

New Class of Nucleophiles for Palladium-Catalyzed Asymmetric Allylic Alkylation. Total Synthesis of Agelastatin A

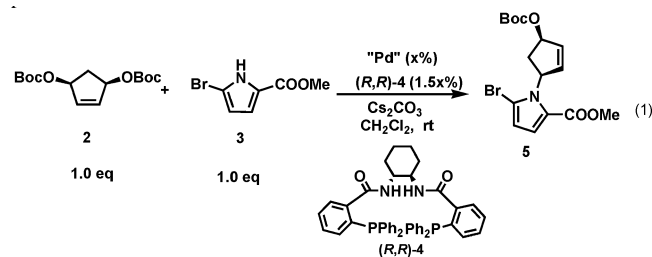
Barry M. Trost* and Guangbin Dong

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

Received February 15, 2006; E-mail: bmtrost@stanford.edu

Metal-catalyzed allylic alkylations increase in importance as a synthetic method as the ability to expand their scope increases. A major feature of this method is its applicability for formation of a broad array of bond types, including carbon–carbon and carbon–heteroatom bonds. The importance of nitrogen-containing bioactive molecules¹ directs special attention to the formation of carbon–nitrogen bonds.² The recent revelation of bromopyrroles as a growing family of bioactive natural products represented by the manzacidines, axinellamine A, dibromophakellstatin, and palau'amine, typically derived from marine organisms,³ led us to consider the use of pyrroles as nucleophiles in AAA (asymmetric allylic alkylation) reactions. The agelastatins (**1**), a family of four tetracyclic compounds (see Figure 1), possess nanomolar activity against several cancer cell lines.⁴ Furthermore, agelastatin A inhibits glycogen synthase kinase-3 β (GSK-3 β), a behavior that may provide an approach for the treatment of Alzheimer's disease.^{4a} In this paper, we report the use of pyrroles as nucleophiles in the Pd AAA and the use of such a process for a facile asymmetric synthesis of agelastatin A.

Initial studies examined the reaction between the Boc-activated cyclopentene-1,4-diol **2** and methyl 5-bromopyrrole-2-carboxylate **3** (eq 1). After a general screening, Cs₂CO₃ and DCM proved to be the base and best solvent combination.



The yield and enantioselectivity were optimized by varying the palladium source and loading, base loading, and concentration (Table 1). From these studies emerged the most practical set of conditions, as shown in entry 6, which gives the *N*-alkyl pyrrole **5** in 83% yield and 92% ee. Direct transformation of the carboxylate ester **5** to the *N*-methoxyamide **6** failed,⁵ but a two-step process (hydrolysis, condensation) gave a high yield (Scheme 1). Although the chiral ligand was not necessary for cyclization to piperazinone **7**, the intramolecular Pd-catalyzed AAA with the *N*-methoxyamide as the nucleophile gave a higher yield when (R,R)-4 was used as a ligand (91%) compared to dppp (70%). At this point, the absolute configuration was assigned by analogy to other reactions of substrate **2**.

With success of both the pyrrole and the *N*-methoxyamide as nucleophiles, respectively, and considering that the nitrogen on the *N*-methoxyamide is more nucleophilic than the one on the pyrrole, we designed a cascade reaction to further extend this methodology. Theoretically, piperazinone **9** could be synthesized in one pot from

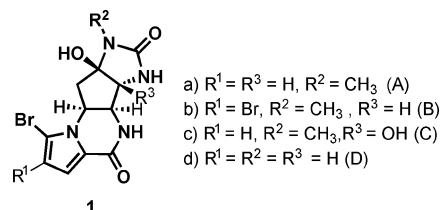


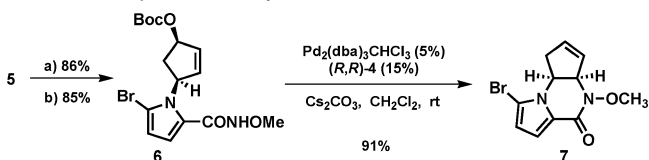
Figure 1. Agelastatins.

Table 1. Selected Optimization Studies

entry	Pd source (mol %)	Cs ₂ CO ₃ (equiv)	concentrated (M)	yield (%) ^a	ee (%) ^b
1	Pd ₂ (dba) ₃ CHCl ₃ (5)	1.0	0.02	90	84
2	Pd ₂ (dba) ₃ CHCl ₃ (5)	0.7	0.02	75	92
3	Pd ₂ (dba) ₃ CHCl ₃ (2.5)	1.0	0.02	89	66
4	Pd ₂ (dba) ₃ CHCl ₃ (1.25)	1.0	0.08	75	85
5	[Pd(C ₃ H ₅)Cl] ₂ (2)	1.0	0.17	88–93	87
6	[Pd(C ₃ H ₅)Cl] ₂ (1.25)	1.0	0.08	83	92

^a Isolated yield. ^b Enantioselectivities were determined by chiral HPLC.

Scheme 1. Piperazinone Synthesis^a



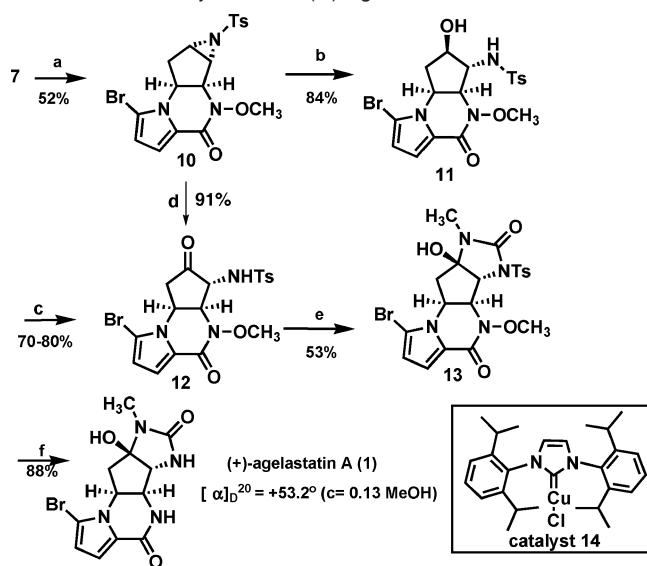
^a Conditions: (a) LiOH (1 N), THF/water = 3/1, 48 h, rt; (b) oxalyl chloride, cat. DMF in THF, then NH₂OMe·HCl, K₂CO₃, and H₂O, rt.

Table 2. Synthesis of Piperazinone 9^a

entry	Pd source (mol %)	ligand (mol %)	additive (mol %)	temp (°C)	yield (%) ^b	ee (%) ^c
1	[Pd(C ₃ H ₅)Cl] ₂ (2)	(R,R)-4 (6)	none	rt	trace	NA
2	[Pd(C ₃ H ₅)Cl] ₂ (2)	(R,R)-4 (6)	Cs ₂ CO ₃ (100)	rt	0	NA
3	[Pd(C ₃ H ₅)Cl] ₂ (5)	(R,R)-4 (15)	HOAc (10)	rt	trace ^d	NA
4	Pd ₂ (dba) ₃ CHCl ₃ (5)	(R,R)-4 (15)	HOAc (10)	rt	51	NA
5	Pd ₂ (dba) ₃ CHCl ₃ (5)	(R,R)-4 (15)	BSA (100)	rt	50	NA
6	Pd ₂ (dba) ₃ CHCl ₃ (5)	(R,R)-4 (15)	HOAc (10)	0 to rt	65 ^e	89
7	Pd ₂ (dba) ₃ CHCl ₃ (5)	rac-4 (15)	HOAc (10)	rt	88 ^e	NA
8	Pd ₂ (dba) ₃ CHCl ₃ (5)	(R,R)-4 (15)	HOAc (10)	0 to rt	80 ^{e,f}	96
9	Pd ₂ (dba) ₃ CHCl ₃ (5)	(R,R)-4 (15)	HOAc (10)	0 to rt	82 ^{e,g}	97.5

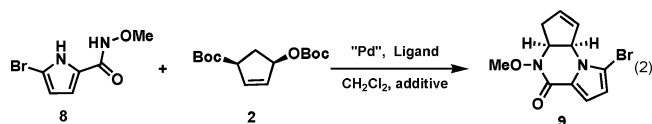
^a Unless otherwise indicated, all reactions were performed with 1.0 equiv of **2** and 1.0 equiv of **8** at 0.2 M in DCM. ^b Isolated yield. ^c Enantioselectivities were determined by chiral HPLC. ^d Single alkylation product was the main product. ^e The reaction was performed with 1.5 equiv of **2** and 1.0 equiv of **8**. ^f Another portion of Pd₂(dba)₃CHCl₃ (5 mol %), (R,R)-4 (15 mol %) was added after 1 h. ^g Another portion of Pd₂(dba)₃CHCl₃ (5 mol %), rac-4 (15 mol %) was added after 3.5 h.

successive alkylations with the *N*-methoxyamide **8**⁶ as nucleophile. Surprisingly, almost no reaction occurred when base was present (see Table 2). We hypothesized that after deprotonation, **8** could act as a good bidentate ligand for palladium, and the first ionization might be inhibited. On the basis of this hypothesis, 10 mol % of

Scheme 2. Total Synthesis of (+)-Agelastatin A^a

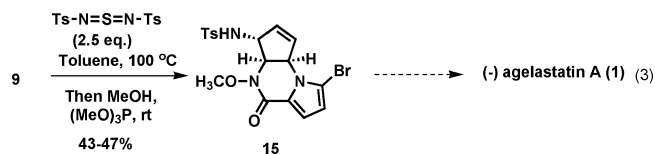
^a Conditions: (a) catalyst **14** (0.5 equiv), $\text{PhI}=\text{NTs}$ (5 equiv), 4 Å M.S., benzene, 0 °C to rt; (b) TFA (10 equiv), microwave, dioxane/water = 3/2, 150 °C, 2.5 h; (c) DMP, DCM, rt; (d) $\text{In}(\text{OTf})_3$ (0.7 equiv), DMSO, 80 °C, 6 h; (e) CH_3NCO (1.2 equiv), Cs_2CO_3 (0.2 equiv), DCM, 0 °C to rt; (f) SmI_2 (10 equiv), THF, 0 °C to rt.

HOAc was added to the reaction. To our delight, piperazinone **9** was obtained in 51% yield when $\text{Pd}_2(\text{dba})_3\text{CHCl}_3$ was used as the palladium source. After optimization, piperazinone **9** could be obtained in up to 82% yield, 97.5% ee (entry 9). Thus, by proper choice of pyrrole nucleophiles in the Pd-catalyzed AAA, access to either piperazinone regioisomer is possible.



For agelastatin A^{4,7} (Scheme 2) starting with piperazinone **7**, we envisioned aziridination of the double bond followed by transformation to the required urea. The aziridination which we anticipated to be difficult led us to explore the *N*-heterocyclic carbene complex **14**⁸ which, to our knowledge, has not previously been explored for aziridination. Indeed, this catalyst performed well for this difficult rather electron-deficient cyclopentene. Hydrolytic ring opening of **10** occurs best upon heating in a microwave. Dess–Martin oxidation then gives α -amino ketone **12**. A more efficient direct oxidative opening with DMSO, for which few cases previously existed,⁹ was explored. While following the previously reported thermal protocol proved inefficient, heating *N*-tosyl aziridine **10** in the presence of 0.7 equiv of $\text{In}(\text{OTf})_3$ ¹⁰ in DMSO at 80 °C provides the α -amino ketone **12** in excellent yield. Finally, addition of methyl isocyanate to **12**, followed by SmI_2 -mediated cleavage of *N*-OMe and *N*-Ts, completed the total synthesis of (+)-agelastatin A (**1**).¹¹ This completion also established the absolute configuration of the Pd AAA, as shown in Scheme 1.

Access to the natural (–)-enantiomer simply requires use of the *S,S*-ligand in eq 1. Alternatively, the product of the one-pot annulation **9** could also provide access to the (–)-enantiomer based upon the work of Weinreb.^{7a} To explore this prospect, piperazinone **9** was subjected to allylic amination,¹² as shown in eq 3. A single regio- and diastereomer was obtained which, by analogy to other reactions of this reagent, is assigned as **15**. Given Weinreb's synthesis, it is reasonable to propose that (–)-**1** could be accessed from **15**.



In conclusion, we have developed new classes of nucleophiles, pyrroles and *N*-alkoxyamides, for palladium-catalyzed AAA reactions. By varying the functional groups at the 2-position of pyrroles, we can efficiently and enantioselectively access either regioisomer of the piperazinones. Using one regioisomer, we completed the total synthesis of (+)-agelastatin A in a short and concise way (10 steps total), during the course of which we developed a new copper catalyst for aziridination, and an $\text{In}(\text{OTf})_3$ –DMSO system to oxidatively open an *N*-tosyl aziridine. We further show the prospect to access (–)-agelastatin A using the same enantiomer of the chiral catalyst in the Pd AAA by using the other piperazinone regioisomer.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health (GM13598) for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center for the University of California—San Francisco, supported by the NIH Division of Research Resources. We are indebted to Johnson-Matthey who generously provided palladium salts.

Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) Cordell, G. A., Ed. *The Alkaloids. Chemistry and Biology*; Academic Press: San Diego, 2005, Vol. 62 and earlier volumes in the series. (b) Hesse, M. *Alkaloids: Nature's Curse or Blessing*; Wiley-VCH: New York, 2002.
- (2) For a recent review: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Trost, B. M. *Chem. Pharm. Bull.* **2004**, *50*, 1.
- (3) (a) Gribble, G. W. *J. Nat. Prod.* **1992**, *55*, 1353. Also see: (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1. (c) Berlinck, R. G. S.; Kosuga, M. H. *Nat. Prod. Rep.* **2005**, *22*, 516 and references therein.
- (4) For the isolation and biological activities of (–)-agelastatin A: (a) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Puset, J.; Leroy, S.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1305. (b) D'Ambrosio, M.; Guerriero, A.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1994**, *77*, 1895. (c) D'Ambrosio, M.; Guerriero, A.; Ripamonti, M.; Debitus, C.; Waikadre, J.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 727. (d) Majier, L.; Thunnissen, A. M.; White, A. W.; Garnier, M.; Nikolic, M.; Tsai, L. H.; Walter, J.; Cleverley, K. E.; Salinas, P. C.; Wu, Y. Z.; Biernat, J.; Mandelkov, E. M.; Kim, S. H.; Pettit, G. R. *Chem. Biol.* **2000**, *2*, 51.
- (5) Reagents that have been tried: AlMe_3 , CIMg^iPr , KCN , MgCl_2 , $\text{Zr}(\text{OBu}^t)_4$, an *N*-heterocyclic carbene, $\text{Sn}[\text{N}(\text{TMS})_2]_2$, etc.
- (6) See Supporting Information for the synthesis of **8**.
- (7) For previous total syntheses: (a) Stien, D.; Anderson, G. T.; Chase, C. E.; Koh, Y.; Weinreb, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 9574. (b) Feldman, K. S.; Saunders, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 9060. (c) Domostoj, M. M.; Irving, E.; Scheinmann, F.; Hale, K. J. *Org. Lett.* **2004**, *6*, 2615. (d) Davis, F. A.; Deng, J. *Org. Lett.* **2005**, *7*, 621.
- (8) (a) Fructos, M. R.; Belderrain, T. R.; Nicasio, M. C.; Nolan, S. P.; Kaur, H.; Díaz-Requejo, M. M.; Pérez P. J. *J. Am. Chem. Soc.* **2004**, *126*, 10846. (b) Fructos, M. R.; Belderrain, T. R.; de Frément, P.; Scott, N. M.; Nolan, S. P.; Kaur, H.; Díaz-Requejo, M. M.; Pérez P. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5284. (c) Gawley, R. E.; Narayan, S. *Schem. Commun.* **2005**, *40*, 5109.
- (9) For *N*-aroylaziridines: (a) Heine, H. W.; Newton, T. *Tetrahedron Lett.* **1967**, *8*, 1859. For *N*-alkoxycarbonylaziridines: (b) Fujita, S.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1969**, *10*, 1677. (c) Fujita, S.; Hiyama, T.; Nozaki, H. *Tetrahedron* **1970**, *26*, 4347. We thank J. Du Bois and K. Guthikonda for drawing our attention to application of this thermal method for opening trichloroethoxysulfamoylaziridines.
- (10) Yadav, J. S.; Subba Reddy, B. V.; Mahesh Kumar, G.; Murthy, Ch. V. S. R. *Synth. Commun.* **2002**, *32*, 1797 and earlier references therein.
- (11) The spectroscopic data are identical to the reported data except for $[\alpha]_D^{20}$, +53.2° ($c = 0.13$, MeOH), while $[\alpha]_D^{20}$ for (–)-agelastatin A is –59.3° ($c = 0.13$, MeOH) given by Hong, T. W.; Jimenez, D. R.; Molinski, T. F. *J. Nat. Prod.* **1998**, *61*, 158.
- (12) (a) Sharpless, K. B.; Hori, T. *J. Org. Chem.* **1976**, *41*, 176. (b) Bussas, R.; Kresze, G. *Liebigs Ann. Chem.* **1980**, 629.

JA061105Q