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Tuning the Reaction Paths in Palladium(0)-Catalyzed Coupling–Cyclization Reaction of β-Amino Allenes with Organic Halides: A Substituent Switch

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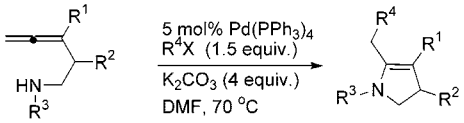
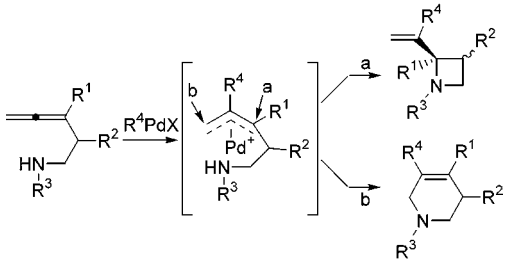
ABSTRACT



Substituent effects on the allene moiety and the N-protecting group were found to be the dominant factor in determining the reaction paths in the Pd(0)-catalyzed coupling–cyclization reaction of β-amino allenes with organic halides.

Recently, much attention has been paid to the coupling−cyclization of organic halides with functionalized allenes.[1,2] During our systematic study of allene chemistry,[3] we noted that palladium-catalyzed coupling−cyclization reaction of acyclic 3,4-dienylamine derivatives with organic halides[4,5] or hypervalent iodonium salts[6] leads to the formation of azetidine and/or tetrahydropyridine with selectivity. In these reactions, the amino allene undergoes carbopalladation at the central sp-carbon atom to afford a π-allyl palladium intermediate,[7] which was followed by the intramolecular nucleophilic attack of the nitrogen atom to give cyclic products (Scheme 1). Here, we wish to communicate our recent results on the Pd(0)-catalyzed coupling−cyclization reaction of acyclic β-amino allenes with organic halides,[8] in which the

Scheme 1



(1) For reviews, see: (a) Zimmer, R.; Dinesh, C. U.; Nadanan, E.; Hhan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (b) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199.

(2) For some of the most recent publications, see: (a) Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 343. (b) Ha, Y.-H.; Kang, S.-K. *Org. Lett.* **2002**, *4*, 1143. (c) Liu, G.; Lu, X. *Org. Lett.* **2001**, *3*, 3879. (d) Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855. (e) Kang, S.-K.; Kim, K.-J.; Yu, C.-M.; Hwang, J.-W.; Do, Y.-K. *Org. Lett.* **2001**, *3*, 2851. (f) Bates, R. W.; Satcharoen, V. *Synlett* **2001**, 532. (g) Kang, S.-K.; Kim, K.-J. *Org. Lett.* **2001**, *3*, 511. (h) Karstens, W. F. J.; Klomp, D.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron* **2001**, *57*, 5123.

(3) For some of the most recent results from this group, see: (a) Ma, S.; Wu, S. *Chem. Commun.* **2001**, 441. (b) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **2001**, *123*, 5578. (c) Ma, S.; Shi, Z. *Chem. Commun.* **2002**, 540. (d) Ma, S.; Gao, W. *Synlett* **2002**, 65. (e) Ma, S.; Yin, S.; Li, L.; Tao, F. *Org. Lett.* **2002**, *4*, 505. (f) Ma, S.; Jiao, N.; Zhao, S.; Hou, H. *J. Org. Chem.* **2002**, *67*, 2837. (g) Ma, S.; Duan, D.; Wang, Y. *J. Comb. Chem.* **2002**, *4*, 239. (h) Ma, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2002**, *41*, 1775.

(4) Rutjes, F. P. J. T.; Tjen, K. C. M. F.; Wolf, L. B.; Karstens, W. F. J.; Schoemaker, H. E.; Hiemstra, H. *Org. Lett.* **1999**, *1*, 717.

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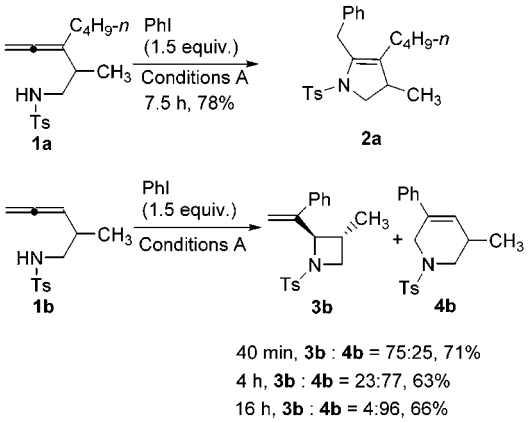
substituent on the allene moiety as well as the nitrogen atom is a decisive factor for determining the pathways of this intramolecular amination reaction.

Our initial observation began with the reaction of *N*-(2-methyl-3-(*n*-butyl)-3,4-pentadienyl) toluenesulfonamide **1a**[9] with 1.5 equiv of iodobenzene under conditions A for 7.5 h (conditions A = 5 mol % $Pd(PPh_3)_4$, K_2CO_3 (4 equiv), DMF, 70 °C). Much to our surprise, the reaction proceeded smoothly to afford a five-membered product **2a** in 78% yield together with less than 3% of other isomers, if any (Scheme 2). The structure of **2a** was unambiguously determined by

Scheme 2



the single-crystal X-ray diffraction study (Figure 1).[10,11] This result is quite different from what was observed with *N*-(2-methyl-3,4-pentadienyl) toluenesulfonamide **1b**,[4−6,12] with which a mixture of four-membered *trans*-**3b** and six-membered product **4b** were found, indicating a dramatic substituent effect of the R^1 group (Scheme 1). The ratio of **3b**/**4b** depends on the reaction time. After 16 h, the ratio of **3b**/**4b** can reach as high as 4/96 (Scheme 2).

Subsequently, the cyclization reactions of β-amino allene **1a** with a number of differently substituted aryl halides were

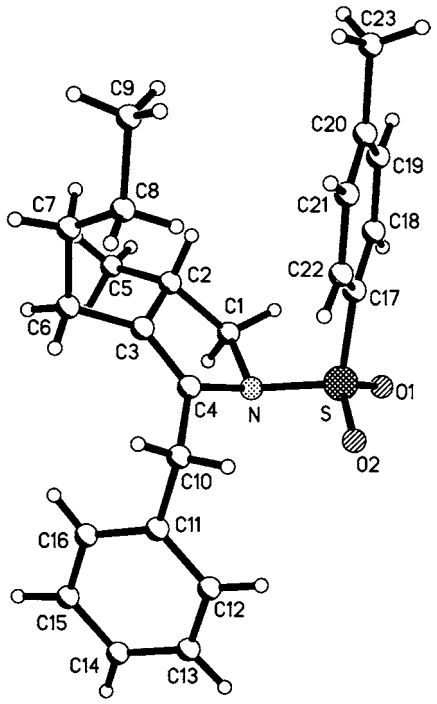
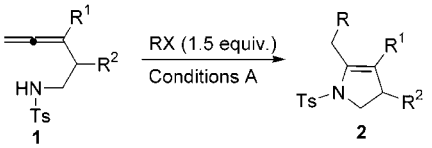


Figure 1. Molecular structure of **2a**.

performed, and the results are summarized in Table 1. All reactions afforded five-membered products in good yields. Both electron-donating and electron-withdrawing aryl iodides can react to afford the corresponding 2,3-dihydropyrrole products in good yields (entries 1 and 2, Table 1). When *p*-bromophenyl iodide was submitted to the identical cyclization conditions, only the carbon−iodine bond was

Table 1. Pd(0)-Catalyzed Coupling−Cyclization Reaction of 2-Alkyl-Substituted-β-Amino Allenes with Organic Halides[9,11] [a]



entry	β-amino allene R^1	β-amino allene R^2		RX	time (h)	yield of **2** (%)[b]
1	C_4H_9-*n*	CH_3	(**1a**)	*p*-$MeOC_6H_4I$	5.5	79 (**2b**)
2	C_4H_9-*n*	CH_3	(**1a**)	*p*-$MeO_2CC_6H_4I$	24	73 (**2c**)
3	C_4H_9-*n*	CH_3	(**1a**)	*p*-BrC_6H_4I	10	82 (**2d**)
4	C_4H_9-*n*	CH_3	(**1a**)	*o*-MeC_6H_4I	10	84 (**2e**)
5	C_4H_9-*n*	CH_3	(**1a**)	*p*-MeC_6H_4I	8	83 (**2f**)
6	C_4H_9-*n*	CH_3	(**1a**)	1-iodonaphthalene	12	80 (**2g**)
7	C_4H_9-*n*	CH_3	(**1a**)	2-iodothiophene	36	68 (**2h**)
8	C_4H_9-*n*	CH_3	(**1a**)	2-bromopyridine	12	68 (**2i**)
9	C_4H_9-*n*	C_3H_7-*n*	(**1c**)	C_6H_5I	24	74 (**2j**)

[a] Reaction was carried out at 70 °C using β-amino allene **1** (0.3 mmol), aryl halide (0.45 mmol), K_2CO_3 (1.2 mmol), and $Pd(PPh_3)_4$ (5 mol %) in DMF (2 mL). [b] Isolated yields based on **1**.

(5) (a) Ohno, H.; Anzai, M.; Toda, A.; Ohishi, S.; Fujii, N.; Tanaka, T.; Takemoto, Y.; Ibuka, T. *J. Org. Chem.* **2001**, *66*, 4904. (b) Anzai, M.; Toda, A.; Ohno, H.; Takemoto, Y.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **1999**, *40*, 7393.

(6) Kang, S.-K.; Baik, T.-G.; Kulak, A. N. *Synlett* **1999**, 324.

(7) (a) Shimizu, I.; Tsuji, J. *Chem. Lett.* **1984**, 233. (b) Vicart, N.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1995**, *36*, 5015.

(8) For a similar observation with cyclic acetamides, see: (a) Karstens, W. F. J.; Stol, M.; Rutjes, F. P. J. T.; Hiemstra, H. *Synlett* **1998**, 1126. (b) Karstens, W. F. J.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron Lett.* **1997**, *38*, 6275.

(9) The staring sulfonamides were prepared according to a known amination procedure reported in ref 2g starting from the corresponding allenols, which, in turn, were synthesized according to the published method; see: (a) Lai, G.; Anderson, W. K. *Synth. Commun.* **1995**, 4087. (b) Kimura, M.; Tanaka, S.; Tamaru, Y. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1689.

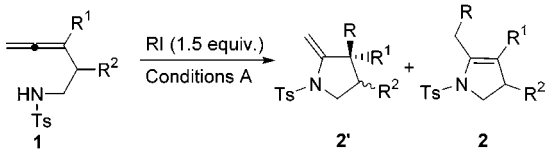
(10) X-ray data for compound **2a**: $C_{23}H_{29}NO_2S$, MW = 383.53, monoclinic, space group *P*2(1)/*n*, Mo Kα, final R indices ($I > 2\sigma(I)$), R_1 = 0.0485, wR_2 = 0.1004, a = 13.8973(12) Å, b = 11.0808(10) Å, c = 14.1022(13) Å, β = 99.199(2)°, V = 2143.7(3) Å^3, T = 20.0 °C, Z = 4, reflections collected/unique 12808/4949 (R_{int} = 0.0568), no observation ($I > 2\sigma(I)$) 2046, parameters 331. CCDC 188167.

(11) All new products were characterized by ^{1}H NMR, ^{13}C NMR, MS, IR, and elemental analysis or HRMS data.

cleaved and the carbon−bromine bond was intact, which leaves opportunity for further elaboration (entry 3, Table 1). The steric effect of the substituent in aryl iodides has limited influence on the outcome of the reaction: the reactions of 2-iodotoluene, 4-iodotoluene, and 1-iodonaphthalene with **1a** produced the corresponding 2,3-dihydropyrroles **2e**−**g**, respectively, in high yields (entries 4−6, Table 1). Heteroaromatic halides such as 2-iodothiophene and 2-bromopyridine could also be used in this transformation (entries 7 and 8, Table 1).

The reaction of **1c** provided five-membered ring **2j** in 74% yield indicating that R^2 can be a general alkyl group (entry 9, Table 1). However, the reaction of **1d** ($R^1 = C_4H_9$-*n*, $R^2 = H$) afforded a mixture of five-membered product with an exo cyclic carbon−carbon double bond **2k′** and 2,3-dihydropyrrole product **2k** in a combined 65% yield in a ratio of 15:85 (entry 1, Table 2). The structure of **2k′** was

Table 2. Control of Regioselectivity in Pd(0)-Catalyzed Coupling−Cyclization Reaction of *β*-Amino Allenes with Organic Halides[9,11] [a]



entry	*β*-amino allene R^1	*β*-amino allene R^2		RI	time (h)	% yield[b] (**2′**/**2**)
1	C_4H_9-*n*	H	(**1d**)	C_6H_5I	8	65 (**2k′**/**2k** = 15/85)[c]
2	C_4H_9-*n*	H	(**1d**)	*p*-$MeOC_6H_4I$	5.5	68 (**2l′**/**2l** = 14/86)[d]
3	C_4H_9-*n*	H	(**1d**)	*p*-$MeO_2CC_6H_4I$	10	77 (**2m′**/**2m** = 15/85)[d]
4	C_4H_9-*t*	H	(**1e**)	C_6H_5I	48	65 (**2n**)
5	C_4H_9-*t*	H	(**1e**)	*p*-$MeOC_6H_4I$	60	77 (**2o**)
6	C_4H_9-*t*	H	(**1e**)	*p*-$MeO_2CC_6H_4I$	96	45 (**2p**)[e]
7	C_4H_9-*t*	CH_3	(**1f**)	C_6H_5I	16	76 (**2q**)
8	C_4H_9-*t*	CH_3	(**1f**)	(*E*)-1-iodohex-1-ene	11	62 (**2r**)

[a] See Table 1. [b] Isolated yields based on **1**. [c] Ratios were determined by isolation. [d] Ratios were determined by ^{1}H NMR spectra (300 MHz). [e] Starting material (28%) **1e** was recovered.

unambiguously determined by a single-crystal X-ray diffraction study (Figure 2).[13] Similar results were obtained when toluene, 1,4-dioxane, or CH_3CN was applied as the reaction solvent. The reaction of **1d** with *p*-methoxyphenyl

(12) We have repeated the Pd(0)-catalyzed coupling−cyclization reaction of simple *N*-(3,4-pentadienyl)sulfonamide with PhI,[4] and the reaction did afford a mixture of four- and six-membered products in a ratio of 79:21. As compared with the literature data,[6] due to the difference of ^{1}H NMR data we observed for the six-membered product, the structure of the six-membered product was established by X-ray diffraction study: $C_{18}H_{19}NO_2S$, MW = 313.40, orthorhombic, space group *P*2(1)2(1)2(1), Mo Kα, final R indices ($I > 2\sigma(I)$), $R_1 = 0.0398$, w$R_2 = 0.0647$, $a = 6.9454(6)$ Å, $b = 11.7277(10)$ Å, $c = 19.6975(18)$ Å, $\beta = 90°$, $V = 1604.4(2)$ Å^3, $T = 20.0$ °C, $Z = 4$, reflections collected/unique 9887/3737 ($R_{int} = 0.0427$), no observation ($I > 2\sigma(I)$) 2403, parameters 275. CCDC 188166.

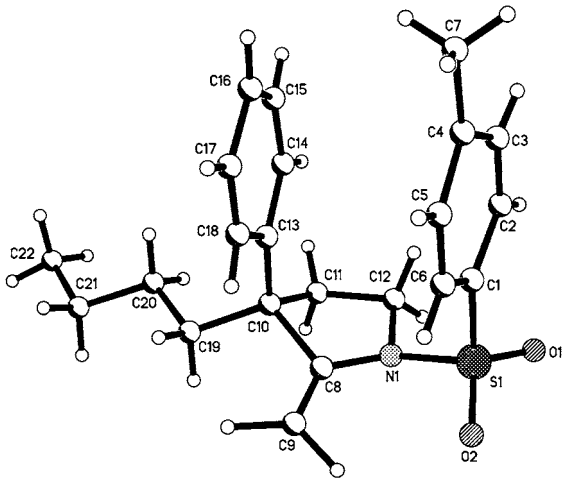
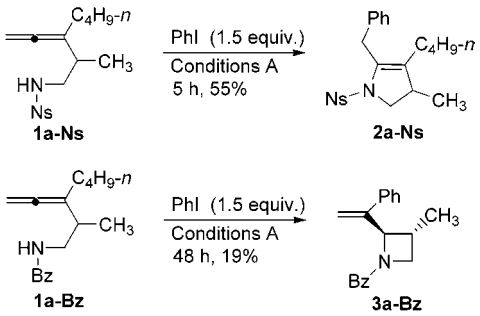


Figure 2. Molecular structure of **2k′**.

iodide or *p*-methoxycarbonylphenyl iodide also afforded a mixture of corresponding five-membered cycles **2′** and **2** in ratios of 14:86 and 15:85, respectively (entries 2 and 3, Table 2). Furthermore, it is interesting to note that with increased steric hindrance of the R^1 group at the 3-position of allenylamine, the regioselectivity of the coupling−cyclization of **1e** or **1f** with aryl iodides gave 2,3-dihydropyrroles **2n**−**r** as the only products (entries 4−8, Table 2). However, prolonged reaction time was necessary to achieve high conversion due to the increased steric hindrance of the allene moiety (compare entries 1−3 with 4−6, Table 2).

Further studies show that the protecting group of the nitrogen atom can also control the reaction pathway. The reaction of N−Ns-substituted *β*-amino allene **1a-Ns**[9] (Ns = 4-nitrobenzenesulfonyl) afforded five-membered product **2a-Ns**,[11] while the reaction of **1a-Bz** (Bz = benzoyl)[9] afforded four-membered azetidine **3a-Bz**[11] as the only product, albeit in low yields (Scheme 3).

Scheme 3



Conclusion

In conclusion, we have observed a unique reaction pathway in the Pd(0)-catalyzed coupling−cyclization reaction of *β*-amino allenes with organic halides leading to the exclusive

formation of 2,3-dihydropyrrole products in good yield. (1) With substituent R^1 in the allene moiety of β-amino allene being an alkyl group, the reaction afforded five-membered products in good yields, while the nonsubstituted substrate gave a mixture of four- and six-membered products. (2) With the N-protecting group R^3 being Bz, the reaction afforded a four-membered product with high selectivity, albeit in low yields. The regioselectivity for the formation of five-membered 2,3-dihydropyrrole was also controlled by the steric hindrance of R^1 and R^2 groups in β-amino allenes.

(13) X-ray data for compound **2k′**: $C_{44}H_{54}N_2O_4S_2$, MW = 739.01, triclinic, space group $P1$, Mo Kα, final R indices ($I > 2\sigma(I)$), $R_1 = 0.0513$, w$R_2 = 0.0798$, $a = 8.073(3)$ Å, $b = 9.733(3)$ Å, $c = 12.997(4)$ Å, $\beta = 76.017(6)°$, $V = 968.5(5)$ Å^3, $T = 20.0$ °C, $Z = 1$, reflections collected/unique 3760/3504 ($R_{int} = 0.0535$), no observation ($I > 2\sigma(I)$) 3760, parameters 509. CCDC 188168.

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Supporting Information Available: Typical experimental procedures and analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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