (f) Faller, J. W.; Wilt, J. C. *Org. Lett.* **2005**, *7*, 633. (g) Johns, A. M.; Liu, Z.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7259. (h) Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 17516. (i) Dubovyk, I.; Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 14172. Etherification:(j) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074.

(8) (a) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590. (b) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548. (c) Trost, B. M.; Zhang, Y. *Chem.—Eur. J.* **2010**, *16*, 296.

(9) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(10) Trost, B. M.; Crawley, M. L. *Chem.—Eur. J.* **2004**, *10*, 2237. Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968.

(11) For selected publications, see: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545. (b) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (c) Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323. (d) You, S. L.; Zhu, X. Z.; Luo, Y. M.; Hou, X. L.; Dai, L. X. *J. Am. Chem. Soc.* **2001**, *123*, 7471. (e) Zheng, W. H.; Sun, N.; Hou, X. L. *Org. Lett.* **2005**, *7*, 5151.

(12) Regioselectivity for the branched product has also been demonstrated in the reaction with butadiene and isoprene monoxide. See: Trost, B. M.; Jian, C.; Hammer, K. *Synthesis* **2005**, *19*, 3335 and references therein.

(13) Products **3a** and **4a** were separable by chromatography. Employing the isomeric electrophile had a minimal impact on the regiocontrol, but a significant decrease in conversion was observed.

(14) (a) See the Supporting Information for the preparation of substrates. (b) The assignment of the relative stereochemistry of **6** is detailed in the Supporting Information, and the absolute stereochemistry was assigned by analogy with the stereochemical outcome of the asymmetric prenylation reactions.

(15) Rivera-Becerril, E.; Joseph-Nathan, P.; Pérez-Álvarez, V. M.; Morales-Ríos, M. S. *J. Med. Chem.* **2008**, *51*, 5271.

(16) The slow interconversion of η^3-geranylpalladium and η^3-neryl palladium complexes has previously been implicated in ref 7c.

(17) Regioselectivity differences between geranyl and neryl geometrical isomers have been reported previously in refs 7a and 7c.

(18) Kawasaki, T.; Shinada, M.; Kamimura, D.; Ohzono, M.; Ogawa, A. *Chem. Commun.* **2006**, 420.

(19) For previous syntheses of racemic flustramines A and B, see: (a) Hino, T.; Tanaka, T.; Matsuki, K.; Nakagawa, M. *Chem. Pharm. Bull.* **1983**, *5*, 1806. (b) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Trujillo-Serrato, J. J.; Joseph-Nathan, P. *J. Org. Chem.* **2001**, *66*, 1186. (c) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2005**, *7*, 677. For asymmetric syntheses of flustramines A and B, see:(d) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482. (e) Morales-Ríos, M. S.; Rivera-Becerril, E.; Joseph-Nathan, P. *Tetrahedron: Asymmetry* **2005**, *16*, 2493. (f) Kawasaki, T.; Shinada, M.; Kamimura, D.; Ohzono, M.; Ogawa, A. *Chem. Commun.* **2006**, 420. (g) Kawasaki, T.; Shinada, M.; Ohzono, M.; Ogawa, A.; Terashima, R.; Sakamoto, M. *J. Org. Chem.* **2008**, *73*, 5959. (h) Hirano, T.; Iwakiri, K.; Miyamota, H.; Nakazaki, A.; Kobayashi, S. *Heterocycles.* **2009**, *79*, 805.

(20) Sjoeblom, T.; Bohlin, L.; Christophersen, C. *Acta Pharm. Suec.* **1983**, *20*, 415.

(21) Peters, L.; König, G. M.; Terlau, H.; Wright, A. D. *J. Nat. Prod.* **2002**, *65*, 1633.

(22) (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545. (b) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747.

(23) For a detailed mechanistic discussion and transition-state structures, see: Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P.-O.; Sale, D. A.; Schramm, Y. *J. Am. Chem. Soc.* **2009**, *131*, 9945.