Cyclization Reactions

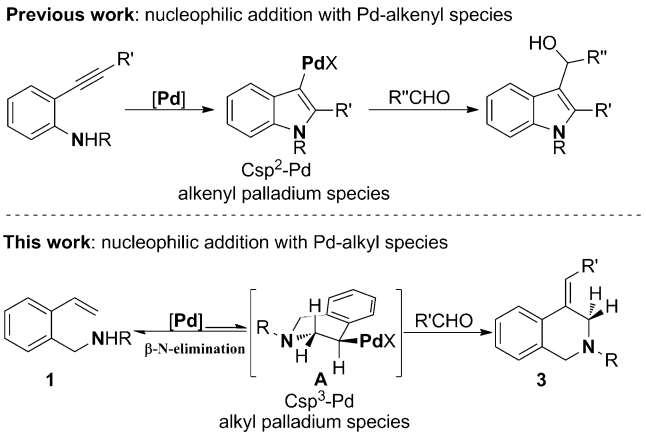
International Edition: DOI: 10.1002/anie.201611853
German Edition: DOI: 10.1002/ange.201611853

Palladium-Catalyzed Ring-Forming Aminoalkenylation of Alkenes with Aldehydes Initiated by Intramolecular Aminopalladation

*Yue Hu, Yinjun Xie, Zhiqiang Shen, and Hanmin Huang**

Abstract: *A palladium-catalyzed aminopalladation reaction followed by nucleophilic addition with aldehydes and dehydration is described. This direct and operationally simple procedure provides a rapid and reliable approach to a wide range of functionalized tetrahydroisoquinolines with high selectivity. Mechanistic studies disclosed that the nucleophilic addition, performed via a highly ordered transition-state, is the turnover-limiting step in which the inherent β-hydride elimination of the key Csp³–Pd species was controlled by the confined conformation and the nucleophilicity of the Csp³–Pd bond was enhanced by the strong electron-donating effect of the nitrogen atom.*

Transition-metal-catalyzed nucleophilic addition of organometallics to carbon–heteroatom multiple bonds is widely used in synthetic organic chemistry.[1] Crucial to the scenario was the formation of active transition-metal–carbon species through transmetalation with stoichiometric amounts of organometallics, which often produced a large amount of wasteful byproducts. To avoid the use of stoichiometric amounts of organometallics, Lu and co-workers developed an elegant strategy for the generation of active Csp²–Pd species through acetoxypalladation, aminopalladation, or hydropalladation of alkynes, which established a series of Pd-catalyzed tandem reactions without wasteful byproducts generation.[2] Despite tremendous efforts over the last decade, such reactions only can be performed with alkynes as coupling partners (Scheme 1). The same type of tandem reactions using alkenes as coupling partners has remained largely unexplored, and the underlying reason for this deficiency may stem from the rapidly occurring β-hydride elimination of the alkylpalladium species resulting from the corresponding nucleopalladation of alkenes.[3] Herein, we report a unified approach for realizing this kind of tandem reaction with an alkene as the coupling partner by controlling the inherent β-hydride elimination of the resulting alkylpalladium species, and tuning the electronic nature of the amine moiety. Such a reaction would be particularly valuable for the synthesis of tetrahydroisoquinolines, which represent a ubiquitous motif widely found in many natural alkaloids and biologically active compounds.[4]



Scheme 1. Palladium-catalyzed nucleophilic addition initiated by aminopalladation.

Aminopalladation of alkenes is a fundamental process for generation of alkylpalladium intermediates, which commonly undergo β-hydride elimination to produce oxidative amination products.[5] On the other hand, such intermediates could be further converted into valuable functionalized products by controlling the inherent β-hydride elimination. Previous work pioneered by Sanford and co-workers has demonstrated that oxidizing the alkylpalladium(II) species to a high-valent alkyl-Pd^{IV} complex is an efficient strategy for direct conversion of the Csp³–Pd bond into diverse C–X bonds by suppressing the β-hydride elimination.[6,7] However, such interception is not compatible with non-redox addition reactions, and stoichiometric amounts of strong oxidants were also needed, leading to the generation of wasteful byproducts. In principle, β-hydride elimination occurs most readily from metal–alkyl complexes that can adopt a *syn*-coplanar arrangement of the metal and the hydride groups.[8] On the basis of this concept, we reasoned that the intermediate **A**, accessed from the reversible intramolecular aminopalladation of 2-vinylbenzylamine **1**, could slow the β-hydride elimination due to the unfavorable conformation. Because the nucleophilicity of the Csp³–Pd species is stronger than that of Csp²–Pd species and the polarity of the Csp³–Pd bond in intermediate **A** would be increased by the electron-donating effect of the nitrogen atom located at the β-position,[2] it would be expected that the intermediate **A**

[*] Y. Hu, Dr. Y. Xie, Z. Shen, Prof. Dr. H. Huang
State Key Laboratory for Oxo Synthesis and Selective Oxidation
Lanzhou Institute of Chemical Physics
Chinese Academy of Sciences
Lanzhou 730000 (P. R. China)
E-mail: hanmin@ustc.edu.cn
Prof. Dr. H. Huang
Department of Chemistry
University of Science and Technology of China
Hefei, 230026 (P. R. China)
Y. Hu
University of Chinese Academy of Sciences
Beijing 100049 (P. R. China)

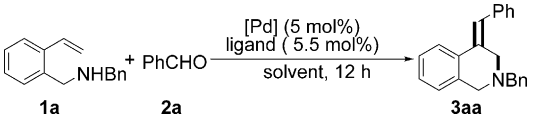
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201611853.

might be intercepted by a electrophile through irreversible nucleophilic addition to drive the equilibrium toward the product. One potential problem facing the development of this tandem reaction is the competition between β-nitrogen elimination and the proposed nucleophilic addition with aldehydes. We believed that these rates could be controlled by tuning the electronic nature of the nitrogen and the ligand environment in the palladium complex. Given the formidable challenge of controlling the β-hydride elimination of alkyl-palladium species, this investigation should be of great interest for the development of palladium-catalyzed alkene difunctionalization reactions.

To test the viability of the envisioned strategy, we started the investigation by exploring the reaction of *N*-benzyl-1-(2-vinylphenyl)methanamine (**1a**) with benzaldehyde (**2a**) in the presence of palladium catalyst. To our delight, the trisubstituted alkene **3aa** with a tetrahydroisoquinoline skeleton was obtained in 47% yield when the reaction was conducted at 110°C in 2-PrOH with $PdCl_2$/Xantphos as catalyst. The solid structure of **3aa** was unambiguously determined by single-crystal X-ray diffraction analysis.[9] The product of **3aa** could be viewed as the dehydration product of the corresponding alcohol derived from nucleophilic addition, which indicated that the tandem aminopalladation and nucleophilic addition indeed took place. Inspired by this result, we started to optimize the reaction condition by screening the catalyst system (Supporting Information) and observed that [Pd(allyl)Cl]$_2$/Xantphos turned out to be far superior, providing **3aa** in 72% yield (Table 1, entries 4). In contrast, no reaction occurred when $Pd_2(dba)_3$/Xantphos was utilized as catalyst, which indicated that this reaction was most likely initiated with Pd^{II}. Moreover, other typical Lewis acids, such as $Zn(OTf)_2$, $AlCl_3$, and $Fe(OTs)_3$, were ineffective for promoting this reaction (Supporting Information), suggesting that the reaction is most likely not Lewis-acid-catalyzed. Apart from 2-PrOH, the reaction could also be conducted in other protic solvents such as CH_3OH, C_2H_5OH, and *n*-PrOH (Table 1, entries 7–9). Other non-protic solvents like CH_3CN were also suitable for this reaction, but only moderate yields were obtained (Table 1, entry 10). Among the solvents tested, C_2H_5OH was found to be the most effective. Further examination showed that when the ratio of **1a**:**2a** was changed from 1:1 to 1:1.5, the yield of **3aa** was raised to 86% (Table 1, entry 8 and entries 11–12). Subsequently, the effect of temperature was also investigated. When the temperature raised to 120°C, the yield of **3aa** was increased to 86% while the ratio of **1a**:**2a** was kept in 1:1.2 (Table 1, entry 13). However, when the temperature decreased to 100°C, the yield of **3aa** sharply dropped to 56% (Table 1, entry 14). Finally, control experiments showed that the desired product **3aa** was not formed in the absence of palladium catalyst (Supporting Information). It is worth mentioning that the reaction is highly selective to give the Z-isomer as the only product and no β-hydride elimination product was observed.

With the optimized conditions in hand, we next examined the scope of aldehydes for this reaction. A series of aromatic aldehydes with electron-donating or -withdrawing groups gave the desired products **3aa**–**3ai** in good yields (Table 2). The steric hindrance of the substituents on the aryl ring of the aldehydes exerted a strong influence on the reactivity (**3aa** vs. **3ab**). Several valuable functional groups, such as methyl (**3ab** and **3ac**), fluoro (**3ad** and **3ag**), chloro (**3ae** and **3ah**), and trifluoromethyl (**3ai**) groups, were tolerated at different positions of product **3**, providing ample opportunity for

Table 1: Screening of reaction conditions.[a]

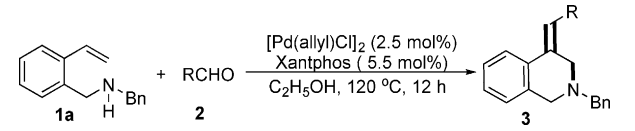


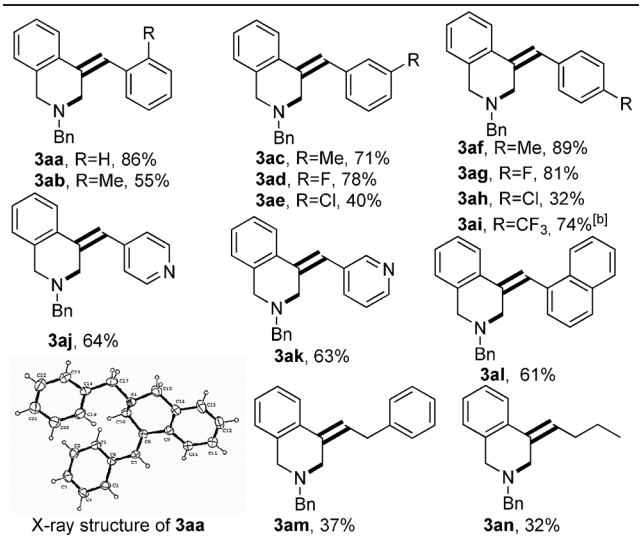
1a 2a 3aa

Entry	[Pd]	Ligand	Solvent	*T* [°C]	Yield [%][b]
1	$PdCl_2$	Xantphos	2-PrOH	110	47
2	$Pd(OAc)_2$	Xantphos	2-PrOH	110	trace
3	Pd_2dba_3	Xantphos	2-PrOH	110	NR
4	[Pd(allyl)Cl]$_2$	Xantphos	2-PrOH	110	72
5	[Pd(allyl)Cl]$_2$	DPEphos	2-PrOH	110	41
6	[Pd(allyl)Cl]$_2$	BINAP	2-PrOH	110	29
7	[Pd(allyl)Cl]$_2$	Xantphos	CH_3OH	110	79
8	[Pd(allyl)Cl]$_2$	Xantphos	C_2H_5OH	110	81
9	[Pd(allyl)Cl]$_2$	Xantphos	n-PrOH	110	80
10	[Pd(allyl)Cl]$_2$	Xantphos	CH_3CN	110	48
11[c]	[Pd(allyl)Cl]$_2$	Xantphos	C_2H_5OH	110	82
12[d]	[Pd(allyl)Cl]$_2$	Xantphos	C_2H_5OH	110	86
13[c]	[Pd(allyl)Cl]$_2$	Xantphos	C_2H_5OH	120	86
14[c]	[Pd(allyl)Cl]$_2$	Xantphos	C_2H_5OH	100	56

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), [Pd] (5 mol%), ligand (5.5 mol%), solvent (2 mL), 12 h, unless otherwise noted. [b] Isolated yield. Bn = benzyl. [c] **2a** (0.6 mmol). [d] **2a** (0.75 mmol).

Table 2: Substrate scope of aldehydes.[a]



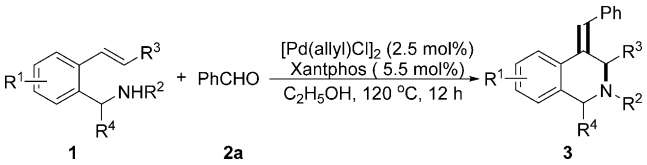


[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.6 mmol), [Pd(allyl)Cl]$_2$ (0.0125 mmol), Xantphos (0.0275 mmol), C_2H_5OH (2 mL), 120°C for 12 h, unless otherwise noted, isolated yields are shown. Bn = benzyl. [b] 15 h.

further elaboration of the products. Aside from the benzaldehydes, naphthyl-derived aldehyde **2l** was also compatible with this process to afford the desired product **3al** in 61% yield. Furthermore, heterocyclic aldehydes such as isonicotinaldehyde and nicotinaldehyde were also suitable for this reaction to provide the desired products **3aj** and **3ak** in 64% and 63% yields, respectively. In addition, aliphatic aldehydes were also applicable, but showed much lower reactivities, only moderate yields were obtained (**3am** and **3an**), which may arise from their inherently lower electrophilicity.

Next, the scope and generality of substituted 2-vinylbenzylamines were also explored under the optimized reaction conditions. First, as expected, the substituent on the nitrogen atom of **1a** significantly impacted the reactivity. It was found that the electron-donating alkyl groups could promote the reaction (Table 3, entries 1–3). In contrast, no

Table 3: Substrate scope of 2-vinylbenzylamines.[a]



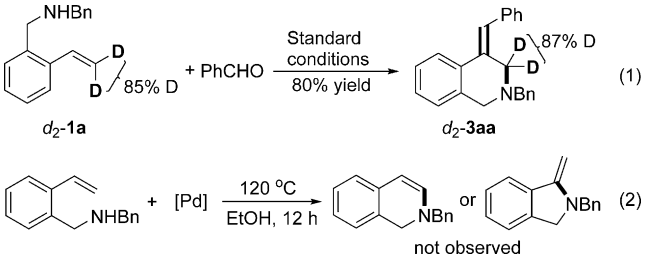
1 2a 3

Entry	R^1	R^2	R^3	R^4	Yield [%][b]
1	H	Bn	H	H	**3aa**, 86
2[c]	H	*n*-Pr	H	H	**3ba**, 81
3[d]	H	c-C_6H_{11}	H	H	**3ca**, 69
4	H	H	H	H	**3da**, NR
5	H	Ac	H	H	**3ea**, NR
6	H	Ts	H	H	**3fa**, NR
7	5-Me	Bn	H	H	**3ga**, 70
8	4-Me	Bn	H	H	**3ha**, 78
9	5-F	Bn	H	H	**3ia**, 73
10[e]	5-Cl	Bn	H	H	**3ja**, 75
11[f]	H	Bn	Ph	H	**3ka**, 86
12[c]	H	Bn	H	CH_3	**3la**, 70

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), $[Pd(allyl)Cl]_2$ (0.0125 mmol), Xantphos (0.0275 mmol), C_2H_5OH (2 mL), 120°C for 12 h, unless otherwise noted. [b] Isolated yields. Bn = benzyl. [c] 24 h. [d] 140°C for 48 h. [e] 18 h. [f] 140°C for 24 h.

reaction occurred when an electron-withdrawing group such as tosyl and acetyl was installed onto the nitrogen atom (Table 3, entries 5–6). This is in sharp contrast with the many reported aminopalladation reactions in which substrates with electron-withdrawing groups on the nitrogen atom showed higher reactivity.[5–7] We attribute this difference in reactivity to the electron-donating group at the nitrogen atom, which could increase the electron-donating effect of the nitrogen to enhance the nucleophilicity of the resulting alkylpalladium species. Substrates without substituent on the nitrogen atom were also tried, and the corresponding imine resulting from the aldehyde was obtained and no desired product was detected (Table 3, entry 4). Next, the substituents on the benzene ring were investigated and found that substrates with electron-donating or electron-withdrawing groups gave the corresponding adducts in good yields (Table 3, entries 7–10). Interestingly, the internal alkene **1k** proved amenable to the standard conditions, affording **3ka** in 86% yield (Table 3, entry 11). In addition, a substrate with a methyl group at the α-position of the amine could be easily converted into the desired product **3la** in 70% yield (Table 3, entry 12). The structure of products **3ka** and **3la** were confirmed by X-ray single-crystal diffraction analysis.[9]

To illustrate the mechanism of the present palladium-catalyzed tandem reaction, d_2-**1a** was first synthesized and subjected to the standard reaction conditions to evaluate whether or not the β-hydride elimination occurred in the present reaction. The result demonstrated that the content of deuterium in the desired product d_2-**3aa** was almost the same as that in substrate d_2-**1a** [Scheme 2, Eq. (1)]. Furthermore,



Scheme 2. Preliminary mechanistic studies.

treatment of **1a** with stoichiometric amounts of palladium complex under the standard reaction conditions, resulted in complete recovery of **1a**, and no oxidative amination products derived from β-hydride elimination were observed [Scheme 2, Eq. (2)]. The above results support the supposition that β-hydride elimination indeed did not take place in the present reaction system, and suggest that the aminopalladation is reversible. To gain further mechanistic insights, we examined the kinetics for the reactions of **1a** and **2a**. Initial rates for the reactions were then measured by varying the concentrations of **1a** and **2a** as well as the palladium catalyst. These experiments revealed a first-order dependence of the rate on the concentrations of both 2-vinylbenzylamine **1a** and aldehyde **2a**. Moreover, a first-order dependence of the rate on catalyst concentration was also observed (Supporting Information). These results indicated that the two substrates, **1a** and **2a**, and the catalyst were involved in the turnover-limiting step. Because the aminopalladation is reversible, we believe that the nucleophilic addition is most likely to be a turnover-limiting step.[10]

On the basis of the kinetic analysis and control experiments, a plausible reaction mechanism for this process is proposed (Figure 1).

Initially, the coordination of the C–C double bond to the Pd^{II} center followed by aminopalladation produces the alkylpalladium species **I**, which is reversible, to convert into the reactant **1** via β-nitrogen elimination. The strong electron-donating effect of the nitrogen atom makes the transient alkylpalladium species nucleophilic enough to be trapped by an aldehyde through the highly ordered transition state **II**, leading to the intermediate **III** to drive the equilibrium toward the product. Protonolysis of intermediate **III** gives rise

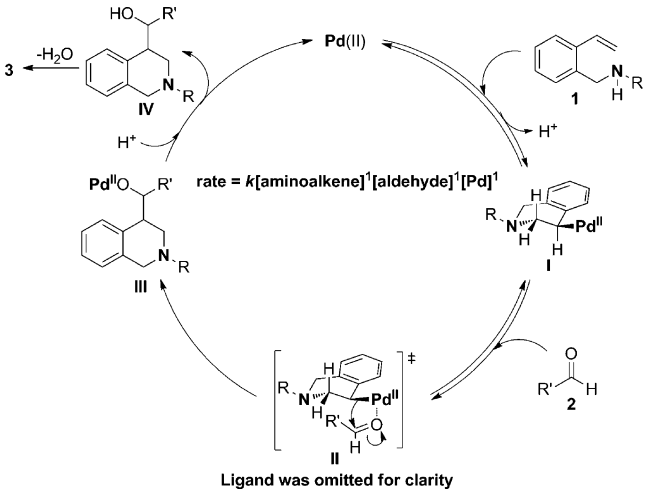


Figure 1. Plausible reaction mechanism.

to intermediate **IV** with regeneration of the palladium catalyst. Dehydration of intermediate **IV** takes place at high temperature to release the final product **3** together with one equivalent of H_2O as the sole byproduct.

In summary, a strategy for controlling the inherent β-hydride elimination and enhancing the nucleophilicity of alkylpalladium (Csp^3–Pd) species generated in the aminopalladation of alkenes was established and enabled the development of a new palladium-catalyzed tandem reaction of aminoalkenes with aldehydes. One C–N and one C=C bond are formed in this transformation, providing facile access to a wide range of biologically active functionalized tetrahydroisoquinolines. Mechanistic studies demonstrated that the effective C–N and C–C bond formation possibly results from the confined conformation and strong electron-donating effect of the nitrogen atom of the alkylpalladium species. Further detailed mechanistic studies and applications based on this chemistry are currently in progress.

Acknowledgements

This research was supported by the CAS Interdisciplinary Innovation Team, and the National Natural Science Foundation of China (21672199 and 21372231).

Conflict of interest

The authors declare no conflict of interest.

Keywords: aminopalladation · β-hydride elimination · nucleophilic addition · palladium · tandem reactions

[1] For reviews, see: a) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069; b) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731; c) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169; d) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; e) L. Yang, H. Huang, *Chem. Rev.* **2015**, *115*, 3468; f) J. R. Hummel, J. A. Boerth, J. A. Ellman, *Chem. Rev.* **2016**, DOI: 10.1021/acs.chemrev.6b00661.

[2] For leading references, see: a) A. Lei, X. Lu, *Org. Lett.* **2000**, *2*, 2357; b) A. Lei, X. Lu, *Org. Lett.* **2000**, *2*, 2699; c) L. Zhao, X. Lu, *Org. Lett.* **2002**, *4*, 3903; d) L. Zhao, X. Lu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4343; *Angew. Chem.* **2002**, *114*, 4519; e) B. Zhao, X. Lu, *Org. Lett.* **2006**, *8*, 5987; f) J. Song, Q. Shen, F. Xu, X. Lu, *Org. Lett.* **2007**, *9*, 2947; g) X. Yu, X. Lu, *Org. Lett.* **2009**, *11*, 4366; h) X. Han, X. Lu, *Org. Lett.* **2010**, *12*, 3336; i) G. Xia, X. Han, X. Lu, *Adv. Synth. Catal.* **2012**, *354*, 2701; j) K. Shen, X. Han, X. Lu, *Org. Lett.* **2013**, *15*, 1732; k) G. Xia, X. Han, X. Lu, *Org. Lett.* **2014**, *16*, 2058.

[3] For reviews on the preference of β-hydride elimination of alkylpalladium species, see: a) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, New York, **2004**; b) *Handbook of Organopalladium Chemistry for Organic Synthesis*, *Vol. 1* (Ed.: E.-i. Negishi), Wiley-Interscience, New York, **2002**; c) D. J. Cárdenas, *Angew. Chem. Int. Ed.* **1999**, *38*, 3018; *Angew. Chem.* **1999**, *111*, 3201; d) T.-Y. Luh, M.-K. Leung, K.-T. Wong, *Chem. Rev.* **2000**, *100*, 3187; e) D. J. Cárdenas, *Angew. Chem. Int. Ed.* **2003**, *42*, 384; *Angew. Chem.* **2003**, *115*, 398.

[4] a) J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669; b) K. W. Bentley, *Nat. Prod. Rep.* **2006**, *23*, 444; c) L. Liu, B. C. Finzel, *J. Med. Chem.* **2014**, *57*, 2714.

[5] For leading reviews on palladium-catalyzed oxidative amination of alkenes, see: a) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644; b) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795; c) L. Huang, M. Arndt, K. Gooßen, H. Heydt, L. J. Gooßen, *Chem. Rev.* **2015**, *115*, 2596; For selected examples, see: d) V. I. Timokhin, N. R. Anastasi, S. S. Stahl, *J. Am. Chem. Soc.* **2003**, *125*, 12996; e) G. L. J. Bar, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2005**, *127*, 7308; f) J. L. Brice, J. E. Harang, V. I. Timokhin, N. R. Anastasi, S. S. Stahl, *J. Am. Chem. Soc.* **2005**, *127*, 2868; g) V. I. Timokhin, S. S. Stahl, *J. Am. Chem. Soc.* **2005**, *127*, 17888; h) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.* **2007**, *129*, 6328; i) P. B. White, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 18594; j) G. Yang, W. Zhang, *Org. Lett.* **2012**, *14*, 268; k) C. C. Pattillo, I. I. Strambeanu, P. Calleja, N. A. Vermeulen, T. Mizuno, M. C. White, *J. Am. Chem. Soc.* **2016**, *138*, 1265.

[6] For leading references, see: a) L. V. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 9542; b) A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 2300; c) L. V. Desai, M. S. Sanford, *Angew. Chem. Int. Ed.* **2007**, *46*, 5737; *Angew. Chem.* **2007**, *119*, 5839; d) D. Kalyani, M. S. Sanford, *J. Am. Chem. Soc.* **2008**, *130*, 2150; e) D. Kalyani, A. D. Satterfield, M. S. Sanford, *J. Am. Chem. Soc.* **2010**, *132*, 8419; f) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936.

[7] For leading reviews on Pd-catalyzed difunctionalization of alkenes via aminopalladation with Pd^{II}/Pd^{IV} species, see: a) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981; b) M. S. Sigman, E. W. Werner, *Acc. Chem. Res.* **2012**, *45*, 874; c) G. Yin, X. Mu, G. Liu, *Acc. Chem. Res.* **2016**, *49*, 2413. For selected examples, see: d) E. J. Alexanian, C. Lee, E. J. Sorensen, *J. Am. Chem. Soc.* **2005**, *127*, 7690; e) J. E. Ney, J. P. Wolfe, *J. Am. Chem. Soc.* **2005**, *127*, 8644; f) J. Streuff, C. H. Hövelmann, M. Nieger, K. Muñiz, *J. Am. Chem. Soc.* **2005**, *127*, 14586; g) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.* **2006**, *128*, 7179; h) C. F. Rosewall, P. A. Sibbald, D. V. Liskin, F. E. Michael, *J. Am. Chem. Soc.* **2009**, *131*, 9488; i) T. Wu, G. Yin, G. Liu, *J. Am. Chem. Soc.* **2009**, *131*, 16354; j) E. L. Ingalls, P. A. Sibbald, W. Kaminsky, F. E. Michael, *J. Am. Chem. Soc.* **2013**, *135*, 8854; k) H. Zhu, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2014**, *136*, 1766; l) J. Cheng, X. Qi, M. Li, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2015**,

137, 2480; m) C. Chen, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2015**, *137*, 15648.

[8] J. F. Hartwig, *Organotransition Metal Chemistry: From Bonding to Catalysis*, University Science Books, Sausalito California, **2010**, p. 398.

[9] CCDC 1518059 (**3aa**), 1518060 (**3ka**), and 1518918 (**3la**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[10] The Eyring plot generated from these data was obtained and the activation parameters of $\Delta H^{\neq} = 47.7\,\mathrm{kJ\,mol^{-1}}$ and $\Delta S^{\neq} = -99.96\,\mathrm{J\,mol^{-1}\,K^{-1}}$ for the present reaction were also obtained (see the Supporting Information).

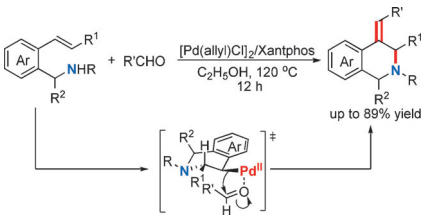
Manuscript received: December 6, 2016
Revised: December 28, 2016
Final Article published: ■■ ■■, ■■■■

Communications

Cyclization Reactions

Y. Hu, Y. Xie, Z. Shen,
H. Huang* ——————— ■■■–■■■

Palladium-Catalyzed Ring-Forming Aminoalkenylation of Alkenes with Aldehydes Initiated by Intramolecular Aminopalladation



Controlling β-hydride elimination: An palladium-catalyzed tandem reaction of aminoalkenes with aldehydes provides a simple and reliable approach for the synthesis of biologically active tetrahydroisoquinolines. The turnover-limiting step is shown to be nucleophilic addition via a highly ordered transition state.

