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Palladium- or Iridium-Catalyzed Allylic Substitution of Guanidines: Convenient and Direct Modification of Guanidines

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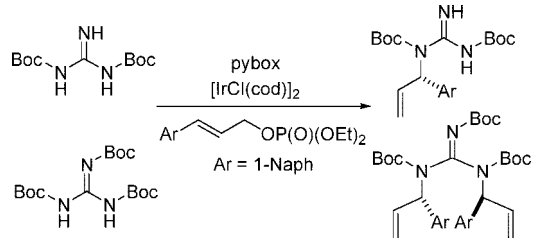

As a convenient and direct functionalization of guanidines, the transition metal-catalyzed allylic substitution of guanidines was studied. The guanidine derivatives bearing two electron-withdrawing substituents acted as reactive nucleophiles in the allylic substitution to give the monoallylated products. The double allylic substitution was achieved by using tri-Boc-guanidine bearing three electron-withdrawing substituents as a nucleophile to give the diallylated products. The regiocontrol in the allylic substitution of unsymmetrical allylic substrates has been investigated by employing the palladium or iridium catalysts. The iridium complex of chiral pybox ligand allowed the regio- and enantioselective allylic substitution. Asymmetric double allylic substitution of tri-Boc-guanidine with phosphate bearing the 1-naphthyl group gave the diallylated product with high diastereo-, regio-, and enantioselectivities.

Introduction

Guanidine functionality is found in many biologically active natural products and pharmaceutically relevant compounds, and it plays a key role in their activities.[1,2] In addition to pharmaceutical roles, the guanidines have been recently utilized in organic synthesis as general strong bases and organocatalysts.[3] The utility of guanidine-derived ionic liquids was also shown in organic synthesis.[4] Hence, a significant number of methods and reagents for preparation of guanidines have been developed.[5−9] Traditionally, guanidines are prepared by the reaction of amines with cyanamides or *S*-alkylisothiouronium salts;[10] thus, the synthetic studies of guanidines have mainly focused on the development of efficient guanylating-agents of amine and diamine precursors.[11]

In contrast to the numerous studies on constructing the guanidine structures,[5−11] the direct modification of guanidines has received much less attention. Until recently, there have been only two methods those are commonly used for the function-

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(1) (a) Berlinck, R. G. S. *Fortschr. Chem. Org. Naturst.* **1995**, *66*, 119. (b) Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, *16*, 339.

(2) For reviews on guanidine-containing natural products, see: (a) Aron, Z. D.; Overman, L. E. *Chem. Commun.* **2004**, 253. (b) Heys, L.; Moore, C. G.; Murphy, P. J. *Chem. Soc. Rev.* **2000**, 57.

(3) For examples of strong bases or organocatalysts containing guanidine functionality, see: (a) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 9228. (b) Leow, D.; Lin, S.; Chittimalla, S. K.; Fu, X.; Tan, C.-T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5641. (c) Ryoda, A.; Yajima, N.; Haga, T.; Kumamoto, T.; Nakanishi, W.; Kawahata, M.; Yamaguchi, K.; Ishikawa, T. *J. Org. Chem.* **2008**, *73*, 133. (d) Takada, K.; Takemura, N.; Cho, K.; Sohtome, Y.; Nagasawa, K. *Tetrahedron Lett.* **2008**, *49*, 1623. (e) Terada, M.; Ikehara, T.; Ube, H. *J. Am. Chem. Soc.* **2007**, *129*, 14112. (f) Fu, X.; Jiang, Z.; Tan, C.-T. *Chem. Commun.* **2007**, 5058. (g) Ye, W.; Jiang, Z.; Zhao, Y.; Goh, S. L. M.; Leow, D.; Soh, Y.-T.; Tan, C.-H. *Adv. Synth. Catal.* **2007**, *349*, 2454. (h) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044. (i) Shen, J.; Nguyen, T. T.; Goh, Y.-P.; Ye, W.; Fu, X.; Xu, J.; Tan, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 13692. (j) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454. (k) Ye, W.; Leow, D.; Goh, S. L. M.; Tan, C.-T.; Chian, C.-H.; Tan, C.-H. *Tetrahedron Lett.* **2006**, *47*, 1007. (l) Kitani, Y.; Kumamoto, T.; Isobe, T.; Fukuda, K.; Ishikawa, T. *Adv. Synth. Catal.* **2005**, *347*, 1653. (m) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643. (n) Allingham, M. T.; Howard-Jones, A.; Murphy, P. J.; Thomas, D. A.; Caulkett, P. W. R. *Tetrahedron Lett.* **2003**, *44*, 8677. (o) Ishikawa, T.; Isobe, T. *Chem. Eur. J.* **2002**, *8*, 552. (p) Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T. *Chem. Commun.* **2001**, 245. (q) Isobe, T.; Fukuda, K.; Araki, Y.; Ishikawa, T. *Chem. Commun.* **2001**, 243. (r) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.

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alization of guanidines. The first method involves the reaction of guanidine with alcohols under Mitsunobu reaction conditions.[12] The second method is the alkylation of guanidine with electrophiles such as alkyl halides under basic conditions.[13] Recently, several new methods for the modification of guanidines have been reported.[14,15] However, the transition metal-catalyzed modification of guanidines has not been widely studied,[16] probable due to their strong basic character and high metal-coodination ability.[17] We focused our attention on the transition metal-catalyzed allylic substitution of guanidines from the point of view of synthetic application. Our recent studies show that the nitrogen atom of guanidine derivatives having two *N*-electron-withdrawing substituents acted as a reactive nucleophile in the allylic substitution.[18,19] In this paper, we describe full details of a convenient and direct modification of guanidines based on palladium- or iridium-catalyzed allylic substitution to address the functionalized guanidines. As shown below, this reaction is extremely facile and gives the allylated guanidines in good yields under mild reaction conditions. Regio- and enantioselective allylic substitution was also achieved by using the iridium complex of the chiral pybox ligand.

Results and Discussion

Palladium-Catalyzed Allylic Substitution of Guanidines. The utility of guanidines in allylic substitution has not been investigated, though guanidines are attractive reagents for the synthesis of functionalized allylic compounds. Our methodology utilizes guanidines as a nucleophile in the transition metal-catalyzed allylic substitution. Significant advances were achieved with the introduction of electron-withdrawing substituents on nitrogen atoms of guanidine that allowed for the direct synthesis

(4) (a) Shah, J.; Blumenthal, H.; Yacob, Z.; Liebscher, J. *Adv. Synth. Catal.* **2008**, *350*, 1267. (b) Li, S.; Lin, Y.; Xie, H.; Zhang, S.; Xu, J. *Org. Lett.* **2006**, *8*, 391. (c) Jiang, T.; Gao, H.; Han, B.; Zhao, G.; Chang, Y.; Wu, W.; Gao, L.; Yang, G. *Tetrahedron Lett.* **2004**, *45*, 2699.

(5) For recent synthetic studies on guanidine-containing natural products, see:(a) Vergne, C.; Appenzeller, J.; Ratinaud, C.; Martin, M.-T.; Debitus, C.; Zaparucha, A.; Al-Mourabit, A. *Org. Lett.* **2008**, *10*, 493. (b) Moore, C. G.; Murphy, P. J.; Williams, H. L.; McGown, A. T.; Smith, N. K. *Tetrahedron* **2008**, *64*, 3176. (c) Shirai, A.; Miyata, O.; Tohnai, N.; Miyata, M.; Procter, D. J.; Sucunza, D.; Naito, T. *J. Org. Chem.* **2008**, *73*, 4464. (d) Lanman, B. A.; Overman, L. E.; Paulini, R.; White, N. S. *J. Am. Chem. Soc.* **2007**, *129*, 12896. (e) Tsuchiya, S.; Sunazuka, T.; Hirose, T.; Mori, R.; Tanaka, T.; Iwatsuki, M.; Omura, S. *Org. Lett.* **2006**, *8*, 5577. (f) Li, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2006**, *47*, 385. (g) Garrido-Hernandez, H.; Nakadai, M.; Vimolratana, M.; Li, Q.; Doundoulakis, T.; Harran, P. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 765. (h) Ravinder, K.; Reddy, A. V.; Krishnaiah, P.; Ramesh, P.; Ramakrishna, S.; Laatsch, H.; Venkateswarlu, Y. *Tetrahedron Lett.* **2005**, *46*, 5475. (i) DeMong, D. E.; Williams, R. M. *J. Am. Chem. Soc.* **2003**, *125*, 8561. (j) Moore, C. G.; Murphy, P. J.; Williams, H. L.; McGown, A. T.; Smith, N. K. *Tetrahedron Lett.* **2003**, *44*, 251. (k) Nagasawa, K.; Georgieva, A.; Koshino, H.; Nakata, T.; Kita, T.; Hashimoto, Y. *Org. Lett.* **2002**, *4*, 177. (l) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913. (m) Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179. (n) Snider, B. B.; Ahn, Y.; O'Hare, S. M. *Org. Lett.* **2001**, *3*, 4217. (o) Batey, R. A.; Powell, D. A. *Chem. Commun.* **2001**, 2362. (p) Exposito, A.; Fernandez-Suarez, M.; Iglesias, T.; Munoz, L.; Riguera, R. *J. Org. Chem.* **2001**, *66*, 4206. (q) Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **2000**, *122*, 4893. (r) Coffey, D. S.; Overman, L. E.; Stappenbeck, F. *J. Am. Chem. Soc.* **2000**, *122*, 4904.

(6) For synthetic studies on cylindrospermopsin, see: (a) Looper, R. E.; Runnegar, M. T. C.; Williams, R. M. *Tetrahedron* **2006**, *62*, 4549. (b) Looper, R. E.; Runnegar, M. T. C.; Williams, R. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3879. (c) Looper, R. E.; Williams, R. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2930. (d) Heintzelman, G. R.; Fang, W.-K.; Keen, S. P.; Wallace, G. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 3939. (e) White, J. D.; Hansen, J. D. *J. Am. Chem. Soc.* **2002**, *124*, 4950. (f) Xie, C.; Runnegar, M. T. C.; Snider, B. B. *J. Am. Chem. Soc.* **2000**, *122*, 5017.

(7) For synthetic studies on batzelladines, see: (a) Evans, P. A.; Qin, J.; Robinson, J. E.; Bazin, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 7417. (b) Arnold, M. A.; Day, K. A.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 13255. (c) Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2006**, *128*, 2604. (d) Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2006**, *128*, 2594. (e) Shimokawa, J.; Ishiwata, T.; Shirai, K.; Koshino, H.; Tanatani, A.; Nakata, T.; Hashimoto, Y.; Nagasawa, K. *Chem. Eur. J.* **2005**, *11*, 6878. (f) Cohen, F.; Collins, S. K.; Overman, L. E. *Org. Lett.* **2003**, *5*, 4485. (g) Ishiwata, T.; Hino, T.; Koshino, H.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Org. Lett.* **2002**, *4*, 2921. (h) Duron, S. G.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 1551. (i) Cohen, F.; Overman, L. E.; Ly, S. K. *Org. Lett.* **1999**, *1*, 2169. (j) Franklin, A. S.; Ly, S. K.; Mackin, G. H.; Overman, L. E.; Shaka, A. J. *J. Org. Chem.* **1999**, *64*, 1512.

(8) For synthetic studies on tetrodotoxin, see: (a) Sato, K.-I.; Akai, S.; Sugita, N.; Ohsawa, T.; Kogure, T.; Shoji, H.; Yoshimura, J. *J. Org. Chem.* **2005**, *70*, 7496. (b) Nishikawa, T.; Urabe, D.; Isobe, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4782. (c) Nishikawa, T.; Urabe, D.; Yoshida, K.; Iwabuchi, T.; Asai, M.; Isobe, M. *Chem. Eur. J.* **2004**, *10*, 452. (d) Nishikawa, T.; Urabe, D.; Yoshida, K.; Iwabuchi, T.; Asai, M.; Isobe, M. *Org. Lett.* **2002**, *4*, 2679. (e) Hinmam, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510.

(9) For synthetic studies on saxitoxin, see: (a) Iwamoto, O.; Koshino, H.; Hashizume, D.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 8625. (b) Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964. (c) Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, *128*, 3926.

(10) (a) Kampf, A. *Chem. Ber.* **1904**, 1681. (b) Davis, T. L. *Org. Synth.* **1927**, *7*, 46. (c) Rasmussen, C. R.; Villani, F. J., Jr.; Reynolds, B. E.; Plampin, J. N.; Hood, A. R.; Hecker, L. R.; Nortey, S. O.; Hanslin, A.; Costanzo, M. J.; Howse, R. M.; Molinari, A. J. *Synthesis* **1988**, 460. (d) Braun, C. E. *J. Am. Chem. Soc.* **1993**, *55*, 1280.

(11) (a) Maryanoff, C. A.; Stanzione, R. C.; Plampin, J. N.; Mills, J. E. *J. Org. Chem.* **1986**, *51*, 1882. (b) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497. (c) Katritzky, A. R.; Parris, R. L.; Allin, S. M. *Synth. Commun.* **1995**, *25*, 1173. (d) Bergeron, R. J.; McManis, J. S. *J. Org. Chem.* **1987**, *52*, 1700. (e) Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933. (f) Verdini, A. S.; Lucietto, P.; Fossati, G.; Giordani, C. *Tetrahedron Lett.* **1992**, *33*, 6541. (g) Kowalski, J.; Lipton, M. A. *Tetrahedron Lett.* **1996**, *37*, 5839. (h) Kent, D. R.; Cody, W. L.; Doherty, A. M. *Tetrahedron Lett.* **1996**, *37*, 8711. (i) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677.

(12) (a) Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432. (b) Chen, L.; Trilles, R. V.; Tilley, J. W. *Tetrahedron Lett.* **1995**, *36*, 8715. (c) Dodd, D. S.; Kozikowski, A. P. *Tetrahedron Lett.* **1994**, *35*, 977.

(13) (a) Powell, D. A.; Ramsden, P. D.; Batey, R. A. *J. Org. Chem.* **2003**, *68*, 2300. (b) Dennis, M.; Hall, L. M.; Murphy, P. J.; Thornhill, A. J.; Nash, R.; Winters, A. L.; Hursthouse, M. B.; Light, M. E.; Horton, P. *Tetrahedron Lett.* **2003**, *44*, 3075. (c) Isobe, T.; Fukuda, K.; Yamaguchi, K.; Seki, H.; Tokunaga, T.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7779. (d) Vaidyanathan, G.; Zalutsky, M. R. *J. Org. Chem.* **1997**, *62*, 4867. (e) Ko, S. Y.; Lerpiniere, J.; Christofi, A. M. *Synlett* **1995**, 815.

(14) Oxidative addition of guanidine, see: (a) Schroif-Gregoire, C.; Travert, N.; Zaparucha, A.; Al-Mourabit, A. *Org. Lett.* **2006**, *8*, 2961. (b) Abou-Jneid, R.; Ghoulami, S.; Martin, M.-T.; Dau, E. T. H.; Travert, N.; Al-Mourabit, A. *Org. Lett.* **2004**, *6*, 3933. (c) del Rayo Sanchez Salvatori, M.; Abou-Jneid, R.; Ghoulami, S.; Martin, M.-T.; Zaparucha, A.; Al-Mourabit, A. *J. Org. Chem.* **2005**, *70*, 8208.

(15) (a) Zeghida, W.; Debray, J.; Chierici, S.; Dumy, P.; Demeunynck, M. *J. Org. Chem.* **2008**, *73*, 2473. (b) Albrecht, C.; Barnes, S.; Böckemeier, H.; Davies, D.; Dennis, M.; Evans, D. M.; Fletcher, M. D.; Jones, I.; Leitmann, V.; Murphy, P. J.; Rowles, R.; Nash, R.; Stephenson, R. A.; Horton, P. N.; Hursthouse, M. B. *Tetrahedron Lett.* **2008**, *49*, 185. (c) Nilsson, B. L.; Overman, L. E. *J. Org. Chem.* **2006**, *71*, 7706. (d) Zhao, J.-F.; Xie, C.; Xu, S.-Z.; Ding, M.-W.; Xiao, W.-J. *Org. Biomol. Chem.* **2006**, 130. (e) Nishiwaki, N.; Ogihara, T.; Takami, T.; Tamura, M.; Ariga, M. *J. Org. Chem.* **2004**, *69*, 8382. (f) Zapf, C. W.; Goodman, M. *J. Org. Chem.* **2003**, *68*, 10092. (g) Lasri, J.; Gonzalez-Rosende, M. E.; Sepulveda-Arques, J. *Org. Lett.* **2003**, *5*, 3851. (h) Overman, L. E.; Wolfe, J. P. *J. Org. Chem.* **2001**, *66*, 3167. (i) McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520. (j) Esser, F.; Ehrengart, P.; Ignatow, H. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1153. (k) Okawa, T.; Kawase, M.; Eguchi, S.; Kakehi, A.; Shiro, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2277.

(16) For metal-catalyzed reactions of guanidines, see: (a) Hövelmann, C. H.; Streuff, J.; Brelot, L.; Muñiz, K. *Chem. Commun.* **2008**, 2334. (b) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.* **2006**, *8*, 1073. Miller, C. A.; Batey, R. A. *Org. Lett.* **2004**, *6*, 699. (c) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133.

(17) For examples of guanidine as ligands, see: (a) Ajellal, N.; Lyubov, D. M.; Sinenkov, M. A.; Fukin, G. K.; Cherkasov, A. V.; Thomas, C. M.; Carpentier, J.-F.; Trifonov, A. A. *Chem. Eur. J.* **2008**, *14*, 5440. (b) Li, S.; Lin, Y.; Cao, J.; Zhang, S. *J. Org. Chem.* **2007**, *72*, 4067. (c) Pi, C.; Zhu, Z.; Weng, L.; Chen, Z.; Zhou, X. *Chem. Commun.* **2007**, 2190. (d) Trifonov, A. A.; Skvortsov, G. G.; Lyubov, D. M.; Skorodumova, N. A.; Fukin, G. K.; Baranov, E. V.; Glushakova, V. N. *Chem. Eur. J.* **2006**, *12*, 5320. (e) Köhn, U.; Schulz, M.; Görls, H.; Anders, E. *Tetrahedron: Asymmetry* **2005**, *16*, 2125. (f) Holland, A. W.; Bergman, R. G. *J. Am. Chem. Soc.* **2002**, *124*, 9010. (g) Foley, S. R.; Yap, G. P. A.; Richeson, D. S. *Chem. Commun.* **2000**, 1515. (h) Thirupathi, N.; Yap, G. P. A.; Richeson, D. S. *Chem. Commun.* **1999**, 2483.

(18) Miyabe, H.; Matsumura, A.; Yoshida, K.; Yamauchi, M.; Takemoto, Y. *Lett. Org. Chem.* **2004**, *1*, 119.

(19) Relative palladium-catalyzed reaction was reported, see Zhou, H.-B.; Alper, H. *Tetrahedron* **2004**, *60*, 73.

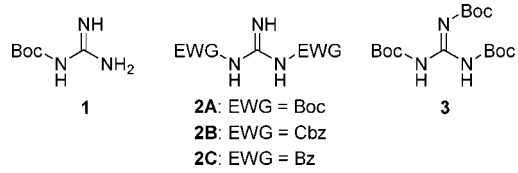
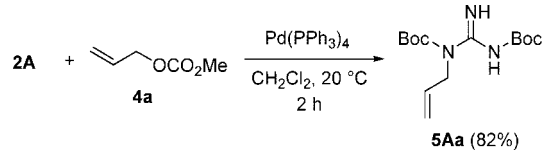


FIGURE 1. Guanidines **1**−**3** having electron-withdrawing substituents.

SCHEME 1. Palladium-Catalyzed Allylic Substitution of Guanidine 2A



of protected guanidines. We recently observed that hydroxylamines having an *N*-electron-withdrawing substituent acted as a reactive nucleophile in allylic substitution.[20a] A similar trend was observed in our recent studies on *O*-allylic substitution of oximes.[20b,c] On the basis of these results, we suggest that electron-withdrawing substituents would be important for the nucleophilic property of guanidines. Therefore, the substrates of choice were guanidines **1**−**3** bearing electron-withdrawing substituents (Figure 1). Additionally, the advantage of *N*-protected guanidines is that the purification of products by chromatography has been facile due to their less polar nature.

The viability of guanidines in the palladium-catalyzed reaction is the first focus of our effort.[21] The reaction of guanidines **1** and **2A** with allylic carbonate **4a** was investigated in the presence of $Pd(PPh_3)_4$. However, mono-Boc-guanidine **1**[22] did not exhibit a good reactivity toward the π-allyl palladium complex.[18] In contrast, guanidine **2A** bearing two Boc groups has shown excellent reactivity (Scheme 1). In the presence of $Pd(PPh_3)_4$ (8 mol %), the reaction of guanidine **2A** with allylic carbonate **4a** (2.2 equiv) was run in CH_2Cl_2 at 20 °C for 2 h. ^{1}H NMR measurement of the crude product showed almost quantitative conversion of **2A** to the monoallylated product **5Aa** with excellent selectivity. The product **5Aa** was obtained in 82% yield after purification by preparative TLC. The structure of **5Aa** was confirmed by the comparison of spectra of authentic allylated guanidine.[13a] The allylation took place selectively at the nitrogen atom bearing the Boc group. It is also noteworthy that the formation of diallylated product was not observed under the reaction conditions.

We next investigated the palladium-catalyzed reaction of guanidines **1**−**2B** with allylic carbonate **4b** and allylic acetate

SCHEME 2. Palladium-Catalyzed Allylic Substitution of Guanidine Derivatives

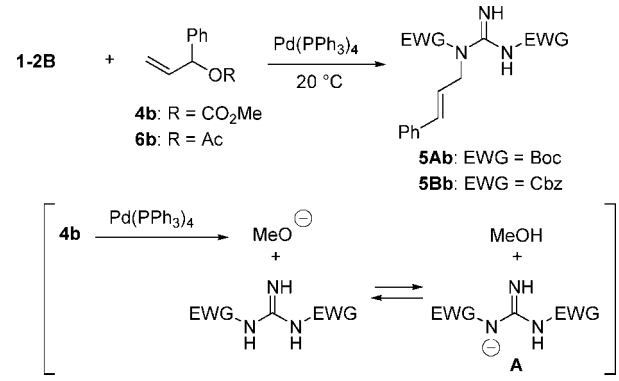


TABLE 1. The Palladium-Catalyzed Allylic Substitution of Guanidines 1−2B[a]

entry	guanidine	reagent	time (h)	product	yield (%)
1	**1**	**4b**	24		NR
2	**2A**	**4b**	2	**5Ab**	86
3	**2A**	**6b**	24		NR
4	**2B**	**4b**	2	**5Bb**	88
5	**2B**	**6b**	24		NR

[a] Reactions were carried out with guanidine **1**−**2B** and reagent **4b** or **6b** (2.2 equiv) in the presence of $Pd(PPh_3)_4$ (8 mol%) in CH_2Cl_2 at 20 °C.

6b having a phenyl group in CH_2Cl_2 (Scheme 2). In the case of the reaction of mono-Boc-guanidine **1** with allylic carbonate **4b**, no reaction occurred after 24 h of stirring at 20 °C (Table 1, entry 1). In contrast to **1**, the di-Boc-guanidine **2A** worked well as a nucleophile. In the presence of $Pd(PPh_3)_4$ (8 mol %), a reaction of guanidine **2A** with allylic carbonate **4b** (2.2 equiv) gave the linear product **5Ab** in 86% yield, after 2 h of stirring (entry 2). These observations suggest that the stability of conjugate base **A** of guanidine would be of key importance in the present reaction. Thus, a rational hypothesis of this reaction is that guanidine **2A** would be effectively deprotonated by methoxide generated from carbonate **4b**. The solvent influenced the reactivity of guanidines. In regard to the solvent effect, the replacement of CH_2Cl_2 with MeCN also gave a good result, while nonpolar solvents such as toluene gave a poor yield of product **5Ab**. The allylic substitution with acetate **6b** did not take place (entry 3). The observed beneficial effect of carbonate **4b** over acetate **6b** is noteworthy. This observation suggests that acetate anion, generated from palladium and acetate **6b**, is less effective for activation of guanidine **2A** as a base. Although the effect of bases on the reaction of guanidine **2A** with acetate **6b** was investigated by employing K_2CO_3, Et_2Zn, and KOH, only low yields of product **5Ab** were observed due to the formation of insoluble complex from guanidine **2A** and bases. Thus, the combination of allylic carbonates and guanidines having two electron-withdrawing substituents is a highly promising approach to the direct functionalization of guanidines. We next investigated the reaction of di-Cbz-guanidine **2B** (entries 4 and 5). As expected, the di-Cbz-guanidine **2B** worked well and a similar trend was observed. The selective formation of monoallylated product **5Bb** was observed in the reaction with carbonate **4b** (entry 4), although the acetate **6b** was less effective (entry 5).

Iridium-Catalyzed Allylic Substitution of Guanidines. The regiocontrol has been of great importance in allylic substitution.[23] Recently, the iridium-catalyzed regioselective allylic

(20) For the allylic substitution with hydroxylamines having an *N*-electron-withdrawing substituent or oximes; see: (a) Miyabe, H.; Yoshida, K.; Matsumura, A.; Yamauchi, M.; Takemoto, Y. *Synlett* **2003**, 567. (b) Miyabe, H.; Matsumura, A.; Yoshida, K.; Yamauchi, M.; Takemoto, Y. *Synlett* **2004**, 2123. (c) Miyabe, H.; Yoshida, K.; Reddy, V. K.; Matsumura, A.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 5630.

(21) For reviews on allylic substitution, see: (a) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (d) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. 2, pp 833−884. (e) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203. (f) Trost, B. M.; Lee, C. B. In *Catalytic Asymmetric Synthesis II*; Ojima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; pp 593−650. (g) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1. (h) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (i) Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2580. (j) Trost, B. *J. Org. Chem.* **2004**, *69*, 5813. (k) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258.

(22) Zapf, C. W.; Creighton, C. J.; Tomioka, M.; Goodman, M. *Org. Lett.* **2001**, *3*, 1133.

SCHEME 3. Iridium-Catalyzed Allylic Substitution of Guanidine Derivatives

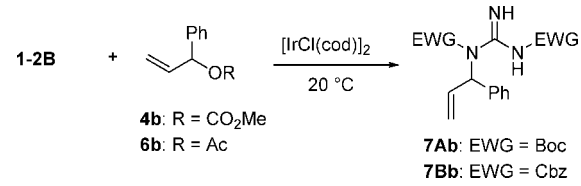


TABLE 2. The Iridium-Catalyzed Allylic Substitution of Guanidines 1−2B[a]

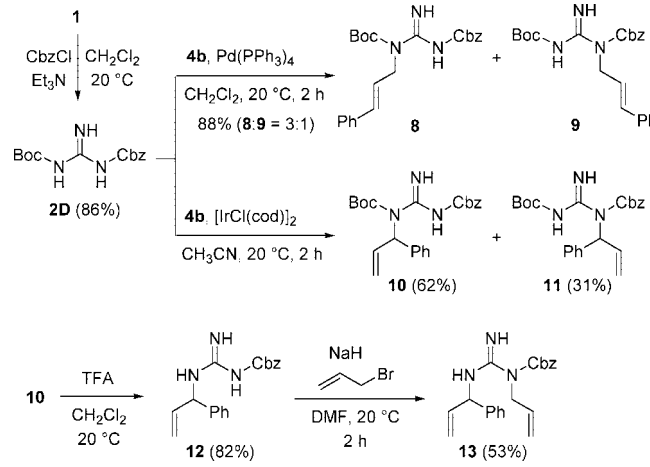
entry	guanidine	reagent	solvent	time (h)	product	yield (%)
1	**1**	**4b**	CH_2Cl_2	24		NR
2	**2A**	**4b**	CH_2Cl_2	3	**7Ab**	63
3	**2A**	**4b**	CH_3CN	2	**7Ab**	88
4	**2A**	**6b**	CH_3CN	24		NR
5	**2B**	**4b**	CH_3CN	2	**7Bb**	87
6	**2B**	**6b**	CH_3CN	24		NR

[a] Reactions were carried out with guanidine **1**−**2B** and reagent **4b** or **6b** (2.2 equiv) in the presence of $[IrCl(cod)]_2$ (4 mol %) at 20 °C.

amination of unsymmetrical acyclic substrates giving the branched products was studied by Takeuchi's group.[24] Therefore, the iridium-catalyzed allylic substitution has been a subject of current interest.[23,25] Recently, important contributions in this area come from Helmchen and Hartwig.[26,27]

For the selective preparation of the branched products, the iridium-catalyzed reaction was investigated (Scheme 3). Although the mono-Boc-guanidine **1** did not work (Table 2, entry 1), the guanidines **2A** and **2B** bearing two electron-withdrawing substituents have shown a good reactivity. The reaction of di-Boc-guanidine **2A** with allylic carbonate **4b** (2.2 equiv) was run in CH_2Cl_2 in the presence of $[IrCl(cod)]_2$ (4 mol %) at 20 °C (entry 2). As expected, the reaction proceeded smoothly with excellent regioselectivity to give the branched product **7Ab** in 63% yield without the formation of the linear product **5Ab**. The formation of diallylated products was not observed in the iridium-catalyzed reaction as well as the palladium-catalyzed reaction. The reaction proceeded effectively in CH_3CN to give the branched product **7Ab** in 88% yield, after being stirred for 2 h (entry 3). The use of toluene as solvent led to a prolonged reaction time. The reaction of di-Cbz-guanidine **2B** with carbonate **4b** afforded a good yield of the branched product **7Bb** with excellent regioselectivities (entry 5). The scope of suitable electrophiles was limited to carbonates; thus, acetate **6b** did not work (entries 4 and 6).

SCHEME 4. Reaction of Unsymmetrical Guanidine



For the further modification of guanidines, the reaction of unsymmetrical guanidine **2D** bearing different electron-withdrawing substituents was tested. Guanidine **2D** was prepared from mono-Boc-guanidine **1** (Scheme 4). At first, we investigated the palladium-catalyzed reaction of guanidine **2D** with carbonate **4b** in CH_2Cl_2. Although the reaction of **2D** proceeded smoothly to give a 3:1 mixture of allylated products **8** and **9** in 88% combined yield, these isomers **8** and **9** could not be separated by preparative TLC or flash column chromatography. In contrast, the iridium-catalyzed reaction of **2D** with carbonate **4b** in MeCN gave the branched products **10** and **11**. These isomers could be easily separated by preparative TLC and the products **10** and **11** were obtained in 62% and 31% yields, respectively. Next, the further allylation of allylated product **10** was examined. However, allylation of **10** did not proceed even under the basic reaction conditions with allyl halides. The further allylation was achieved after the deprotection of the Boc group on **10**. Treatment of **10** with trifluoroacetic acid in CH_2Cl_2 gave the deprotected product **12** in 82% yield. The allylation of **12** under the basic reaction conditions with allyl bromide gave the diallylated product **13** in 53% yield.

Double Allylic Substitution of Guanidines. As mentioned above, the diallylation is a challenging task; thus, the double allylic substitution of guanidines is the next focus of our effort. To test the reactivity of guanidines toward the π-allyl complex, we reexamined the palladium-catalyzed reaction by employing guanidines **2A**−**C** and **3** (Scheme 5). In the presence of $Pd(PPh_3)_4$, the reaction of di-Boc-guanidine **2A**, di-Cbz-guanidine **2B**, and di-Bz-guanidine **2C** bearing two electron-withdrawing substituents gave the monoallylated products **5Ab**−**5Cb** even under reflux (Table 3, entries 1−3). The double allylic substitution was achieved by using tri-Boc-guanidine **3** as a nucleophile. The palladium-catalyzed reaction of tri-Boc-guanidine **3** with allylic carbonate **4b** (4 equiv) gave the

(23) For reviews, see: (a) Takemoto, Y.; Miyabe, H. In *Comprehensive Organometallic Chemistry*, 3rd ed. (COMC-III); Crabtree, R. H., Mingos, D. M. P., Eds.; Elsevier: Oxford, UK, 2006; Vol. 10.15, pp 695−724. (b) Lee, C.; Matunas, R. In *Comprehensive Organometallic Chemistry*, 3rd ed. (COMC-III); Crabtree, R. H., Mingos, D. M. P., Eds.; Elsevier: Oxford, UK, 2006; Vol. 10.14, pp 649−693.

(24) For some selected examples, see: (a) Kezuka, S.; Kanemoto, K.; Takeuchi, R. *Tetrahedron Lett.* **2004**, *45*, 6403. (b) Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525. (c) Takeuchi, R.; Ue, N.; Tanabe, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1975. (d) Takeuchi, R.; Shiga, N. *Org. Lett.* **1999**, *1*, 265. (e) Takeuchi, R.; Kashio, M. *J. Am. Chem. Soc.* **1998**, *120*, 8647. (f) Takeuchi, R.; Kashio, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 263. For a review, see: (g) Takeuchi, R. *Synlett* **2002**, 1954.

(25) For reviews on the iridium-catalyzed allylic substitution, see: (a) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675. (b) Takeuchi, R.; Kezuka, S. *Synthesis* **2006**, 3349.

(26) (a) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164. (b) López, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426. (c) Kiener, C. A.; Shu, C.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272. (d) Shu, C.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4794. (e) Shu, C.; Leitner, A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4797. (f) Leitner, A.; Shu, C.; Hartwig, J. F. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5830. (g) Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506. (h) Leitner, A.; Shu, C.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1093. (i) Shekhar, S.; Trantow, B.; Leitner, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 11770. (j) Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7508. (k) Pouy, M. J.; Leitner, A.; Weix, D. J.; Ueno, S.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 3949. (l) Marković, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 11680. (m) Ueno, S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 1928.

(27) (a) Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 116. (b) Welter, C.; Koch, O.; Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 896. (c) Weihofen, R.; Dahnz, A.; Brunner, B.; Streiff, S.; Duebon, P.; Helmchen, G. *Org. Lett.* **2005**, *7*, 1239. (d) Weihofen, R.; Dahnz, A.; Tverskoy, O.; Helmchen, G. *Chem. Commun.* **2005**, 3541. (e) Welter, C.; Moreno, R. M.; Streiff, S.; Helmchen, G. *Org. Biomol. Chem.* **2005**, *3*, 3266. (f) Weihofen, R.; Tverskoy, O.; Helmchen, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 5546.

SCHEME 5. Double Allylic Substitution of Guanidine

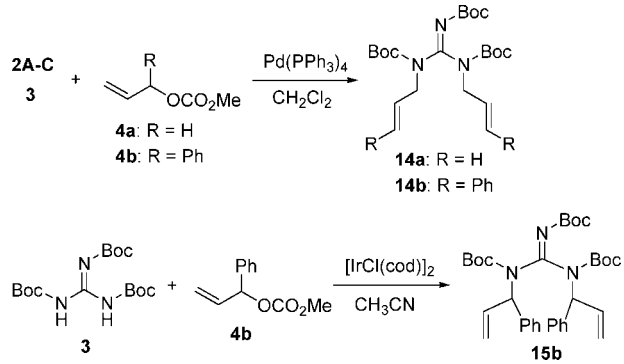
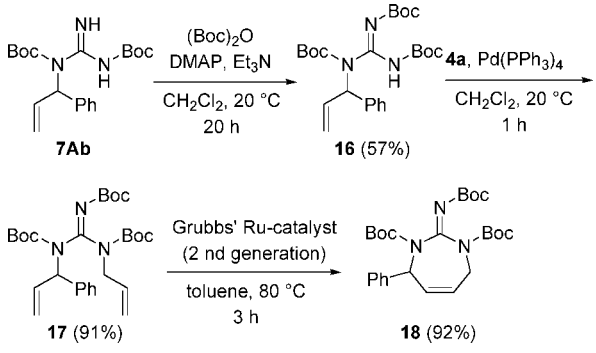


TABLE 3. The Double Allylic Substitution of Guanidines 2A−3

entry	guanidine	reagent	catalyst	*T* (°C)	time (h)	product	yield (%)
1[a]	**2A**	**4b**	$Pd(PPh_3)_4$	reflux	2	**5Ab**	90
2[a]	**2B**	**4b**	$Pd(PPh_3)_4$	reflux	2	**5Bb**	86
3[a]	**2C**	**4b**	$Pd(PPh_3)_4$	reflux	2	**5Cb**	89
4[a]	**3**	**4b**	$Pd(PPh_3)_4$	20	1	**14b**	94
5[a]	**3**	**4a**	$Pd(PPh_3)_4$	20	1	**14a**	99
6[b]	**3**	**4b**	$[IrCl(cod)]_2$	20	1	**15b**	85

[a] Reactions were carried out with guanidine **2A−3** and reagent **4a**,**b** (4 equiv) in CH_2Cl_2 in the presence of $Pd(PPh_3)_4$ (8 mol %). [b] Reaction was carried out with guanidine **3** and reagent **4b** (4 equiv) in CH_3CN in the presence of $[IrCl(cod)]_2$ (4 mol %).

SCHEME 6. Sequential Allylic Substitution of Guanidine

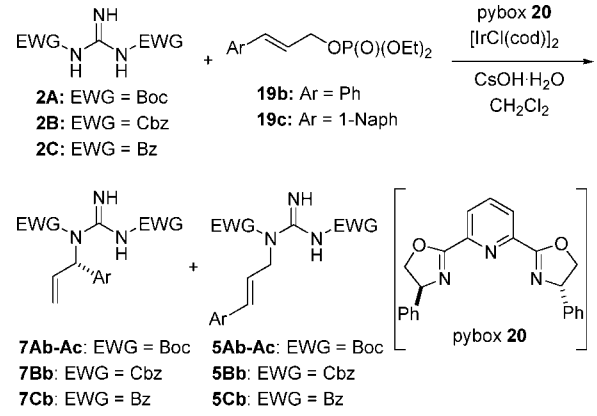


diallylated product **14b** in 94% yield (entry 4). Good chemical yield was also observed in the reaction of tri-Boc-guanidine **3** with carbonate **4a** (entry 5). The iridium-catalyzed reaction of **3** with **4b** proceeded smoothly to give the branched and diallylated adduct **15b** in 85% yield.

The diallylation reaction could be extended to the sequential reaction (Scheme 6). The tri-Boc-guanidine **16**, prepared from the allylated di-Boc-guanidine **7Ab**, was used as a precursor for second allylic substitution. As expected, tri-Boc-guanidine **16** displayed an excellent reactivity in the palladium-catalyzed reaction to give the diallylated product **17** in 91% yields. Cyclic guanidine **18** was obtained by the RCM reaction of **17**, using Grubbs' second generation catalyst.

Regio- and Enantioselective Allylic Substitution of Guanidines. Asymmetric allylic substitutions have been developed as fundamentally important reactions.[21,23] The allylic amination of 1,3-symmetrical substrates has been widely studied including enantioselective versions. On the other hand, the allylic amination of unsymmetrical substrates is challenging, since both regio- and enantioselectivities should be controlled to give the desired branched products with high enantiopurity. The pioneering work has been done by using chiral ferrocenylphosphine−palladium complexes by Hayashi and Ito.[28] The regio- and stereoselectivities of allylic substitution with iridium catalyst are quite different from those of palladium-catalyzed amination.[23,25,29] In recent years, the control of regio- and enantioselectivities in iridium-catalyzed allylic amination and etherification has been mainly studied by Hartwig[26] and Helmchen,[27] respectively. Hence, the regio- and enantioselective allylic substitution with chiral iridium complex has been a subject of current interest.[30−33]

SCHEME 7. Enantioselective Allylic Substitution of Guanidines



Recently, we reported that the iridium complex of pybox ligand catalyzed the allylic substitution to form the branched product with good enantioselectivity.[34] Therefore, the utility of the iridium−pybox complex in reaction of guanidines has been the new focus of our efforts.[35,36] At first, we investigated the monoallylation reaction of guanidines **2A−C** having two electron-withdrawing substituents with phosphates **19b** and **19b** (Scheme 7). As expected, the chiral iridium complex of the pybox ligand exhibited a good activity under basic reaction conditions, although the reaction of phosphates did not proceed effectively in the absence of the base. The reaction of di-Boc-

(28) Hayashi, T.; Kishi, K.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 1743.

(29) For our studies on the iridium-catalyzed reaction, see: (a) Kanayama, T.; Yoshida, K.; Miyabe, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2054. (b) Kanayama, T.; Yoshida, K.; Miyabe, H.; Kimachi, Y.; Takemoto, Y. *J. Org. Chem.* **2003**, *68*, 6197. (c) Miyabe, H.; Yoshida, K.; Kobayashi, Y.; Matsumura, A.; Takemoto, Y. *Synlett* **2003**, 1031. (d) Miyabe, H.; Takemoto, Y. *Synlett* **2005**, 1641.

(30) (a) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426. (b) Polet, D.; Alexakis, A. *Org. Lett.* **2005**, *7*, 1621. (c) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem. Eur. J.* **2006**, *12*, 3596.

(31) (a) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (b) Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6204. (c) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139.

(32) Kimura, M.; Uozumi, Y. *J. Org. Chem.* **2007**, *72*, 707.

(33) (a) Singh, O. V.; Han, H. *J. Am. Chem. Soc.* **2007**, *129*, 774. (b) Singh, O. V.; Han, H. *Org. Lett.* **2007**, *9*, 4801. (c) Singh, O. V.; Han, H. *Tetrahedron Lett.* **2007**, *48*, 7094.

(34) For our studies on asymmetric iridium-catalyzed allylic substitution with heteroatom nucleophiles, see: (a) Miyabe, H.; Matsumura, A.; Moriyama, K.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 4631. (b) Miyabe, H.; Yoshida, K.; Yamauchi, M.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 2148. (c) Reddy, V. K.; Miyabe, H.; Yamauchi, M.; Takemoto, Y. *Tetrahedron* **2008**, *64*, 1040.

(35) The utility of the C_2-symmetric pybox ligand in transition metal-catalyzed allylic substitution has not been wildly invesitigated. See: (a) Bourguignon, J.; Bremberg, U.; Dupas, G.; Hallman, K.; Hagberg, L.; Hortala, L.; Levacher, V.; Lutsenko, S.; Macedo, E.; Moberg, C.; Quéguiner, C.; Rahm, F. *Tetrahedron* **2003**, *59*, 9583. (b) Chelucci, G.; Deriu, S.; Pinna, G. A.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **1999**, *10*, 3803.

(36) The iridium−idane−pybox catalyst was used in the reductive aldol reaction. See: Zhao, C.-X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829.

TABLE 4. The Enantioselective Allylic Substitution of Guanidines 2A−2C[a]

entry	guanidine	reagent	T (°C)	time (h)	yield (%)[b]	product (ratio[c])	ee (%)[d]
1	**2A**	**19b**	−20	3	83	**7Ab**:**5Ab** (75:25)	90
2	**2A**	**19b**	−30	3	81	**7Ab**:**5Ab** (76:24)	96
3	**2B**	**19b**	−20	3	74	**7Bb**:**5Bb** (60:40)	87
4	**2B**	**19b**	−30	3	70	**7Bb**:**5Bb** (66:34)	87
5	**2C**	**19b**	−20	50	63	**7Cb**:**5Cb** (25:75)	34
6	**2A**	**19c**	−20	8	69	**7Ac**:**5Ac** (>95:5)	96

[a] Reactions were carried out with guanidine **2A−C** and reagent **19b,c** (1.5 equiv) in the presence of $[IrCl(cod)]_2$ (8 mol %) and pybox **20** (16 mol %). [b] Combined yield of **7Ab−Cb** and **5Ab−Cb**. [c] Ratio for **7Ab−Cb**:**5Ab−Cb**. [d] Enantioselectivity was determined by HPLC analysis.

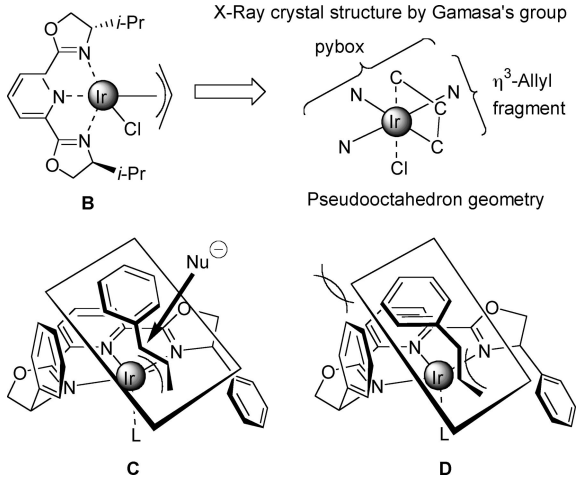


FIGURE 2. Model to explain enantioselectivity.

guanidine **2A** with **19b** proceeded smoothly to give good yields of products **7Ab** and **5Ab**, although a low regioselectivity was observed (Table 4, entry 1). Enantiomeric excess of **7Ab** was determined to be 90% ee by high-performance liquid chromatography analysis. The absolute configuration of product **7Ab** was assumed from the similarity between the present reaction and our previously reported reaction.[34] The reaction of **2A** with **19b** at −30 °C gave 96% ee of branched product **7Ab** with a 76:24 regioselectivity (entry 2). The replacement of di-Boc-guanidine **2A** with di-Cbz-guanidine **2B** or di-Bz-guanidine **2C** led to a decrease in the enantioselectivity and regioselectivity (entries 3−5). The use of phosphate **19c** having a 1-naphthyl group led to an increase in regioselectivity to >95:5 and enantioselectivity to 96% ee (entry 6).

Recently, Gamasa reported the structure of the π-allyl iridium complex with the pybox ligand having isopropyl groups **B** (Figure 2).[37] The stereochemistry of complex **B** has been confirmed by a single-crystal X-ray analysis. The X-ray crystal structure determination shows a pseudooctahedral geometry around the iridium atom, which is bonded to the chloride atom and to the three nitrogen atoms of the pybox ligand. The π-allyl fragment formally occupied two coordination sites. On the basis of Gamasa's study, the stereochemical feature of our reaction can be rationalized in terms of steric control in the π-allyl iridium complex. The complex **C** would be preferred over complex **D** due to repulsion between two phenyl groups of the allyl fragment and the pybox ligand as shown in **D**.

(37) For iridium pybox complexes, see: (a) Diez, J.; Gamasa, M. P.; Gimeno, J.; Paredes, P. *Organometallics* **2005**, *24*, 1799. (b) Paredes, P.; Díez, J.; Gamasa, M. P. *Organometallics* **2008**, *27*, 2597.

SCHEME 8. Enantioselective Double Allylic Substitution of Guanidine

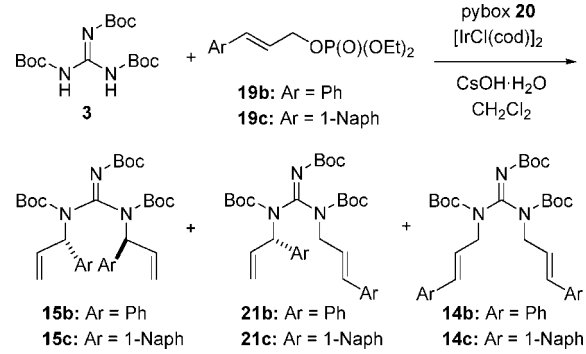


TABLE 5. The Enantioselective Double Allylic Substitution of Guanidine 3[a]

entry	reagent	T (°C)	time (h)	yield (%)	ratio[b]	dr[c]	ee (%)[d] 15b,c	ee (%)[d] 21b
1	**19b**	20	10	88[e]	4:81:15	25:75		64
2	**19b**	–20	20	90[e]	58:30:12	74:26	99	88
3	**19c**	20	10	77[f]	97:3:trace	90:10	99	
4	**19c**	–20	20	81[f]	100:trace:trace	97:3	99	

[a] Reactions were carried out with guanidine **3** and reagent **19b,c** (2.5 equiv) in the presence of $[IrCl(cod)]_2$ (8 mol %) and pybox **20** (16 mol %). [b] Ratio for **15b,c**:**21b,c**:**14b,c**. [c] Dr for *dl*-**15b,c**:*meso*-**15b,c**. [d] Enantioselectivity was determined by HPLC analysis. [e] Combined yield of products. [f] Yield of *dl*-**15c**.

Finally, we studied the viability of the iridium complex of the pybox ligand in the double allylic substitution of tri-Boc-guanidine **3** (Scheme 8). The double allylic substitution is challenging, because chiral iridium complex should control the diastereoselectivity as well as regioselectivity and enantioselectivity. At first, the reaction of tri-Boc-guanidine **3** with allylic phosphate **19b** was carried out in CH_2Cl_2 at 20 °C under basic reaction conditions (Table 5, entry 1). However, the mixture of products **15b**, **21b**, and **14b** was obtained in 88% combined yield in a 4:81:15 ratio. The chemical yield for product **15b** was shown to be dependent on the reaction temperature, thus changing the temperature from 20 to −20 °C led to an effective increase in the yield of the desired compound **15b** (entry 2). The moderate diasteroselectivity was observed to give the diastereomers *dl*-**15b** and *meso*-**15b** in a 74:26 ratio, accompanied by the product **21b** with 88% ee. Enantiomeric excess of major diastereomer *dl*-**15b** was determined to be >99% ee by high-performance liquid chromatography analysis. The enhanced enantioselectivity of *dl*-**15b** can be explained by kinetic resolution during the second allylation step of monoallylated product. The ratio of undesired products to desired products was also dependent on the structure of allylic phosphates (entries 3 and 4). When phosphate **19c** having a 1-naphthyl group was employed, high diastere-, regio-, and enantioselectivities were observed. The reaction conducted at −20 °C gave the desired product *dl*-**15c** in 81% yield with >99% ee (entry 4).

Conclusion

We have demonstrated that the nitrogen atoms of guanidines bearing electron-withdrawing substituents act as reactive nucleophiles in the palladium- or iridium-catalyzed allylic substitution These reactions provided a new method for direct func-

tionalization of protected guanidine derivatives. In addition to the enantioselective monoallylation, the enantioselective double allylic substitution of tri-Boc-guanidine disclosed a broader aspect of the utility of the iridium−pybox complex in allylic substitutions.

Experimental Section

General Procedure for Enantioselective Iridium-Catalyzed Monoallylation. A mixture of guanidine **2A**−**C** (0.15 mmol) and $CsOH·H_2O$ (27 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) was stirred under argon atmosphere at 20 °C for 10 min. To the reaction mixture was added a solution of allylic phosphate **19b**,**c** (0.23 mmol), pybox 20 (9.1 mg, 0.025 mmol), and $[IrCl(cod)]_2$ (8.3 mg, 0.012 mmol) in CH_2Cl_2 (0.5 mL) at −20 or −30 °C. After the reaction was completed, the reaction mixture was diluted with saturated NH_4Cl and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. The ratio of products was determined by ^{1}H NMR analysis of crude products. Purification of the residue by preparative TLC (hexane: AcOEt = 10:1, 2-fold development) afforded the products **7Ab**−**7Cb** and **5Ab**−**5Cb**.

***N*^{1},*N*^{2}-Bis(*tert*-butyloxycarbonyl)-*N*^{1}-(1-phenyl-2-propenyl)guanidine (7Ab).** A white solid. IR ($CHCl_3$) 3384, 1711, 1609 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 9.49 (1H, br s), 9.31 (1H, br s), 7.31−7.24 (2H, m), 7.22−7.15 (4H, m), 6.33 (1H, m), 5.49 (1H, d, J = 17.1 Hz), 5.41 (1H, d, J = 10.1 Hz), 1.48 (9H, s), 1.13 (9H, s); ^{13}C NMR ($CDCl_3$) δ 163.9, 161.1, 154.6, 141.7, 135.0, 128.0, 126.3, 125.5, 120.2, 84.0, 78.7, 58.4, 28.3, 27.5; MS (CI$^+$) *m*/*z* 376 (M + H$^+$, 29.6), 263 (100). HRMS (CI$^+$) calcd for $C_{20}H_{30}N_3O_4$ (M + H$^+$) 376.2236, found 376.2244. HPLC (Chiralcel AD-H, hexane/2-propanol = 90/10, 0.5 mL/min, 254 nm) t_r(S) = 8.8 min, t_r(R) = 7.2 min. A sample of 96% ee (S) by HPLC analysis gave $[\alpha]^{29}_D$ −23.1 (*c* 1.00, $CHCl_3$).

***N*^{1},*N*^{2}-Bis(*tert*-butyloxycarbonyl)-*N*^{1}-(1-naphthyl-2-propenyl)guanidine (7Ac).** Colorless crystals. Mp 98−99 °C (hexane). IR ($CHCl_3$) 3386, 1711, 1610 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 9.50 (2H, br s), 7.98 (1H, d, J = 8.2 Hz), 7.83 (1H, d, J = 7.9 Hz), 7.76 (1H, d, J = 7.9 Hz), 7.59 (1H, d, J = 6.1 Hz), 7.52−7.38 (4H, m), 6.46 (1H, m), 5.43 (1H, d, J = 11.9 Hz), 5.42 (1H, d, J = 15.9 Hz), 1.51 (9H, s), 1.07 (9H, s); ^{13}C NMR ($CDCl_3$) δ 164.0, 160.6, 154.9, 136.1, 135.4, 133.9, 131.3, 128.7, 128.1, 127.3, 126.4, 125.5, 124.5, 124.2, 117.8, 84.1, 78.8, 57.5, 28.3, 27.5; MS (FAB$^+$) *m*/*z* 426 (M + H$^+$, 12), 425 (M$^+$, 9), 167 (100). HRMS (FAB$^+$) calcd for $C_{24}H_{31}N_3O_4$ (M$^+$) 425.2315, found 425.2324. Anal. Calcd for $C_{24}H_{31}N_3O_4$: C, 67.74; H, 7.34; N, 9.88. Found: C, 67.69; H, 7.27; N, 9.84. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 0.5 mL/min, 254 nm) $t_r(S)$ = 10.5 min, $t_r(R)$ = 9.5 min. A sample of 96% ee (*S*) by HPLC analysis gave $[\alpha]^{20}_D$ −185.2 (*c* 1.4, $CHCl_3$).

***N*^{1},*N*^{2}-Bis(benzyloxycarbonyl)-*N*^{1}-(1-phenyl-2-propenyl)guanidine (7Bb).** A white solid. IR ($CHCl_3$) 3389, 1717, 1612 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 9.61 (1H, br s), 9.36 (1H, br s), 7.41−7.10 (14H, m), 6.82 (2H, d, J = 7.0 Hz), 6.28 (1H, m), 5.39 (1H, d, J = 17.1 Hz), 5.33 (1H, d, J = 10.3 Hz), 5.14, 5.13 (2H, AB q, J = 13.4 Hz), 4.96, 4.93 (2H, AB q, J = 12.2 Hz); ^{13}C NMR ($CDCl_3$) δ 163.9, 161.1, 155.7, 140.5, 136.9, 134.7, 134.0, 128.4 (2C), 128.3, 128.2, 128.0, 127.8, 126.6, 125.9, 120.3, 68.7, 67.1, 58.9; one carbon peak was missing due to overlapping. MS (EI$^+$) *m*/*z* 433 (M$^+$, 24), 91 (100). HRMS (EI$^+$) calcd for $C_{26}H_{25}N_3O_4$ (M$^+$) 443.1845, found 443.1850. HPLC (Chiralcel AD-H, hexane/2-propanol = 90/10, 0.5 mL/min, 254 nm) $t_r(S)$ = 27.6 min, $t_r(R)$ = 17.6 min. A sample of 87% ee (*S*) by HPLC analysis gave $[\alpha]^{29}_D$ −44.8 (*c* 1.04, $CHCl_3$).

***N*^{1},*N*^{2}-Bis(phenylcarbonyl)-*N*^{1}-(1-phenyl-2-propenyl)guanidine (7Cb).** A white solid. IR ($CHCl_3$) 3283, 1675, 1616 cm^{-1}.^{1}H NMR ($CDCl_3$) δ 10.02 (1H, d, J = 7.0 Hz), 8.24 (2H, d, J = 6.7 Hz), 8.06 (2H, d, J = 7.3 Hz), 7.65−7.30 (12H, m), 6.20−6.13 (2H, m), 5.39 (1H, d, J = 15.6 Hz), 5.34 (1H, d, J = 9.2 Hz); ^{13}C NMR ($CDCl_3$) δ 178.9, 168.6, 156.2, 140.1, 137.7, 137.0, 133.6, 132.0 (2C), 129.6, 129.2, 128.9, 128.0 (2C), 127.9, 127.2, 116.4, 57.1; MS (FAB$^+$) *m*/*z* 384 (M + H$^+$, 71), 154 (100). HRMS (FAB$^+$) calcd for $C_{24}H_{22}N_3O_2$ (M + H$^+$) 384.1712, found 384.1703. HPLC (Chiralcel AD-H, hexane/2-propanol = 90/10, 0.5 mL/min, 254 nm) $t_r(S)$ = 20.5 min, $t_r(R)$ = 15.6 min. A sample of 34% ee (*S*) by HPLC analysis gave $[\alpha]^{20}_D$ −50.0 (*c* 0.16, $CHCl_3$).

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Supporting Information Available: Experimental procedure and characterization data for all obtained compounds, and ^{1}H and ^{13}C NMR spectra of all obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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