ORGANIC
LETTERS

2013
Vol. 15, No. 17
4370–4373

Pd(II)-Catalyzed Intramolecular 1,2-Aminoalkylation of Conjugated 1,3-Dienes for the Synthesis of Pyrrolizidines

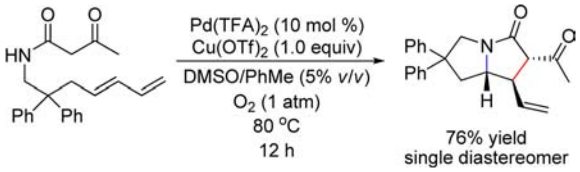
Dong Xing[†,‡] **and Dan Yang**[*,†]

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, China, and Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, No. 3663 North Zhongshan Road, Shanghai, China

yangdan@hku.hk

Received July 7, 2013

ABSTRACT



A palladium(II)-catalyzed tandem cyclization reaction involving an intramolecular 1,2-aminoalkylation of *N*-4,6-dienyl β-keto amides has been developed. This process provides an efficient method for the rapid assembly of pyrrolizidines starting from linear substrates in moderate to good yields and high to excellent diastereoselectivities.

Pd(II)-catalyzed addition of nitrogen nucleophiles to alkenes (aminopalladation) is a well-established process for the construction of C–N bonds in modern organic chemistry.[1] This process has been involved in different types of intramolecular difunctionalization of alkenes for tandem C–N and C–X (X = N, O, C, halide, *etc.*) bond formations.[2–5] Within this context, the intramolecular aminoalkylation of alkenes (tandem C–N and C–C bond formations) is particularly appealing for their efficiency in synthesizing different types of nitrogen-containing heterocycles, which are common motifs widely existing in natural products and pharmaceuticals. Hegedus and Tamaru have extensively developed the Pd(II)-catalyzed aminocarbonylation of alkenes by employing CO as the carbon source.[6]

[†] The University of Hong Kong.

[‡] East China Normal University.

(1) (a) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Sigman, M. S.; Schultz, M. J. *Org. Biomol. Chem.* **2004**, *2*, 2551. (c) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910. (d) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (e) Hartwig, J. F. *Nature* **2008**, *455*, 314. (f) McDonald, R. I.; Liu, G. S.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981.

(2) For selected reviews, see: (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (c) Conreaux, D.; Bouyssi, D.; Monteiro, N.; Balme, G. *Curr. Org. Chem.* **2006**, *10*, 1325. (d) Tietze, L. F.; Kinzel, T. *Pure Appl. Chem.* **2007**, *79*, 629. (e) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142. (f) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083.

(3) For Pd(II)-catalyzed diamination of alkenes, see: (a) Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269. (b) de Figueiredo, R. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1190. (c) Streuff, J.; Hovelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586. (d) Muñiz, K.; Hovelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763. (e) Muñiz, K.; Streuff, J.; Chávez, P.; Hövelmann, C. H. *Chem.—Asian J.* **2008**, *3*, 1248. (f) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945. (g) Muñiz, K.; Martínez, C. *J. Org. Chem.* **2013**, *78*, 2168. (h) Ingalls, E. L.; Sibbald, P. A.; Kaminsky, W.; Michael, F. E. *J. Am. Chem. Soc.* **2013**, *135*, 8854.

(4) For Pd(II)-catalyzed aminoacetoxylation of alkenes, see: (a) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690. (b) Liu, G. S.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179. (c) Martínez, C.; Wu, Y.; Weinstein, A. B.; Stahl, S. S.; Liu, G.; Muñiz, K. *J. Org. Chem.* **2013**, *78*, 6309.

(5) For Pd(II)-catalyzed aminohalogenation of alkenes, see: (a) Lei, A. W.; Lu, X. Y.; Liu, G. S. *Tetrahedron Lett.* **2004**, *45*, 1785. (b) Manzoni, M. R.; Zabawa, T. P.; Kasi, D.; Chemler, S. R. *Organometallics* **2004**, *23*, 5618. (c) Li, G.; Kotti, S. R. S. S.; Timmons, C. *Eur. J. Org. Chem.* **2007**, 2745. (d) Michael, F. E.; Sibbald, P. A.; Cochran, B. M. *Org. Lett.* **2008**, *10*, 793. (e) Wu, T.; Yin, G. Y.; Liu, G. S. *J. Am. Chem. Soc.* **2009**, *131*, 16354. (f) Qiu, S.; Xu, T.; Zhou, J.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 2856. (g) Liu, G. *Org. Biomol. Chem.* **2012**, *10*, 6243.

(6) (a) Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583. (b) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1988**, *110*, 3994. (c) Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5731. (d) Harayama, H.; Abe, A.; Sakado, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1997**, *62*, 2113. (e) Koós, P.; Spánik, I.; Gracza, T. *Tetrahedron: Asymmetry* **2009**, *20*, 2720. (f) Tsujihara, T.; Shinohara, T.; Takenaka, K.; Takizawa, S.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Org. Chem.* **2009**, *74*, 9274.

10.1021/ol401901h

Wolfe and co-workers reported the Pd(0)-catalyzed aminoarylation of amino-tethered alkenes with aryl bromides.[7] Michael and co-workers reported a novel example in which a Pd(II)-catalyzed aminoarylation of alkenes was utilized via C−H activation of arenes.[8] In recent years, our research group has developed a series of Pd(II)-catalyzed intramolecular aminoalkylation of alkenes by applying a Heck-type termination of the aminopalladation process with an intramolecularly tethered alkene moiety.[9] As part of our continuous interest in developing new tandem cyclization reactions under Pd(II)-catalyzed oxidative conditions, herein we report a highly efficient Pd(II)-catalyzed intramolecular 1,2-aminoalkylation of *N*-4,6-dienyl *β*-keto amides for the synthesis of pyrrolizidines.

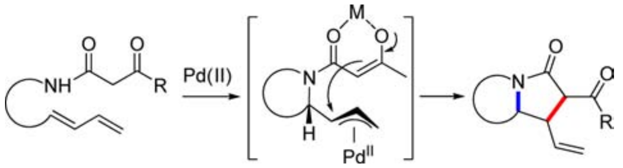
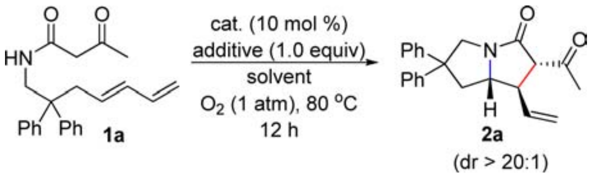


Figure 1. Proposed intramolecular 1,2-aminoalkylation.

It has been reported that, under Pd(II) catalytic conditions, 1,3-dienes could undergo different types of oxidative nucleophilic difunctionalization.[10] In the presence of the adjacent alkene moiety, the Pd(II)-alkyl intermediate generated by the initial nucleopalladation could be rapidly converted into a more electrophilic *π*-allyl species, therefore allowing a second nucleophilic attack to establish an overall tandem sequence.[2f,10] Following Bäckvall's pioneering work on a series of Pd(II)-catalyzed 1,4-difunctionalization of 1,3-dienes,[11] intramolecular 1,4-diamination,[10a] 1,2-diamination,[10b] and 1,2-dialkylation of 1,3-dienes[10c,d] have been recently developed. However, intramolecular transformations involving different bond formations (i.e., C−N and C−C bond formations) have not been explored. Based on this 1,3-diene-involving catalytic mode, we hypothesized that, under Pd(II) catalytic conditions, in the presence of a tethered diene, a *β*-keto amide would act as a 2-fold nucleophile responsible for both C−N and C−C bond formation to undergo an overall intramolecular 1,2-aminoalkylation *via* a sequence of aminopalladation/Pd(II) *π*-allyl species formation/2nd nucleophilic addition (Figure 1).

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	additive	solvent	yield[b] (%)
1	$Pd(OAc)_2$	–	DMSO	24
2	$Pd(OAc)_2$	$Cu(OTf)_2$	DMSO	35
3	$Pd(OAc)_2$	$Cu(OTf)_2$	DMSO/PhMe (1/4)	47
4	$Pd(OAc)_2$	$Cu(OTf)_2$	DMSO/PhMe (5% *v*/*v*)	56
5[c]	$Pd(OAc)_2$	$Cu(OTf)_2$	PhMe	<5
6	$Pd(TFA)_2$	$Cu(OTf)_2$	DMSO/PhMe (5% *v*/*v*)	78(76)[d]
7	$Pd(TFA)_2$	$Cu(OAc)_2$	DMSO/PhMe (5% *v*/*v*)	<5
8	$Pd(TFA)_2$	–	DMSO/PhMe (5% *v*/*v*)	34
9	–	$Cu(OTf)_2$	DMSO/PhMe (5% *v*/*v*)	<5

[a] All reactions were carried out on a 0.3 mmol scale. [b] Yield determined by ^{1}H NMR using nitrobenzene as internal standard. [c] With 20 mol % (0.06 mmol) DMSO. [d] Isolated yield shown in the parentheses.

The Pd(II) catalyst in DMSO has been proven as an efficient catalyst system for both oxidative amination reactions[12] and the alkylation of Pd(II) *π*-allyl species;[13] therefore it would be a good catalytic system for the initial investigation of our hypothesized intramolecular 1,2-aminoalkylation. As the starting point, (*E*)-*N*-(2,2-diphenylhepta-4,6-dienyl)-3-oxobutanamide **1a** was synthesized and subjected to 10 mol % of $Pd(OAc)_2$ in DMSO under 1 atm of O_2. To our delight, the desired product **2a** was obtained as a single diastereomer in 24% yield (Table 1, entry 1). Inspired by this result, further optimizations were conducted to improve the efficiency of this transformation. To enhance the nucleophilic ability of the acidic methylene moiety, different Lewis acids were tested,[14] however, only $Cu(OTf)_2$ could slightly enhance the product yield (Table 1, entry 2). Changing the solvent from DMSO to a 1:4 mixture of DMSO in toluene enhanced the yield to 47% (Table 1, entry 3); an even higher yield was achieved when 5% v/v DMSO in toluene was used (Table 1, entry 4).

---

(7) For a review and selected examples, see: (a) Schultz, D. M.; Wolfe, J. P. *Synthesis-Stuttgart* **2012**, *44*, 351. (b) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605. (c) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644. (d) Mai, D. N.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 12157.

(8) Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 9488.

(9) (a) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130. (b) He, W.; Yip, K.-T.; Zhu, N.-Y.; Yang, D. *Org. Lett.* **2009**, *11*, 5626. (c) Yip, K. T.; Zhu, N. Y.; Yang, D. *Org. Lett.* **2009**, *11*, 1911. (d) Yip, K.-T.; Yang, D. *Org. Lett.* **2011**, *13*, 2134. (e) Yip, K.-T.; Yang, D. *Chem.—Asian. J.* **2011**, *6*, 2166.

(10) (a) Andersson, P. G.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 8696. (b) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308. (c) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066. (d) Coscia, R. W.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 2496. (e) Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 6950. (f) Liao, L.; Jana, R.; Urkalan, K. B.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 5784. (g) McCammant, M. S.; Liao, L.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 4167.

(11) For selected examples, see: (a) Bäckvall, J. E.; Bystroem, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619. (b) Bäckvall, J. E.; Nystroem, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676. (c) Bäckvall, J. E.; Andersson, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 3683. (d) Bäckvall, J. E.; Andersson, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 6374. (e) Castano, A. M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1995**, *117*, 560.

(12) (a) van Benthem, R. A. T. M.; Hiemstra, H.; Longarela, G. R.; Speckamp, W. N. *Tetrahedron Lett.* **1994**, *35*, 9281. (b) Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749. (c) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584. (d) Liu, G. S.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328.

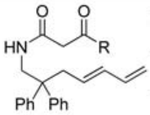
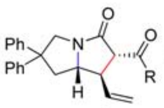
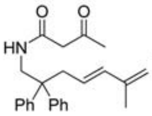
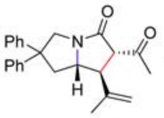
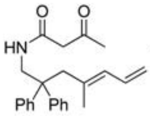
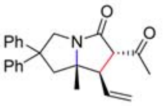
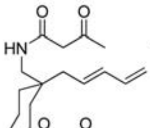
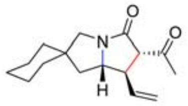
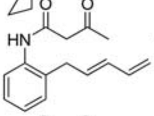
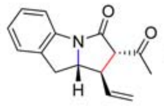
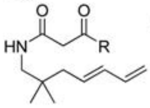
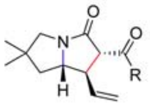
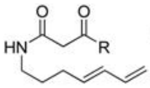
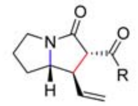
(13) Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090.

(14) For details, see Supporting Information.

However, the use of 10 mol % of $Pd(OAc)_2$ and 20 mol % of DMSO in toluene resulted in a poor yield (Table 1, entry 5), indicating that the role of DMSO is not merely a ligand. The best result was achieved when $Pd(TFA)_2$ was used as a palladium source, yielding the desired product in 76% isolated yield as a single diastereomer (Table 1, entry 6). Replacing $Cu(OTf)_2$ with $Cu(OAc)_2$ gave no desired product (Table 1, entry 7), indicating that $Cu(OTf)_2$ acts as a Lewis acid rather than a co-oxidant. However, at this stage we could not preclude the possibility that $Cu(OTf)_2$ played both roles. Control experiments revealed that both the Pd(II) salt and $Cu(OTf)_2$ are indispensable for this transformation (Table 1, entries 8 and 9).

With the optimized reaction conditions in hand, the substrate scope of this Pd(II)-catalyzed tandem cyclization reaction was investigated. Different substituents on the amide unit were first tested. With a 3-oxopropanoate substituent (**1b**), no desired product was observed (Table 2, entry 2). However, in the presence of a 3-oxo-3-phenylpropanamide unit (**1c**), the corresponding product **2c** was obtained in 86% yield with high diastereoselectivity (> 20:1) (Table 2, entry 3). Since **1b** did not give an efficient keto–enol tautomerization compared with **1a** and **1c**, these experimental outcomes indicated that the efficiency of the second nucleophilic addition from the acidic methylene unit to the Pd(II) π-allyl species is highly responsible for the overall transformation. Different (*E*)-dienyl units were further investigated. Substrates with methyl substituents at the C6 (**1d**) or C4 position (**1e**) could be readily converted to the corresponding products in good yields with excellent diastereoselectivities (> 20:1) (Table 2, entries 4 and 5). Other substrates bearing different *gem*-disubstituents at the C2 position were also tested. With cyclohexyl (**1f**) or dimethyl substituents (**1h**) at the C2 position, the transformation was less efficient, yielding the desired product **2f** and **2h** in 59% and 54% yield, respectively (Table 2, entries 6 and 8). When there was no additional substituent on the alkyl chain (**1j**), an even poorer reactivity was observed, and the desired product **2j** could only be formed in 32% yield (Table 2, entry 10). These results indicate that the C2-diphenyl substituent is crucial for this tandem process to proceed in good yield, probably because it promotes the ring closure by restricting the substrate to a more rigid structure and therefore shortening the distance between the β-keto amide and the diene unit (Thorpe–Ingold effect).[15] Aniline-derived substrate **1g** also underwent the desired cyclization to afford tricyclic compound **2g** in 51% yield (Table 2, entry 7). For those substrates bearing less hindered substituents on the alkyl chain, replacing the methyl group on the β-keto amide unit with a phenyl group improved the product yields from 54% to 74% and 32% to 43%, respectively, albeit with slightly decreased diastereoselectivities (Table 2, entries 9 and 11). The relative stereochemistry of products was assigned in analogy with **2c** as determined by single-crystal X-ray diffraction (Figure 2).[16]

Table 2. Substrate Scope of Pd(II)-Catalyzed Intramolecular 1,2-Aminoalkylation of *N*-4,6-Dienyl β-Keto Amides[a]

entry	substrate		product		time (h)	yield[b,c] (%)
1		**1a** R = Me		**2a**	12	76
2		**1b** R = OEt		**2b**	24	< 5
3		**1c** R = Ph		**2c**	12	86
4		**1d**		**2d**	12	76
5		**1e**		**2e**	12	73
6		**1f**		**2f**	12	59
7		**1g**		**2g**	24	51
8		**1h** R = Me		**2h**	24	54
9		**1i** R = Ph		**2i**	24	74 (dr = 11:1)
10		**1j** R = Me		**2j**	24	32
11		**1k** R = Ph		**2k**	24	43 (dr = 9:1)

[a] All reactions were carried out on a 0.3 mmol scale with 10 mol % $Pd(TFA)_2$ and 1 equiv of $Cu(OTf)_2$ in 5% v/v of DMSO/toluene (6 mL). [b] Isolated yield. [c] Diastereomeric ratio determined by ^1H NMR, unless otherwise stated; the diastereoselectivities were larger than 20:1.

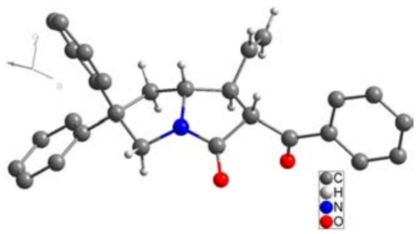


Figure 2. X-ray crystal structure of **2c**.

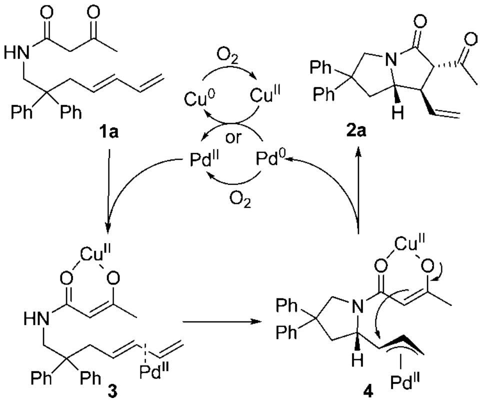
Shown in Scheme 1 is a proposed mechanism for this Pd(II)-catalyzed intramolecular 1,2-aminoalkylation. Substrate **1a** first coordinates with both the Pd(II) catalyst and $Cu(OTf)_2$ to generate complex **3**. Intramolecular nucleophilic attack from the amide nitrogen toward the Pd(II)-coordinated diene (aminopalladation) would form

---

[15] (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1915**, *107*, 1080. (b) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.

[16] A stereoselective intramolecular diamination of urea-tethered 1,3-dienes in which the two hydrogen atoms of the former internal double bond also displayed *anti* positioning was reported; see ref 3e.

Scheme 1. Proposed Mechanism for the Pd(II)-Catalyzed Intramolecular 1,2-Aminoalkylation of *N*-4,6-Dienyl *β*-Keto Amides



a Pd(II)-alkyl intermediate with the five-membered ring formation. This Pd(II)-alkyl intermediate would be rapidly converted into a more electrophilic π-allyl intermediate **4**.[3e,10,17] A second nucleophilic attack from the enol to the π-allyl moiety would produce the desired product **2** and generate a Pd(0) species which, in the presence of O_2, would be oxidized into Pd(II), completing the catalytic cycle.[1f,2f,18]

In summary, we have developed an efficient Pd(II)-catalyzed intramolecular 1,2-aminoalkylation of *β*-keto amide-tethered 1,3-dienes. This tandem cyclization reaction allows the rapid synthesis of a series of pyrrolizidines in moderate to good yields with high to excellent diastereoselectivities. The expansion of this method toward the synthesis of other types of nitrogen-bridged bicyclic compounds and exploration toward the asymmetric control of this transformation are currently underway in our laboratory.

Acknowledgment. We thank the University of Hong Kong and Hong Kong Research Grants Council (HKU 706109P and HKU 706112P) for financial support. We thank Dr. N.-Y. Zhu from the Department of Chemistry, the University of Hong Kong for performing the X-ray crystallographic analysis. We thank Dr. J. F. Zhao from the Department of Chemistry, the University of Hong Kong for proofreading this manuscript.

Supporting Information Available. Experimental procedures, spectral data for **1** and **2**, and X-ray crystal data of compound **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(17) For the involvement of π-allyl intermediates in a series of Pd(0)-catalyzed diamination of butadienes, see: (a) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (b) Xu, L.; Du, H.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 7038. (c) Zhao, B.; Du, H.; Cui, S.; Shi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 3523.

(18) A similar mechanism involving the aminopalladation/π-allyl intermediate formation/second nucleophilic addition sequence was proposed and studied for an intramolecular diamination of urea-tethered 1,3-dienes; see ref 3e.

The authors declare no competing financial interest.