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Asymmetric Construction of Quaternary Centers by Enantioselective Allylation: Application to the Synthesis of the Serotonin Antagonist LY426965

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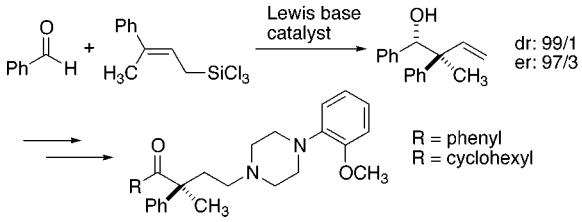
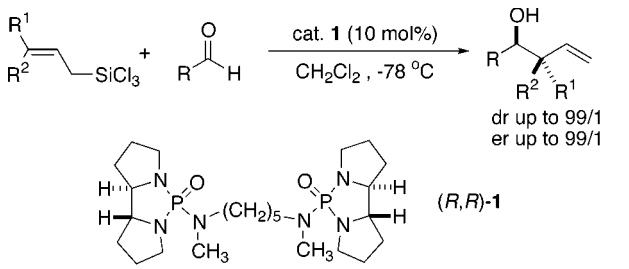
ABSTRACT



Catalytic enantioselective allylation with a chiral bisphosphoramide was applied to the synthesis of LY426965, a serotonin antagonist. The key step, addition of a 3,3-disubstituted allyltrichlorosilane to benzaldehyde, provided the adduct containing a stereogenic quaternary center with excellent diastereoselectivity and enantioselectivity.

The enantioselective addition of allylmetal reagents to aldehydes is well established as a powerful and general method for stereoselective carbon−carbon bond formation.[1] This reaction has seen wide application in organic synthesis, particularly in the total synthesis of polypropionate-derived natural products.[1b] However, few applications of this method in the construction of quaternary carbon centers have been reported.[2,3] The challenges of performing such a reaction are the following: (1) synthesis of geometrically pure 3,3-disubstituted allylmetal reagents; (2) correlation of the geometrical purity of allylmetal reagents to the diastereomeric composition of the product; (3) control of asymmetric induction with internal chiral auxiliaries or external chiral catalysts. Recently, we reported the first application of catalytic, enantioselective allylation to generate quaternary carbon centers.[2a] The addition of geometrically defined 3,3-disubstituted allylic trichlorosilanes to aldehydes is effectively catalyzed by chiral phosphoramides and provides allylation products containing quaternary centers with excellent diastereoselectivities and enantioselectivities (Scheme 1). The ease of preparation of allylic trichlorosilanes and catalyst makes this method very attractive for use in

Scheme 1



(1) For recent review on allylmetal additions, see: (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 10. (b) Chelmer, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J.; Ed.; Wiley-VCH: Weinheim, 2000; Chapter 11. (c) *Stereoselective Synthesis, Methods of Organic Chemistry* (Houben-Weyl), Edition E21; Helmchen, G., Hoffmann, R., Mulzer, J., Schaumann, E., Eds.; Thieme; Stuttgart, 1996; Vol. 3, pp 1357−1602. (d) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

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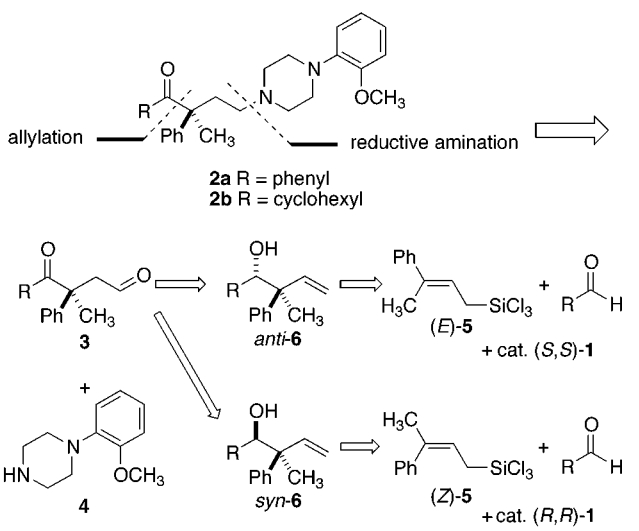
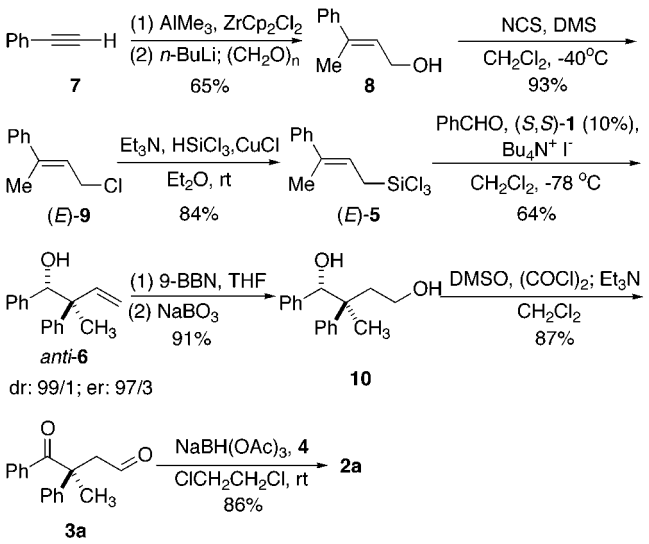
synthesis. We report herein an application of this method to asymmetric synthesis of 5-hydroxytryptamine$_{1A}$ antagonists **2**[4] (Scheme 2) which bear stereogenic quaternary centers.

Scheme 2



(*S*)-1,2-Diphenyl-4-[4-(2-methoxyphenyl)-1-piperazinyl]-2-methyl-1-butanone (**2a)** and (*S*)-1-cyclohexyl-4-[4-(2-methoxyphenyl)-1-piperazinyl]-2-methyl-2-phenyl-1-butanone (**2b**) (LY426965) belong to a family of arylpiperazines that are effective pharmaceutical agents for the treatment of conditions related to or affected by the serotonin 1A receptor.[4] In particular, LY426965 (**2b**) is a full antagonist of the serotonin 1A receptor and has no partial agonist properties. Preclinical studies indicated that LY426965 is a selective, full 5-HT1A antagonist that may have clinical use as pharmacotherapy for smoking cessation and depression related disorders. Structurally, these compounds contain quaternary centers α to a carbonyl group, the synthesis of which represents a long-standing challenge.[3] A common approach to this problem involves asymmetric alkylation of corresponding enolate.[5] However, this method has not found success with acyclic substrates presumably because of the difficulties in controlling the enolate geometry. We envisioned that the enantioselective allylation reaction would provide an alternative and efficient approach to this type of structure.

Scheme 3



The retrosynthetic analysis of **2** shown in Scheme 2 identifies two key disconnections. The first is construction of the C−N bond by combining keto aldehyde **3** with commercially available arylpiperazine **4** by a reductive amination. The second is the construction of the quaternary center by addition of allyltrichlorosilane **5** to the appropriate aldehyde. In this case, the allylation adduct, homoallyl alcohol **6**, contains all the necessary carbon units for synthesis of **2** as well as functionalilty for further manipulations. Because the hydroxyl group in **6** will be oxidized to provide the carbonyl group in the final product **2**, its configuration in the allylation adduct, although highly controlled, is irrelevant for this application. Therefore, the requisite *S* configuration of the quaternary center can be obtained by combination of (*E*)-trichlorosilane (*E*)-**5** and catalyst (*S*,*S*)-**1** or (*Z*)-trichlorosilane (*Z*)-**5** with catalyst (*R*,*R*)-**1**. Preliminary studies from these laboratories revealed that substituents on the double bond significantly affect the reactivity and selectivity of the allylic trichlorosilane. For example, it was found a *Z*-methyl substituent has a beneficial effect on the enantioselectivity, as evidenced by highly selective *syn*-butenylation and prenylation process.[2a] On the other hand, a *Z*-phenyl substituent is deleterious for the reaction. Under standard allylation conditions, the addition of (*Z*)-cinnamyltrichlorosilane to benzaldehyde resulted in only a trace amount of the desired adduct. Accordingly, we selected the combination of (*E*)-trichlorosilane (*E*)-**5** and catalyst (*S*,*S*)-**1** for the synthesis of **6**.

The synthesis of **2a** (Scheme 3) commences with carbometalation of phenylacetylene **7** followed by trapping the vinylalane with formaldehyde to provide the allylic alcohol **8** in geometrically pure form and modest yield.[6] Alcohol **8**

(2) For the most recent advance in chiral Lewis-base-catalyzed enantioselective allylation, see: (a) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488 and reference therein. While this manuscript was in preparation, Hall reported the generation of quaternary centers using chiral allylboronate reagents. (b) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 898.

(3) For reviews on enantioselective construction of quaternary stereocenters, see: (a) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (c) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (d) Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(4) (a) Rasmussen, K.; Calligaro, D. O.; Czachura, J. F.; Dreshfield-Ahmad, L. J.; Evans, D. C.; Hemrick-Luecke, S. K.; Kallman, M. J.; Kendrick, W. T.; Leander, J. D.; Nelson, D. L.; Overshiner, C. D.; Wainscott, D. B.; Wolff, M. C.; Wong, D. T.; Branchek, T. A.; Zgombick, J. M.; Xu, Y.-C. *J. Pharmacol. Exp. Ther.* **2000**, *294*, 688. (b) Kohlman, T. D.; Xu, Y.-C.; Godfrey, A. G.; O′Toole, J. C.; Zhang, T. Y. Eur. Pat. Appl. 1999, 47pp.

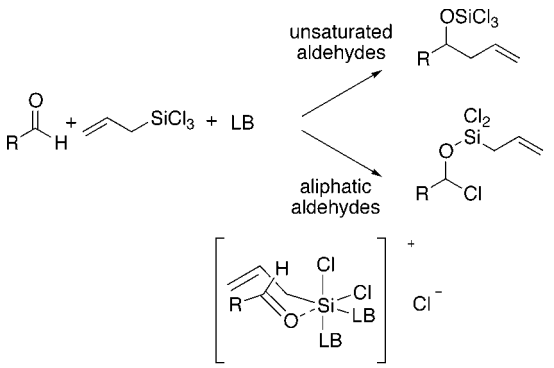
(5) For recent examples, see: (a) Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (b) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2000**, 1107.

(6) Okudado, N.; Negishi, E.-I. *Tetrahedron Lett.* **1978**, *27*, 2357.

was converted by the Corey−Kim procedure to the corresponding chloride **9**, which was then treated with triethylamine, trichlorosilane, and a catalytic amount of CuCl to provide allyllic trichlorosilane (*E*)-**5** also in geometrically pure form and in 81% yield for two steps. The addition of (*E*)-**5** to benzaldehye in the presence of 10 mol % of (*S*,*S*)-**1** provided the key intermediate, *anti*-**6**, with 99/1 dr and 97/3 er. It was found that addition of 0.2 equiv of *n*-$Bu_4N^+I^-$ slightly improved the reaction yield without affecting the selectivity.[7] Hydroboration/oxidation of the vinyl group and Swern oxidation of the diol **10** provided the keto aldehyde **3a** in 80% yield from **6**. Finally, the piperazine moiety **4** was appended by reductive amination of **3a** with **4** and sodium triacetoxyborohydride to provide **2a** in 86% yield.

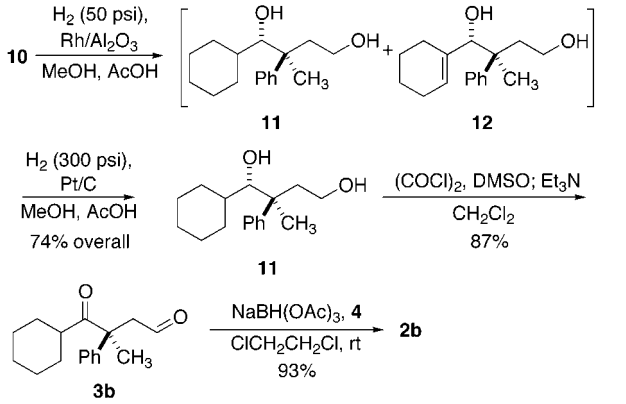
The synthesis of LY426965 (**2b**) required the use of cyclohexanecarboxaldehyde as the electrophile in the allylation reaction. Unfortunately, when this aldehyde was employed under the standard allylation conditions, no desired product was formed. Careful analysis of the reaction mixture by ^1H NMR spectroscopy revealed that an α-chloro silyl ether was formed instead (Scheme 4).[8] Previous mechanistic

Scheme 4



investigations have found that all reactions of chlorosilanes studied to date involved ionization of chloride ions to create cationic silicon species.[9] In the reaction with aliphatic aldehydes, the combination of the chloride ion and the aldehyde results in the formation of an α-chloro silyl ether that precludes addition of the allylating agent. While attempts to solve the problem with aliphatic aldehyde by effecting the equilibrium between the α-chloro silyl ether and the aldehyde were ongoing, we envisioned that **2b** could also be synthesized from diol **10** through selective saturation of the benzylic alcohol. To this end, diol **10** was subjected to a variety of hydrogenation conditions, which involved variations in hydrogen pressure, catalyst, solvent, temperature, and acid additive. Ultimately, selective hydrogenation was achieved in 74% yield by a two-step procedure (Scheme 5). The phenyl group at the 1-position was first reduced to a mixture of cyclohexyl diol **11** and cyclohexenyl diol **12** under 50 psi of hydrogen using Rh/Al_2O_3 as the catalyst. Although a prolonged reaction time led to the hydrogenation of the other phenyl group, the cyclohexenyl diol **12** could be selective reduced under 300 psi of hydrogen using Pt/carbon as the catalyst to give **11** in 74% yield. Finally, oxidation of the diol followed by reductive amination provided LY426965 (**2b**).

Scheme 5



In conclusion, the application of a catalytic enantioselective allylation catalyzed by a chiral phosphoramide has been demonstrated in the asymmetric synthesis of serotonin anagonists **2a** and **2b** (LY426965), which contain α-carbonyl quaternary carbon centers. These syntheses demonstrated not only the efficiency of this allylation method in the generation of quaternary centers but also the versatile functionality provided in such allylation adducts. Extension of the addition of allyltrichlorosilanes to other electrophiles and applications in organic synthesis are currently under investigation.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2**−**11**. This material is available via the Internet at http://pubs.acs.org.

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(7) Short, J. D.; Attenoux, S.; Berrisford, D. J. *Tetrahedron Lett.* **1997**, *38*, 2351.

(8) Formation of chlorohydrins has also been observed in other reactions of chlorosilanes with aldehydes: Wynn, T.; Ghosh, S. K. Unpublished results from these laboratories.

(9) For mechanistic studies, see: (a) Denmark, S. E.; Su, X.; Nishigaichi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12990. (b) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2000**, *122*, 12021.