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Highly Efficient Syntheses of Azetidines, Pyrrolidines, and Indolines via Palladium Catalyzed Intramolecular Amination of C(sp^3)−H and C(sp^2)−H Bonds at γ and δ Positions

Gang He, Yingsheng Zhao, Shuyu Zhang, Chengxi Lu, and Gong Chen*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802, United States

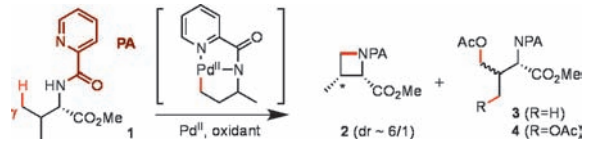
Supporting Information

ABSTRACT: Efficient methods have been developed to synthesize azetidine, pyrrolidine, and indoline compounds via palladium-catalyzed intramolecular amination of C−H bonds at the γ and δ positions of picolinamide (PA) protected amine substrates. These methods feature relatively a low catalyst loading, use of inexpensive reagents, and convenient operating conditions. Their selectivities are predictable. These methods highlight the use of unactivated C−H bond, especially the C(sp^3)−H bond of methyl groups, as functional groups in organic synthesis.

Catalytic functionalization of unactivated sp^3 hybridized C−H bonds under relatively mild reaction conditions remains one of the biggest challenges in organometallic and synthetic chemistry.[1] Compared with the increasingly available methods for C(sp^2)−H functionalizations of various arenes and heteroarenes, chemo- and stereoselective replacement of C(sp^3)−H bonds of commonly used aliphatic substrates with C−C and C−heteroatom bonds will provide unique accesses to a large array of structurally diverse products.[2,3] Among these transformations, amination of C(sp^3)−H bonds has been particularly attractive since N-containing compounds especially N-heterocycles are ubiquitous in natural products and pharmaceuticals.[4−7] Synthesis of aliphatic N-heterocycles via the C−H functionalization can be traced back to the classic Hofmann−Löffler−Freytag reaction mediated through the radical mechanism.[8] More recently, metal-catalyzed insertions of nitrenes and nitrenoids into C(sp^3)−H bonds via the "outer-sphere mechanism" have provided another set of powerful tools to synthesize complex heterocyclic amines.[9] However, the metal-catalyzed amination of C(sp^3)−H bonds via the "inner-sphere mechanism" remains underdeveloped.[10−12] These transformations could potentially provide different reactivities and selectivities complementary to those of the radical and nitrene insertion reactions, which are more amenable to substrates with relatively weaker secondary and tertiary C(sp^3)−H bonds.[13] Herein, we report a new set of methods to synthesize azetidines, pyrrolidines, and indolines via palladium-catalyzed picolinamide-directed intramolecular amination of the C(sp^3)−H and C(sp^2)−H bonds at the remote γ and δ positions of amine substrates.

Over the past three years, our laboratory has developed synthetically useful methods based on Pd-catalyzed C−H functionalizations of picolinamide protected amine substrates.[14] The picolinamide (PA) group, originally introduced by Daugulis in 2005,[15] has demonstrated superior directing abilities to enable a number of transformations including arylation and alkenylation of γ-C(sp^3)−H bonds with aryl and vinyl iodides and alkylation of γ-C(sp^2)−H with β-H containing alkyl halides. Strict γ selectivities were observed in all of these reactions, presumably due to the formation of a kinetically favored five-membered palladacycle intermediate. To further expand the synthetic utility of this PA-directed C−H functionalization strategy, we investigated whether γ-C(sp^3)−H bonds could be transformed into C−O, C−N, or C−halogen bonds under

Table 1. Pd-Catalyzed Intramolecular Amination of γ-C(sp^3)−H Bonds[a]



entry	catalysis (mol%)	additive (equiv)	solvent /atmosphere[b]	temp (°C)	yield (%)[c] 2	+ 3/4
1	$Pd(OAc)_2$ (10)	AgOAc (2)	Toluene/Air	110	<2%	<2%
2	$Pd(OAc)_2$ (10)	BQ (2)	Toluene/Air	110	<2%	<2%
3	$Pd(OAc)_2$ (10)	$Ce(SO_4)_2$ (2)	Toluene/Air	110	<2%	<2%
4	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (2)	Toluene/Air	110	<2%	<2%
5	$Pd(OAc)_2$ (10)	NIS (2)	Toluene/Air	110	<2%	<2%
6	$Pd(OAc)_2$ (10)	F^+(2)[d]	Toluene/Air	110	<2%	<2%
7	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (2)	Toluene/Air	110	<2%	<2%
8	$Pd(OAc)_2$ (10)	$PhI(OCOCF_3)_2$ (2)	Toluene/Air	110	10	<2%
9	$Pd(OAc)_2$ (10)	$PhI(OPiv)_2$ (2)	Toluene/Ar	110	56	2/5
10	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)	Toluene/Air	110	71	8/7
11	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)	Toluene/O_2	110	55	2/2
12	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)	Toluene/Ar	110	73	2/5
13	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (2.5)	Toluene/Ar	110	78	2/5
14	$Pd(OAc)_2$ (2.5)	$PhI(OAc)_2$ (2.5)	Toluene/Ar	110	81	6/3
15	$Pd(OAc)_2$ (2.5)	$PhI(OAc)_2$ (2.5)	Toluene/Ar	70	40	2/4
16	$Pd(OAc)_2$ (1)	$PhI(OAc)_2$ (2.5)	Toluene/Ar	110	52[e]	7/2
17	$Pd(OAc)_2$ (2.5)	$PhI(OAc)_2$ (2.5)	AcOH/Ar	110	19	23/2
18	$Pd(TFA)_2$ (2.5)	$PhI(OAc)_2$ (2.5)	Toluene/Ar	110	32	<3%
19	$Pd(OAc)_2$ (2.5)	$PhI(OAc)_2$ (2.5) + AcOH (2)	Toluene/Ar	110	88 (85)[f]	2/8
20	$Pd(OAc)_2$ (0)	$PhI(OAc)_2$ (2.5) + I_2 (2.5)	Toluene/Ar	110	<2%	<2%

[a]Reagents and conditions: All the screening reactions were carried out in a 10 mL glass vial with a PETF-lined cap at 0.2 mmol scale. [b]The reaction vial was purged with gas (1 atm) and then sealed. [c]Yields were based on ^{1}H NMR analysis of reaction mixture after 24 h (see Supporting Information (SI)). [d]1-Fluoro-2,4,6-trimethylpyridinium triflate. [e]48 h. [f]Isolated yield.

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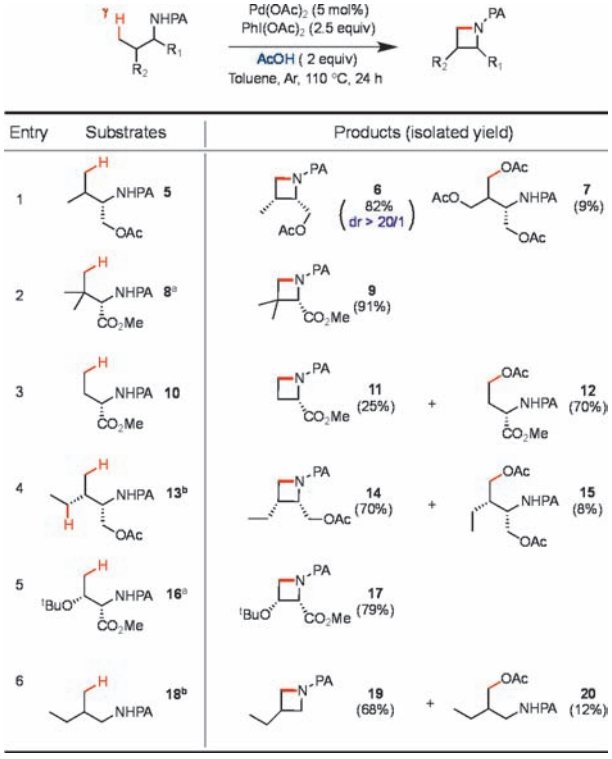
certain oxidative conditions through a Pd^{II}/Pd^{IV} catalytic cycle.[16] Accordingly, reactions of the valine substrate **1** and different oxidizing reagents were examined under palladium catalysis (Table 1). While oxidants such as Ag^+, BQ, NIS, Cu^{2+}, and F^+-based reagents completely failed to promote any useful transformations, $PhI(OAc)_2$ clearly stood out and afforded promising initial results (entry 10). To our surprise, the seemingly unfavorable four-membered azetidine **2** was obtained as the major product, in an easily separable diastereomeric mixture (dr ~6/1), along with minor mono- and diacetoxylated products **3** and **4**. Toluene was found to be the best solvent, and 100−110 °C was the optimal temperature range. The cyclization reaction performed better under an Ar atmosphere than Air or O_2 (entries 11−13). Interestingly, lowering the $Pd(OAc)_2$ catalysis loading from 10 to 2.5 mol % effected slightly higher yields (entries 12−14). The reaction using 1 mol % $Pd(OAc)_2$ could afford a 52% yield with a prolonged reaction time of 2 days (entry 16). Finally, addition of 2 equiv of AcOH further improved the reaction to provide **2** in 85% isolated yield in 24 h (entry 19). No desired product was formed when $Pd(OAc)_2$ was replaced with 2 equiv of I_2 (entry 20).[17]

With the optimal azetidine formation conditions in hand, we then tested them on other picolinamide substrates bearing primary γ-C(sp^3)−H bonds (Table 2).[18] The OAc-protected valinol substrate **5** gave a similar cyclization yield but surprisingly high diastereoselectivity (only one diastereomer was clearly detected based on ^{1}H NMR, entry 1). Substrates **5**, **8**, **13**, and **16**, bearing both α and β substituents, afforded 70−90% yields (entries 1, 2, 4, 5). In contrast, the substrate **10**, bearing no β substituent, gave only 25% of the cyclized product **11** together with 70% of the acetoxylated product **12** (entry 3). In fact, **12** could be obtained nearly exclusively in good yield when the reaction was carried out in AcOH. β-Substituted aliphatic substrate **18** also gave a satisfying yield (entry 6). We speculated that a Pd^{IV} intermediate was formed via the $PhI(OAc)_2$ oxidation of the palladacycle intermediate and the subsequent C−N and C−O reductive elimination pathways would lead to the formation of the cyclized and acetoxylated products.[19] The rate of the subsequent reductive elimination processes could be affected by the associated OAc ligand and the steric effect of the substrates. Only trace amounts of acetoxylated products (<2%) were observed with substrates **8** and **16** bearing R_2 substituents. In contrast, acetoxylated product **12** predominated for the substrate **10** (R_2 = H). One plausible interpretation for the observed selectivities might be the torsional strain imposed by the R_2 substituent on the β position and the γ-C−H bonds (and possibly R_1 group on the α position) during the bond reorganization process for the out-of-palladacycle-plane C−O formation. Such torsional strain might kinetically favor the in-palladacycle-plane C−N cyclization despite the ring strain in the resulting azetidine.[20] It was also noteworthy that no β-H elimination product was detected under the above-mentioned reaction conditions.

Compared with the ring contraction from a five-membered palladacycle to a four-membered azetidine product, formation of a five-membered pyrrolidine product from a six-membered palladacycle intermediate would be much more favorable. However, examples of the formation of kinetically less favored six-membered palladacycles via C(sp^3)−H palladation are scarce.[21] Despite the unanimous γ-selectivity observed in our previous studies, we decided to test the possibility of the δ-C(sp^3)−H activation under these oxidative conditions, in view of the unique driving force for C−N reductive elimination from a

Table 2. Syntheses of Azetidines via Intramolecular Amination of γ-C(sp^3)−H Bonds



[a]Negligible amounts of acetoxylated products (<2%) were formed. [b]No pyrrolidine product was detected.

Pd^{IV} center. To our delight, the cyclization of the leucine substrate **21** bearing both primary δ-C(sp^3)−H bonds and a sterically less accessible γ-C(sp^3)−H bond proceeded smoothly to give the pyrrolidine product **22**, as a mixture of two diastereomers (dr ~7/1), in good yield under the same azetidine formation conditions. The reaction was further optimized with the addition of 10 equiv of AcOH to suppress the formation of the undesired acetoxylated product **23** (entry 1, Table 3).[22] Substrates **24** and **28**, bearing both primary δ-C(sp^3)−H bonds and γ-substituents, also gave satisfying cyclization yields (entries 2, 4). High diastereoselectivity was also obtained for substrate **28**. Similar to the azetidine synthesis, the substrate **26** bearing no γ-substituents gave only 17% of the pyrrolidine product **27** and a trace amount of the acetoxylated side product; no azetidine product was formed, and >70% of unreacted **26** was recovered (entry 3). It is noteworthy that no pyrrolidine products were formed in the cyclization reactions of substrates **13** and **18** bearing methyl groups at both γ and δ positions (Table 2). *ortho-tert*-Butylaniline substrate **30** also cyclized to give the indoline product **31** in good yield (entry 5). *ortho*-Methylbenzylamine substrate **32**, readily prepared from the PA-directed methylation of the *ortho*-C(sp^2)−H bond of the benzyl amine precursor,[14b] gave the cyclized isoindoline product **33** in 56% yield (entry 6).

Encouraged by the success with the PA-directed intramolecular amination of a δ-C(sp^3)−H bond to synthesize indoline **31**, we went on to explore a similar functionalization of the ortho C(sp^2)−H bonds of phenylethylamine substrates. The blueprint for this mode of indoline synthesis has been successfully demonstrated by Yu and co-workers using triflate protected phenylethylamines.[5e] Gratifyingly, cyclization of the phenylalanine **35** proceeded cleanly to afford the indoline product **36** in 81% yield using 2 mol % of $Pd(OAc)_2$ and

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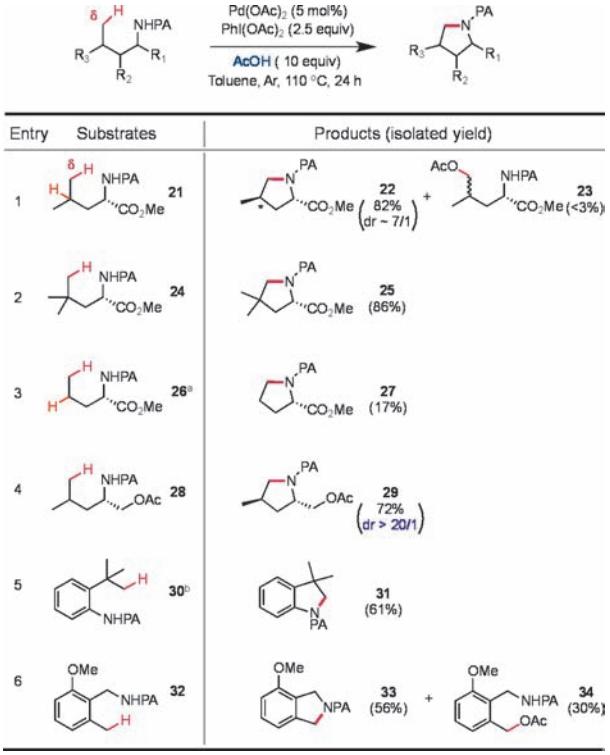
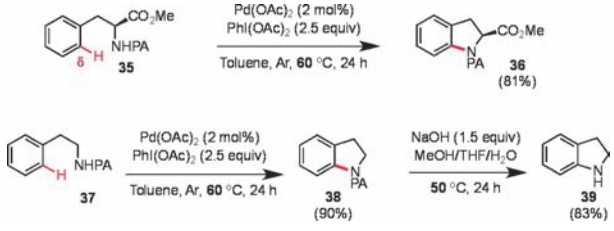
Table 3. Syntheses of Pyrrolidines via Intramolecular Amination of δ-C(sp^3)−H Bonds



[a]>70% of unreacted starting material **26** was recovered. [b]10 mol % of $Pd(OAc)_2$ was used.

2.5 equiv of $PhI(OAc)_2$ in toluene at 60 °C in 24 h (Scheme 1). A similar yield was obtained with 5 mol % of $Pd(OAc)_2$ at 50 °C

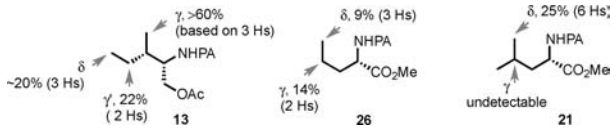
Scheme 1. Syntheses of Indolines via Intramolecular Amination of δ-C(sp^2)−H Bonds



in 24 h. Furthermore, cyclization of the unsubstituted phenylethylamine substrate **37** also performed well to give **38**, which was readily hydrolyzed to afford the free indoline **39** by treatment of 1.5 equiv of NaOH in MeOH/THF/H_2O at 50 °C.

The following substrate deuteration experiments were performed to map the relative reactivities of different C(sp^3)−H bonds under the Pd-catalyzed C−H activation conditions in the absence of $PhI(OAc)_2$ (Scheme 2). Isoleucinol substrate **13** showed >60% deuteration at the γ-CH_3, 22% deuteration at the γ'-CH_2, and ~20% deuteration at the δ-CH_3. However, no pyrrolidine product was formed under the corresponding oxidative conditions with $PhI(OAc)_2$ (entry 4, Table 2). Substrate **26** showed that both the γ-CH_2 and δ-CH_3 groups were deuterated to a smaller extent (14% and 9% respectively); however, only the pyrrolidine product **27** was formed in 17% yield under the corresponding oxidative amination conditions (entry 3, Table 3). Deuteration incorporation of the leucine

Scheme 2. Substrate Deuteration Studies[a]

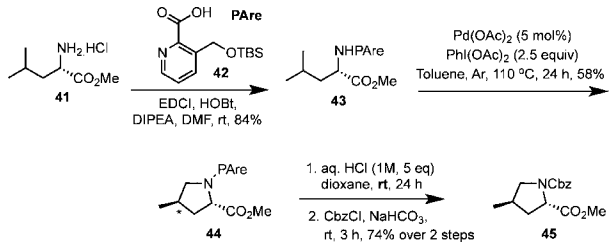


[a]Deuterium incorporation of substrates **13**, **26**, and **21** under the conditions of 2.5 mol % of $Pd(OAc)_2$, AcOD (10 equiv), toluene (solvent), at 110 °C for 24 h. The resulting deuterated products were purified and then analyzed by ^{1}H NMR (see SI).

substrate **21** exclusively occurred at the δ-CH_3 at the 25% level. The following order of relative reactivities of different C(sp^3)−H bonds under these reaction conditions was concluded: primary γ-C−H > primary δ-C−H > secondary and tertiary γ-C−H bonds.[23]

Although the picolinamide group could be readily installed via the standard amide coupling, its cleavage under mild reaction conditions was quite challenging. In our previous report of the PA-directed arylation of γ-C(sp^3)−H bonds, a more easily removable auxiliary PAre **42** was introduced to enable its deprotection under mild acidic conditions, which significantly improved its synthetic utility (Scheme 3).[14a] Here, PAre-

Scheme 3. Employment of a More Easily Removable PA Group



protected leucine substrate **43** underwent the desired C−N cyclization under slightly different conditions, in which 10 equiv of AcOH was omitted to avoid the unwanted cleavage of the TBS group.[24] To our delight, cleavage of the PAre group using 5 equiv of 1 M aq. HCl in dioxane proceeded smoothly even at room temperature to give the product **45** following the subsequent Cbz protection.[25]

In summary, we have developed a new set of methods to synthesize azetidine, pyrrolidines, and indolines via Pd-catalyzed picolinamide-directed intramolecular C−H amination. Complementary to the reactivity patterns observed in the radical and nitrene-mediated C−H activation reactions, primary C(sp^3)−H bonds of methyl groups on both γ and δ positions could be readily functionalized in a selective and predictable manner, even with high diastereoselectivity in certain germinal dimethyl substrates. These methods are efficient, economical, and practical in the laboratory. More detailed mechanistic studies, new development of picolinamide auxiliaries, and applications of these methods in the synthesis of complex molecules are currently under investigation.[24]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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AUTHOR INFORMATION

Corresponding Author
Guc11@psu.edu

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REFERENCES

(1) For selected reviews on C(sp^3)−H functionalizations, see: (a) Crabtree, R. H. *J. Organomet. Chem.* **2004**, *689*, 4083−4091. (b) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654−2672. (c) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992−2002. (d) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191−206.

(2) For selected reviews on C(sp^3)−H functionalization in organic synthesis, see: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417−424. (c) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976−1991.

(3) For selected examples of catalytic C(sp^3)−H functionalization in syntheses of complex molecules: (a) Taber, D. F.; Schuchardt, J. L. *J. Am. Chem. Soc.* **1985**, *107*, 5289−5290. (b) Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2000**, *122*, 6321−6322. (c) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510−11511. (d) Davies, H. M. L.; Dai, X.; Long, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2485−2490. (e) Stang, E. M.; White, M. C. *Nat. Chem.* **2009**, *1*, 547−551. (f) Chaumontet, M.; Piccardi, R.; Baudoin, O. *Angew. Chem., Int. Ed.* **2009**, *48*, 179−182. (g) Feng, Y.; Chen, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 958−961. (h) Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076−19079.

(4) For selected reviews on catalytic C−H amination reactions, see: (a) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Soc. Rev.* **2009**, *38*, 5061−5074. (b) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068−5083.

(5) For selected examples of Pd-catalyzed intramolecular aminations of C(sp^2)−H bonds, see: (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560−14561. (b) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931−2934. (c) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058−14059. (d) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184−16186. (e) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806−10807. (f) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676−3677. (g) Hwan, S.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996−6005.

(6) For selected examples of Pd-catalyzed intermolecular aminations of C(sp^2)−H bonds, see: (a) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862−12864. (b) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466−1474. (c) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694−1697. (d) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652−7655.

(7) For selected examples of Cu and Co-catalyzed aminations of C(sp^2)−H bonds, see: (a) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932−1934. (b) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178−5180. (c) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900−6901. (d) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899−9903.

(8) For FHL reactions, see: (a) Hofmann, A. W. *Ber.* **1883**, *16*, 558−560. (b) Hofmann, A. W. *Ber.* **1885**, *18*, 5−23. (c) Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55−64. (d) For oneclassic synthetic applicationof HLF, see: Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1958**, *80*, 2903−2904.

(9) For metal-catalyzed C−H insertion reactions of nitrenes and nitrenoids, see: (a) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728. (b) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233−2236. (c) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378−15379. (d) Lu, H.; Tao, J.; Jones, J. E.; Wojtas, L.; Zhang, X. P. *Org. Lett.* **2010**, *12*, 1248−1251. (e) Du Bois, J. *Org. Process Res. Dev.* **2011**, *15*, 758−762. (f) Lu, H.; Zhang, X. P. *Chem. Soc. Rev.* **2011**, *40*, 1899−1909. (g) Ichinose, M.; Suematsu, H.; Yasutomi, Y.; Nishioka, Y.; Uchida, T.; Katsuki, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 9884−9887.

(10) For selected examples of Pd-catalyzed aminations of allylic C(sp^3)−H bonds, see: (a) Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316−3318. (b) Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707−11711.

(11) For Pd-catalyzed aminations of unactivated C(sp^3)−H bonds, see: (a) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048−9049. (b) Neumann, J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892−6895. (c) Pan, J.; Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8647−8651.

(12) For discussions on inner- and outer-sphere mechanisms, see: (a) Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, 2437−2450. (b) Dick, A.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439−2463. (c) Reference 1b.

(13) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362−3374.

(14) (a) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192−5196. (b) Zhao, Y.; Chen, G. *Org. Lett.* **2011**, *13*, 4850−4853.

(15) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154−13155. (b) PA-directedacetoxylation of C(sp^2)−H bonds: Gou, F. R.; Wang, X. C.; Huo, P. F.; Bi, H. P.; Guan, Z. H.; Liang, Y. M. *Org. Lett.* **2009**, *11*, 5726−5729.

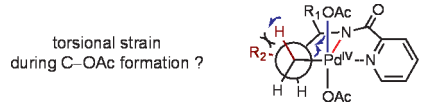
(16) (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542−9543. (b) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420−7424. (c) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974−10983.

(17) Fan, R.; Pu, D.; Wen, F.; Wu, J. *J. Org. Chem.* **2007**, *72*, 8994−8997.

(18) 5 mol% of Pd(OAc)$_2$ was employed because of its better performance with more difficult substrates such as compound **3**. In most cases, 2.5% mol of Pd(OAc)$_2$ and 100 °C afforded similar yields.

(19) For selected reviews on Pd^{IV} chemistry, see: (a) Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83−90. (b) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047−14049. (c) Xu, L.; Li, B.; Yang, Z.; Shi, Z. *Chem. Soc. Rev.* **2010**, *39*, 712−733. (d) Sehnal, P.; Taylor, R. J.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824−889.

(20) The torsional strain was smaller in substrate **10** (R$_2$ = H), and the azetidine's ring strain dictated the out-of-plane C−O formation. The directions of the bond reorganization are marked in blue in the following speculated Pd^{IV} intermediate.



(21) (a) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570−14571. (b) Reference 11b. (c) For a pioneer workon lactone synthesis via intramolecular functionalization of C(sp^3)−H bonds of free amino acid substrates under Pt-catalyzedconditions, see: Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149−8150.

(22) Addition of 10 equiv of AcOH could suppress the formation of acetoxylated products while slighly decreasing the cyclization rate. The role of AcOH in this reaction system will be discussed in a future paper.

(23) For insightful discussions on the relative reactivities of different C(sp^3)−H bonds, see: (a) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783−787. (b) Reference 12.

(24) More readily installable and versatile PA auxiliaries will be discussed in a future paper.

(25) The tertiary amidelinkage in the cyclized product is easier to cleave than the correspondingsecondary amide bond. 1,3-Trans stereochemistry of **45** was assigned based on a known compound (see SI): Xie, W.; Zou, B.; Pei, D.; Ma, D. *Org. Lett.* **2005**, *7*, 2775−2777.