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

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

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

Abstract

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

Prenylated, reverse prenylated, and geranylated hexahydropyrrolo[2,3-*b*]indole natural products exhibit a broad spectrum of biological activities.¹ Current methods to access such motifs include the organotin-mediated diastereo- and regioselective reverse prenylation of organoselenides derived from tryptophan,² the sigmatropic rearrangement of chiral 2-prenyloxy indoles,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 the reverse prenyl group via the catalytic asymmetric addition of oxindoles to π -prenyl organometallic species **I** (Figure 1). Additionally, in the nucleophilic attack using π -geranylmatal species **II** we thought that simultaneous regio- and diastereocontrol could potentially selectively afford any of the four isomeric products. However, the control in regio-, enantio-, and diastereo-selectivity in the generation of quaternary stereocenters, especially vicinal quaternary stereocenters, using such electrophilic species remains to be achieved.⁶

Danishefsky and coworkers have previously proposed a cationic prenyl species to access prenylated indole alkaloids,² but the use of this synthon in the context of an enantioselective transformation has remained undeveloped.⁷ We have previously described the Mo-catalyzed asymmetric allylic alkylation (AAA) towards 3,3'-disubstituted oxindoles in high ee's,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 the 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

Correspondence to: Barry M. Trost.

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becomes magnified when the prochiral nucleophile is tertiary since it leads to formation of adjacent quaternary centers, a truly sterically demanding event.

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

The scope of the regio- and enantioselective reverse prenylation was then evaluated (Table 2).^{14a} Substrate selection was inspired by the development of a general strategy to access 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*-paramethoxybenzyl (PMB), and *N*-methoxymethyl (MOM) groups all afforded products with high regio- and enantio-control (**3a–3c**). The *N*-unsubstituted derivative **1h**, however, resulted in low selectivities. Incorporation of an electron-donating, electron-withdrawing, 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 with slightly lowered regiocontrol.

The prenylation of the same oxindoles was investigated with the aim of obtaining the linear regioisomer (Table 3). All *N*-protecting groups examined afforded linear prenylated products with high enantiocontrol, and the *N*-unsubstituted oxindole **1h** afforded the product **4h** in 62% yield and 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 the linalylated **6**, geranylated **8**, and nerylalated **10** products. Gratifyingly, the linalyl product **6** was formed as a single diastereomer in 90% ee albeit in 46% yield.^{13b} Based on 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**

afforded exclusively the geranylated product **8** in 76% yield and 91% ee. Furthermore, the neryl 2,2,2-trichloroethyl (Troc) carbonate **9** afforded the linalylated product **6** in 92% yield, 91% ee as a single diastereoisomer in methylene chloride and with 13:1 selectivity versus the neryl isomer.¹⁷ Switching the solvent to dioxane afforded the neryl isomer **10** in 94% ee but only 41% yield, a result of the modest regioselectivity (1.5:1 over the linalyl isomer, with a small amount of geranyl isomer also being formed).

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*)-**L1**, *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*)-**L1**, *c* 1.78, EtOH); lit. $[\alpha] -104.2$, *c* 1.75, EtOH), as well as *ent*-D²⁵ flustramine A ($[\alpha]_D^{25} +126.9$ (90% ee from (*R,R*)-**L1**, *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*)-**L1**, *c* 1.50, EtOH); lit. $[\alpha]_D^{23} -93.5$ (*c* 1.5, EtOH)) 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 synthesis of *ent*-flustramides A and B revealed that opposite enantiomers of the reverse prenylated and prenylated species are formed when the same enantiomer of the ligand is 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 minimizes 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 towards the flustramine family of natural products. Results from the geranylation studies present 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 -neryl palladium 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 to direct nucleophilic attack to the internal carbon more generally using π -allylpalladium complexes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Crich D, Banerjee A. *Acc Chem Res.* 2007; 40:151. and references therein. [PubMed: 17309195]
2. Marsden SP, Depew KM, Danishefsky SJ. *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. [PubMed: 18576686]
4. Cardoso ASP, Marques MMB, Srinivasan N, Prabhakar S, Lobo AM. *Tetrahedron.* 2007; 63:10211.

5. Austin JF, Kim SG, Sinz CJ, Xiao WJ, MacMillan DWC. *Proc Nat Acad Sci USA*. 2004; 101:5482. [PubMed: 15067109]
6. Several geranylated hexahydropyrrolo[2,3-b]indole containing natural products have recently been isolated. (a) Okada M, Sato I, Cho SJ, 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. [PubMed: 18323630] (c) Rochfort SJ, Moore S, Craft C, Martin NH, Van Wagoner RM, Wright JLC. *J Nat Prod*. 2009; 72:1773. [PubMed: 19785389]
7. For the use of π -prenyl species (I, M = Pd) towards regioselective allylic alkylations, aminations, and etherifications in the formation of tetra-substituted centers see - alkylation: (a) Trost BM, Verhoeven TR. *J Am Chem Soc*. 1980; 102:4730. (b) For highly enantioselective formation of linear isomer using azalactones see Trost BM, 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 LS, Zetterberg K. *J Am Chem Soc*. 1981; 103:3037. (e) Watson IDG, Styler SA, Yudin AK. *J Am Chem Soc*. 2004; 126:5086. [PubMed: 15099089] (f) Faller JW, Wilt JC. *Org Lett*. 2005; 7:633. [PubMed: 15704912] (g) Johns AM, Liu Z, Hartwig JF. *Angew Chem Int Ed*. 2007; 46:7259. (h) Watson IDG, Yudin AK. *J Am Chem Soc*. 2005; 127:17516. [PubMed: 16332104] (i) Dubovyk I, Watson IDG, Yudin AK. *J Am Chem Soc*. 2007; 129:14172. [PubMed: 17960935] etherification: (j) Trost BM, Toste DF. *J Am Chem Soc*. 1998; 120:9074.
8. (a) Trost BM, Zhang Y. *J Am Chem Soc*. 2006; 128:4590. [PubMed: 16594693] (b) Trost BM, Zhang Y. *J Am Chem Soc*. 2007; 129:14548. [PubMed: 17985899] (c) Trost BM, Zhang Y. *Chem Eur J*. 2010; 16:296.
9. Trost BM, Crawley ML. *Chem Rev*. 2003; 103:2921. [PubMed: 12914486]
10. Trost BM, Crawley ML. *Chem Eur J*. 2004; 10:2237. Trost BM, Bunt RC, Lemoine RC, Calkins TL. *J Am Chem Soc*. 2000; 122:5968.
11. For selected publications see: (a) Trost BM, Toste FD. *J Am Chem Soc*. 1999; 121:4545. (b) Helmchen G, Pfaltz A. *Acc Chem Res*. 2000; 33:336. [PubMed: 10891051] (c) Prétôt R, Pfaltz A. *Angew Chem, Int Ed*. 1998; 37:323. (d) You SL, Zhu XZ, Luo YM, Hou XL, Dai LX. *J Am Chem Soc*. 2001; 123:7471. [PubMed: 11472198] (e) Zheng WH, Sun N, Hou XL. *Org Lett*. 2005; 7:5151. [PubMed: 16268525]
12. Regioselectivity for the branched product has also been demonstrated in the reaction with butadiene and isoprene monoxide. Trost BM, 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 regiocontrol but a significant drop in conversion was observed.
14. a) See 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 is assigned by analogy with the stereochemical outcome of the asymmetric prenylation reactions.
15. Rivera-Becerril E, Joseph-Nathan P, Pérez-Álvarez VM, Morales-Ríos MS. *J Med Chem*. 2008; 51:5271. [PubMed: 18686941]
16. The slow interconversion of η^3 -geranyl palladium and η^3 -neryl palladium complexes has previously been implicated in reference 7c.
17. Regioselectivity differences between geranyl and neryl geometrical isomers has been reported previously in reference 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 MS, Suárez-Castillo OR, Trujillo-Serrato JJ, Joseph-Nathan P. *J Org Chem*. 2001; 66:1186. [PubMed: 11312946] (c) Fuchs JR, Funk RL. *Org Lett*. 2005; 7:677. [PubMed: 15704923] For asymmetric syntheses of flustramines A and B see: (c) Austin JF, Kim SG, Sinz CJ, Xiao WJ, MacMillan DWC. *Proc Nat Acad Sci USA*. 2004; 101:5482. [PubMed: 15067109] (d) Morales-Ríos MS, Rivera-Becerril E, Joseph-Nathan P. *Tetrahedron: Asymmetry*. 2005; 16:2493. (e) Kawasaki T, Shinada M, Kamimura D, Ohzono M, Ogawa A. *Chem Commun*. 2006:420. (f) Kawasaki T, Shinada M, Ohzono M, Ogawa A, Terashima R, Sakamoto M. *J Org Chem*. 2008; 73:5959. [PubMed: 18576686] (g) Hirano T, Iwakiri K, Miyamota H, Nakazaki A, Kobayashi S. *Tetrahedron Lett*. 2009; 79:805.

20. Sjöblom T, Bohlin L, Christophersen C. *Acta Pharm Suec.* 1983; 20:415. [PubMed: 6675420]
21. Peters L, König GM, Terlau H, Wright AD. *J Nat Prod.* 2002; 65:1633. [PubMed: 12444689]
22. (a) Trost BM, Toste FD. *J Am Chem Soc.* 1999; 121:4545. (b) Trost BM, Machacek MR, Aponick A. *Acc Chem Res.* 2006; 39:747. [PubMed: 17042475]
23. For a detailed mechanistic discussion and transition state structures see Butts CP, Filali E, Lloyd-Jones GC, Norrby PO, Sale DA, Schramm Y. *J Am Chem Soc.* 2009; 131:9945. [PubMed: 19435358]

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

Scheme 1.
Pd-AAA using carbonates (±)-5, 7, and 9.

Scheme 2.

Catalytic asymmetric synthesis of *ent*-flustramides and *ent*-flustramines A and B.

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
<i>Tuning Branched Selectivity</i>					
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
<i>Tuning Linear Selectivity</i>					
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

Ligands:

(S,S)-L₁

(S,S)-L₂

^aReactions conducted on a 0.034 mmol scale using 1.5 equiv carbonate and 1.0 equiv nucleophile at 0.17 M.

^bBased on ¹H NMR of crude reaction mixture.

^cIsolated yield.

^dDetermined by chiral HPLC.

ϵ 30 mol % TBAT added.

ϵ ND = not determined.

Table 2Regioselective Pd-catalyzed asymmetric reverse prenylation.^a ^a Reactions conducted on a 0.034 mmol scale using 1.5 equiv carbonate and 1.0 equiv nucleophile at 0.17 M.^b Unless other specified.^c Isolated yield of major product only.^d Regioselectivity determined by ¹H NMR analysis of the crude reaction mixture.

Table 3

Regioselective Pd-catalyzed asymmetric prenylation.^a

<p>71%,^b 96% ee 1:3.2,^c (S,S)-L₁</p>	<p>55%,^b >99% ee 1:2.6,^c (S,S)-L₁</p>	<p>58%,^b 90% ee 1:2.5,^c (S,S)-L₁</p>
<p>50%,^b 98% ee 1:2.4,^c (S,S)-L₁</p>	<p>64%,^b 92% ee 1:2.1,^c (S,S)-L₁</p>	<p>R = PMB: 55%,^b 80% ee 1:2.6,^c (S,S)-L₁ R = MOM: 73%,^b 95% ee 1:2.7,^c (R,R)-L₁</p>
<p>62%,^b 86% ee 1:2.9,^c (S,S)-L₁</p>	<p>71%,^b 77% ee 1:2.9,^c (S,S)-L₁</p>	<p>66%,^b 94% ee 1:2.0,^c (R,R)-L₁</p>

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