

A Facile Highly Regio- and Stereoselective Preparation of *N*-Tosyl Allylic Amines from Allylic Alcohols and Tosyl Isocyanate via Palladium(II)-Catalyzed Aminopalladation– β -Heteroatom Elimination

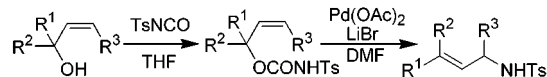
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ABSTRACT

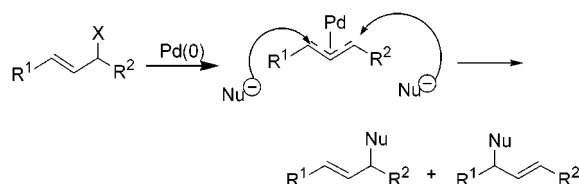


The high regio- and stereoselectivity have been obtained from the allylic substitution reaction catalyzed by palladium(II) species. From allylic alcohols, one-pot reaction with tosyl isocyanate followed by palladium(II)-catalyzed allylic substitution gives *N*-tosyl (*E*)-allylic amines in high yield. The substitution occurs only at the γ -position of the 1- or 3-substituted allylic alcohols.

Allylic amines are important synthetic intermediates for the preparation of a number of biologically active molecules.¹ In recent years, the Pd(0)-catalyzed amination of allylic substrates has been extensively studied for its relevance to organic synthesis.² However, the two terminal carbons of the π -allyl palladium complex are nearly equivalent, and the nucleophilic substitution usually gave a mixture of regioisomers (Scheme 1).³ Thus, controlling of regioselectivity in the unsymmetric π -allylic system has been a major

challenge.⁴ In general, a sterically demanding group at one terminus of the allylic system usually blocks the incoming nucleophile, or an electron-withdrawing group at an allylic carbon atom has been used to change the electronic density of the two carbon atoms of the π -allyl intermediate.⁵ Herein,

Scheme 1



(1) (a) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, 98, 1689. (b) Cheikh, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685. (c) Wei, Z.-Y.; Knaus, E. E. *Synthesis* **1994**, 1463. (d) Spaltenstein, A.; Carpino, P. A.; Miyake, F.; Hopkins, P. B. *J. Org. Chem.* **1987**, 52, 3759.

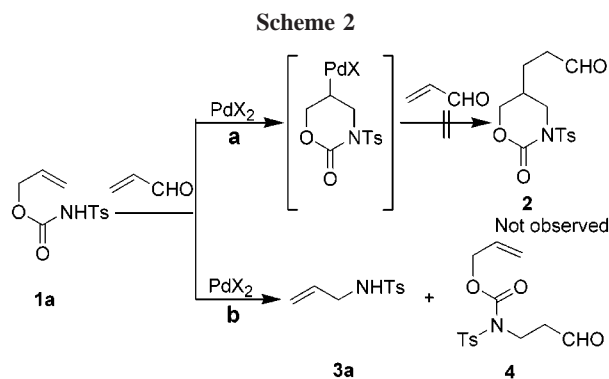
(2) (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, 28, 1173. (b) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelbach, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 585. (c) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley: Chichester, 1995.

(3) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, 121, 4545.

(4) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, 102, 4730. (b) Pretot, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, 37, 323. (c) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Chem. Soc., Chem. Commun.* **1997**, 561. (d) Hayashi, T.; Kishi, K.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1990**, 31, 1743. (e) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, 120, 1681. (f) Trost, B. M.; Krische, M. J.; Radinov, R.; Zanon, G. *J. Am. Chem. Soc.* **1996**, 118, 6297.

we report a facile, highly regio- and stereoselective method for the synthesis of *N*-tosyl allylic amines directly from allylic alcohols via divalent palladium-catalyzed intramolecular allylic substitution.

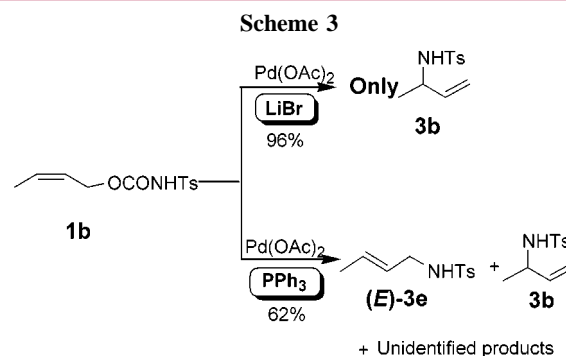
In our laboratory, we have developed a series of regio- and stereoselective reactions based on Pd(II)-mediated nucleopalladation of alkynes and tandem carbon–carbon bond coupling.⁶ With these previous developments, we explored the intramolecular nucleopalladation of alkenes by nitrogen nucleophiles and wished to achieve a tandem nucleopalladation–conjugate addition reaction (Scheme 2, a). However,



when we attempted the reaction of **1a** (0.1 mmol) with acrolein (1.5 mmol) in the presence of $\text{Pd}(\text{OAc})_2$ (0.005 mmol) and LiBr (0.5 mmol) in THF, we only obtained the compounds **3a** (yield: 57%) and **4** (yield: 30%) instead of **2**. The formation of **4** may be explained by the direct Michael addition of **1a** to acrolein; but the formation of **3a** was somewhat unexpected in Pd(II)-catalyzed reactions. Usually, the transformation of **1a** to **3a** could be speculated by a Pd(0)-catalyzed allylic cleavage followed by decarboxylation and nucleophilic substitution by tosylamide anion. This appeared a reasonable supposition in light of the numerous

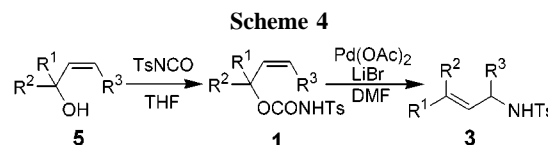
examples of facile reduction of Pd(II) to Pd(0).^{2c,7} However, it is inconsistent with the fact that the control experiment only in the presence of $\text{Pd}(\text{OAc})_2$ without LiBr in DMF gave no reaction. In addition, in a parallel study, when compound **1a** (1 mmol) was subject to a Pd catalytic system ($\text{Pd}(\text{OAc})_2$ (0.05 mmol)) in the presence of LiBr (4 mmol) and CuBr_2 (8 mmol) in DMF (5 mL), **3a** was the sole product in 98% yield. Furthermore, the reaction of **1a** (1 mmol) could proceed with $\text{Pd}(\text{OAc})_2$ (0.05 mmol) and LiBr (4 mmol) without the presence of CuBr_2 in DMF (5 mL) at room temperature to produce **3a** in 95% yield. No reaction occurred in the absence of Pd(II) catalyst even at 100 °C. These observations led us to believe that the reaction is actually catalyzed by Pd(II) instead of Pd(0).

To further clarify the reaction mechanism, we studied the substitution reaction with *O*-[but-(2*Z*)-enyl]tosylcarbamate (**1b**) (Scheme 3). From **1b** (1 mmol), a Pd(0) [$\text{Pd}(\text{OAc})_2$,



(0.05 mmol), PPh_3 , (0.2 mmol)]⁷ catalyzed allylic substitution leads to **3b** and **(E)-3e** as the main products together with a minor amount of unidentified product.⁸ While under $\text{Pd}(\text{OAc})_2$ –LiBr catalysis, only the γ -substituted product **3b** was isolated in 96% yield.

It is significant that the *N*-tosyl carbamates can be prepared in situ from the corresponding allylic alcohols⁹ and undergo allylic substitution without isolation. For example, allyl alcohol **5a** (1 mmol) reacted with TsNCO (1.1 mmol) in THF for 20 min; after THF was removed, the catalytic reaction was carried out in DMF in the presence of $\text{Pd}(\text{OAc})_2$ (0.05 mmol) and LiBr (4 mmol). This procedure afforded **3a** in 96% yield. A wide range of 1-, 3-substituted or 1,3-disubstituted (*Z*)-allylic alcohols were examined under the same conditions (Scheme 4, Table 1), and they all gave exclusively the γ -substitution products.¹⁰



(5) (a) Tetsuo, T.; Horii, Y.; Nakagawa, Y.; Ishida, T.; Saegusa, T. *J. Org. Chem.* **1989**, *54*, 977. (b) Tanikaga, R.; Takeuchi, J.; Takyu, M.; Kaji, A. *J. Chem. Soc., Chem. Commun.* **1987**, 386. (c) Genêt, J. P.; Balabane, M.; Bäckvall, J. E.; Nyström, J. E. *Tetrahedron Lett.* **1983**, *27*, 2745. (d) Tsuji, J.; Ueno, H.; Kobayashi, Y.; Okumoto, H. *Tetrahedron Lett.* **1981**, *22*, 2573. (e) Inami, H.; Ito, T.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1993**, *34*, 5919. (f) Urade, H.; Inami, H.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1595. (g) Tsuji, J.; Yuhara, M.; Minato, M.; Yamada, H.; Sato, F.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 343. (h) Hirao, T.; Enda, J.; Ohshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1981**, *22*, 3079. (i) Trost, B. M.; Self, C. R. *J. Am. Chem. Soc.* **1983**, *105*, 5942. (j) Kang, J.; Cho, W.; Lee, W. K. *J. Org. Chem.* **1984**, *49*, 1838.

(6) (a) Lu, X.; Zhu, G.; Wang, Z. *Synlett* **1998**, 115. (b) Lu, X.; Ma, S. New Age of Divalent Palladium Catalysis. In *Transition Metal Catalyzed Reaction*; Murahashi, S.-I., Davies, S. G., Eds.; 1999; Chapter 6, p 133. (c) Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 733. (d) Ma, S.; Lu, X. *J. Org. Chem.* **1991**, *56*, 5112. (e) Ma, S.; Zhu, G.; Lu, X. *J. Org. Chem.* **1993**, *58*, 3692. (f) Ma, S.; Lu, X. *J. Organomet. Chem.* **1993**, *447*, 305. (g) Ma, S.; Lu, X. *J. Org. Chem.* **1993**, *58*, 1245. (h) Zhu, G.; Ma, S.; Lu, X. *J. Chem. Res. (S)* **1993**, 367. (i) Zhu, G.; Lu, X.; X. *Organometallics* **1995**, *14*, 4899. (j) Zhu, G.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1087.

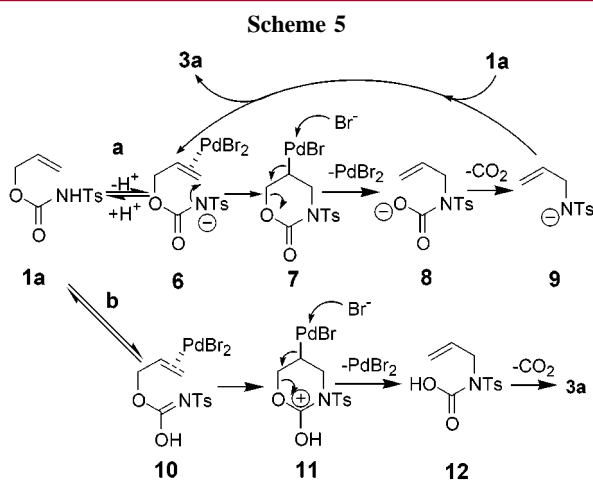
(7) (a) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009. (b) Ozawa, F.; Kabo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177. (c) Hayashi, T.; Kubo, A.; Ozawa, F. *Pure Appl. Chem.* **1992**, *64*, 421.

Table 1. Pd(II)-Catalyzed Synthesis of *N*-Tosyl (*E*)-Allylic Amines^a

$\mathbf{5} \xrightarrow[2, \text{Pd}(\text{OAc})_2, \text{LiBr, DMF}]{1, \text{TsNCO, THF}} \mathbf{3}$						
entry	5	substrate			product	
		R ¹	R ²	R ³	3	yield (%) ^b
1	5a	H	H	H	3a	95
2	5c	H	H	<i>n</i> -C ₄ H ₉	3c	80
3	5d	Ph	H	H	3d	98
4	5e	Me	H	H	3e	96
5	5f	<i>n</i> -C ₅ H ₁₁	H	H	3f	85
6	5g	Ph	H	Ph	3g	98
7	5h	Me	Me	H	3h	58

^a Reaction condition: **5** (1 mmol) reacted with TsNCO (1.1 mmol) in THF for 20 min; then THF was removed, the residue was dissolved in DMF, and then Pd(OAc)₂ (0.05 mmol) and LiBr (4 mmol) were added and stirred at room temperature (for entry 1) or 100 °C (for entries 2–7).
^b Isolated yields.

On the basis of these results, we speculate that the reaction proceeds via a Pd(II)-mediated S_N2' substitution-decarboxylation mechanism (Scheme 5, a): Compound **1a** first



dissociates to give anion **6**. The nitrogen anion attacks the double bond activated by Pd(II), leading to a cyclic intermediate **7**. β-Heteroatom elimination assisted by bromide ions¹¹ then gives **8**, which spontaneously releases CO₂ to afford **9**. The proton exchange between **9** and **1a** gives the neutral product **3a** and anion **6**, which enters a second catalytic cycle. The preferential elimination of the β-oxygen-containing group of **7** results in the high regioselectivity of the reaction.

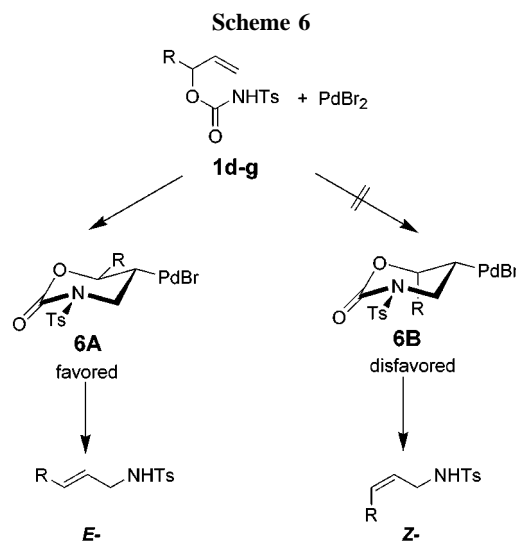
(8) A typical experiment showed that the products contained 37% of **3b**, 51% of (*E*)-**3e**, and other unidentified products as characterized by HPLC.

(9) Tamaru, Y.; Kimura, M.; Tanaka, S.; Kure, S.; Yoshida, Z. *Bull. Chem. Soc. Jpn.* **1994**, 67, 2838.

(10) Using the (*E*)-allylic alcohol as the substrate, no expected product formed.

[3,3]-Sigmatropic rearrangements of allylic acetate is known to be catalyzed efficiently by PdCl₂(PhCN)₂.¹⁴ In addition, conversion of S-allylthioimidates into *N*-allylthioamide, and allylimidates into allylamides, are also catalyzed by Pd(II).¹⁵ The mechanism of the rearrangement reaction of allylic acetate was explained by the oxypalladation of the double bond to form a six-membered cyclic Pd(II) intermediate. Resembling Pd-catalyzed [3,3]-rearrangement, we propose another plausible mechanism of the reaction as route b in Scheme 5.

It is noteworthy that the reaction is highly stereoselective. From 1-substituted or 1,3-disubstituted allylic carbamates (Table 1, entries 3–6), the reaction gives only *N*-tosyl (*E*)-allylic amines: no (*Z*)-products can be detected by ¹H NMR and HPLC. This feature allows for convenient selective synthesis of (*E*)-allylic amines from readily available 1-substituted or 1,3-disubstituted allylic alcohols. The high (*E*)-selectivity can be explained by the favorable conformation of the six-membered cyclic intermediate and the highly specific *trans*-heteroatom elimination^{6b,i} (Scheme 6): The



nucleopalladation of **1d–g** can lead to two possible intermediates in chair conformation: **6A** and **6B**. With the bulky groups, Pd group, Ts, and R in equatorial positions, **6A** is more stable than **6B**. The cyclization preferentially gives **6A**, and then *trans*-elimination of Pd–OCO–R leads to (*E*)-double bond.

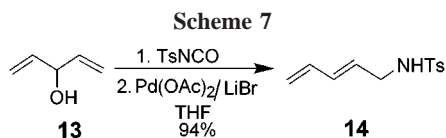
(11) The role of bromide ions might be ascribed to (a) the presence of excess bromide ion makes the Pd coordinatively saturated and the β-H elimination not so feasible;¹² (b) The coordination of bromide ion with Pd increase the electron density of Pd, resulting in the weakening of the carbon–palladium bond.¹³

(12) Wang, Z.; Zhang, Z.; Lu, X. *Organometallics* **2000**, 19, 775.

(13) (a) Markies, B. A.; Canty, A. J.; de Graaf, W.; Boersma, J.; Janssen, M. D.; Hogerheide, M. P.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. J. *Organomet. Chem.* **1994**, 482, 191. (b) Ryabov, A. D.; Sakodinskaya, I.-K.; Titov, V. M.; Yatsimirsky, A. K. *Inorg. Chim. Acta* **1981**, 54, L195. (c) Ryabov, A. D.; Sakodinskaya, I.-K.; Yatsimirsky, A. K. *Inorg. Chim. Acta* **1986**, 116, L55.

(14) (a) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, 23, 579. (b) Henry, P. M. *J. Am. Chem. Soc.* **1972**, 94, 5200.

An important application of the current reaction is the preparation of conjugated *N*-tosyl dienylamines. From 1,4-pentadien-3-ol, which can be easily prepared from acrolein and vinyl Grignard reagent, *N*-tosyl (2*E*)-2,4-pentadienylamines can be synthesized in high yield and stereoselectivity by a two-step reaction sequence (Scheme 7). Conjugated



dienes are important intermediates in the synthesis of complex natural products because of their versatile reactivities, and dienylamines in particular have been used in the synthesis of dihydropyridines et al.¹⁶ Using readily available divinyl carbinols, the present method can provide facile access to a wide range of dienylamines and is expected to have broad applications in natural product synthesis.

In summary, we have developed a highly efficient method for the synthesis of *N*-tosyl allylic amines. From allylic

alcohols, one-pot reaction with tosyl isocyanate followed by divalent palladium-catalyzed allylic substitution gives *N*-tosyl allylic amines in high yield, and high stereo- and regio-selectivity as compared with the drawback of regioselectivity of allylic substitution catalyzed by Pd(0).

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Supporting Information Available: General procedures, spectral data, and the experiment of **1b** under Pd(OAc)₂–PPh₃. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (15) (a) Overman, L. E.; Donde, Y. *J. Am. Chem. Soc.* **1999**, *121*, 2933. (b) Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449. (c) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218. (d) Genda, J.; Helland, A. C.; Ernst, B. E.; Bellus, D. *Synthesis* **1993**, 729. (e) Tamaru, Y.; Kagotani, M.; Yoshida, Z.-I. *J. Org. Chem.* **1980**, *45*, 5221. (f) Tamaru, Y.; Kagotani, M.; Yoshida, Z. *Tetrahedron Lett.* **1981**, *22*, 4245. (g) Tamaru, Y.; Kagotani, M.; Yoshida, Z. *J. Org. Chem.* **1985**, *50*, 764. (h) Schenck, T. G.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2058. (i) Mehmandoust, M.; Petit, Y.; Larchevêque, M. *Tetrahedron Lett.* **1992**, *33*, 4313. (j) Mizutani, M.; Sanemitsu, Y.; Tamrau, Y.; Yoshida, Z.-I. *J. Org. Chem.* **1985**, *50*, 764.
- (16) (a) Wyle, M. J.; Fowler, F. W. *J. Org. Chem.* **1984**, *49*, 4025. (b) Birtwistle, D. H.; Brown, J. M.; Foxton, M. W. *Tetrahedron* **1988**, *44*, 7309.