

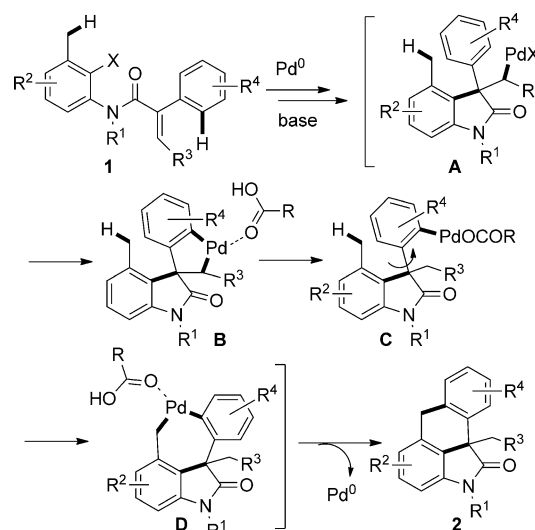
Synthetic Methods

Palladium-Catalyzed Through-Space C(sp³)–H and C(sp²)–H Bond Activation by 1,4-Palladium Migration: Efficient Synthesis of [3,4]-Fused Oxindoles**

Tiffany Piou, Ala Bunesco, Qian Wang, Luc Neuville, and Jieping Zhu*

Oxindoles are highly valuable synthetic targets because of their presence in numerous natural products, pharmaceuticals, and agrochemicals.^[1] Although a plethora of strategies has been developed for the synthesis of spirooxindoles, methods allowing rapid access to the no less important [3,4]-fused oxindoles^[2] remain scarce.^[3] Transition-metal-catalyzed C–H functionalization has emerged recently as a powerful tool for the synthesis of heterocycles.^[4] Despite recent major advancements, palladium-catalyzed functionalization of non-activated C(sp³)–H bonds is still an important challenge.^[5–8] In continuation of our current research on the development of domino processes incorporating a C–H functionalization,^[9] and more specifically a C(sp³)–H activation step,^[10] we became interested in the transformation of the anilides **1** into the [3,4]-fused oxindoles **2**. The underlying principle is shown in Scheme 1. Oxidative addition of **1** to palladium(0) and subsequent intramolecular carbopalladation gives the σ -alkyl/Pd^{II} intermediate **A**. This palladium species is ideally positioned to activate the neighboring aromatic C(sp²)–H bond, thus leading to the five-membered palladacycle **B**. A formal proton transfer from **B** results in a net 1,4-palladium shift^[11] from the alkyl to the aryl position.^[12,13] The so generated Pd^{II}/aryl species **C**, after C–C bond rotation, is expected to activate the neighboring C4 methyl group to furnish the seven-membered palladacycle **D**. Reductive elimination finally affords the tetracyclic oxindole **2** with concurrent regeneration of the palladium(0) species.

To realize this projected domino process, several challenges needed to be addressed: a) Finding reaction conditions to accommodate every elementary step could be a dilemma. Indeed from the perspective of ligand selection, it is known that bidentate phosphine ligands are generally preferred for



Scheme 1. Synthesis of [3,4]-fused oxindoles by a domino carbopalladation/1,4-palladium migration/C(sp³)–H activation sequence. For the sake of simplicity, a hypothetical concerted metalation–deprotonation (CMD) mechanism^[5f] was drawn for C–H activation steps. Ligands on palladium were omitted for clarity.

migration processes,^[14] whereas electron-rich and bulky monodentate phosphine ligands are ideal for C(sp³)–H activation.^[6] b) Very few examples of six-membered-ring formation by C(sp³)–H activation/C–C bond formation are known.^[15] c) Formation of the benzocyclobutane^[16] from **B** instead of palladium migration might also be a competitive side reaction.

Keeping these considerations in mind, reaction conditions were surveyed using the easily accessible *N*-(2-bromo-3-methylphenyl)-*N*-methyl-2-phenylacrylamide (**1a-Br**) as a test substrate.^[17] After an extensive survey of reaction conditions (see the Supporting Information), a combination of Pd(OAc)₂, PCy₃·HBF₄, and CsOPiv^[18] in DMA was found to be effective, thus affording **2a** in 55 % yield (Table 1, entry 3). Importantly, we found that the yield of **2a** increased significantly when a tertiary amine was introduced as an additive (entries 6–9), with *N,N*-diethylaniline being the best. Under the optimum reaction conditions found, the [3,4]-fused oxindole **2a** was isolated in 84 % yield (entry 8).^[19] Interestingly, a chloroanilide (**1a-Cl**) was a competent substrate to afford **2a** in 65 % yield (entry 10). Conversely, a iodoanilide (**1a-I**) was a bad substrate, thus producing the desired product **2a** in only 13 % yield (entry 11).

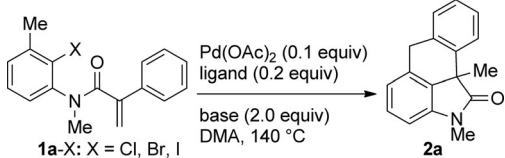
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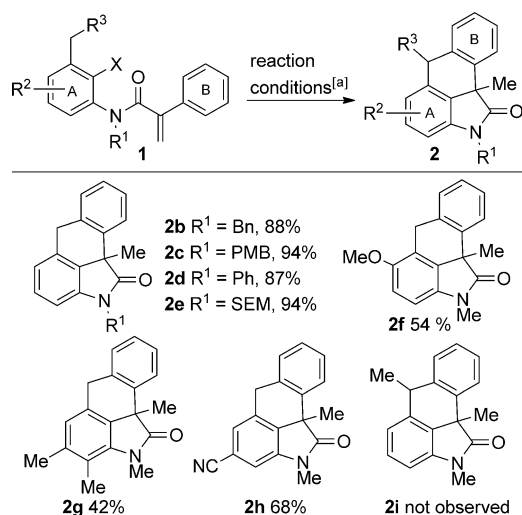
Table 1: Reaction optimization.^[a]



Entry	Ligand	Base(s)	X	Yield [%] ^[b]
1	dppm	CsOPiv	Br	n.d. ^[c]
2	PPh ₃	CsOPiv	Br	53
3	PCy ₃ ·HBF ₄	CsOPiv	Br	55
4	PCy ₃ ·HBF ₄	Cs ₂ CO ₃	Br	trace
5	PCy ₃ ·HBF ₄	CsOPiv/Cs ₂ CO ₃ ^[d]	Br	trace
6	PCy ₃ ·HBF ₄	CsOPiv/ <i>n</i> Bu ₃ ^[d]	Br	75
7	PCy ₃ ·HBF ₄	CsOPiv/PMP ^[d]	Br	63
8	PCy ₃ ·HBF ₄	CsOPiv/PhNEt ₂ ^[d]	Br	84
9	PCy ₃ ·HBF ₄	CsOPiv/DBU ^[d]	Br	51
10	PCy ₃ ·HBF ₄	CsOPiv/PhNEt ₂ ^[d]	Cl	65
11	PCy ₃ ·HBF ₄	CsOPiv/PhNEt ₂ ^[d]	I	13

[a] Reactions were carried out under an argon atmosphere in DMA, *c* = 0.1 M. [b] Yield of isolated product. [c] Low conversion. [d] 1:1 ratio. Bu = butyl, Cy = cyclohexyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMA = *N,N*-dimethylacetamide, dppm = bis(diphenylphosphino)methane, OAc = acetate, Ph = phenyl, Piv = pivalate, PMP = pentamethylpiperidine; n.d. = not determined.

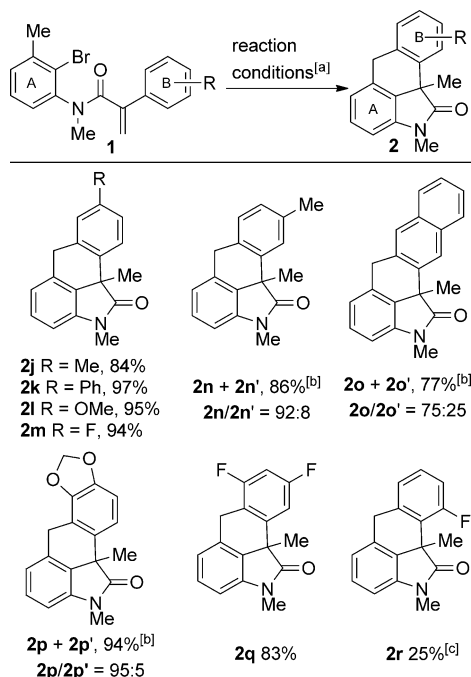
With these optimized reaction conditions in hand [Pd(OAc)₂ (0.1 equiv), PCy₃·HBF₄ (0.2 equiv), CsOPiv (2.0 equiv), and *N,N*-diethylaniline (2.0 equiv) in DMA at 140 °C], the scope of the domino process was investigated. The structural variants on the aniline (ring A) were examined first (Scheme 2). The use of a tertiary amide was proven to be essential to ensure the occurrence of the domino process and double cyclization of *N*-benzyl, *N*-*para*-methoxybenzyl, *N*-phenyl, and *N*-2-(trimethylsilyl)ethoxymethyl anilides took place without event to provide the corresponding oxindoles



Scheme 2. Reaction scope: varying the aniline unit (ring A). [a] Pd(OAc)₂ (0.1 equiv), PCy₃·HBF₄ (0.2 equiv), CsOPiv (2.0 equiv), *N,N*-diethylaniline (2.0 equiv) in DMA at 140 °C. Yields are those for the isolated product. PMB = *para*-methoxybenzyl, SEM = 2-(trimethylsilyl)ethoxymethyl.

(**2b–e**) in excellent yields. In these cases, the carbopalladation and the subsequent domino process was apparently faster than the alternative direct aromatic C(sp²)–H functionalization as the competitive formation of phenanthridine and carbazole was not observed in these cases.^[20] Electron-donating and electron-withdrawing groups located *ortho*, *meta*, or *para* to the nitrogen atom were all well tolerated (**2f–h**). However, an attempt to prepare **2i** by activation of a methylene group failed.

The influence of the substitution on the α-aryl unit (ring B) was next investigated (Scheme 3). Substituents at the *para* position, regardless of their electronic nature (methyl, phenyl, methoxy, and fluoro), exerted a marginal effect on the

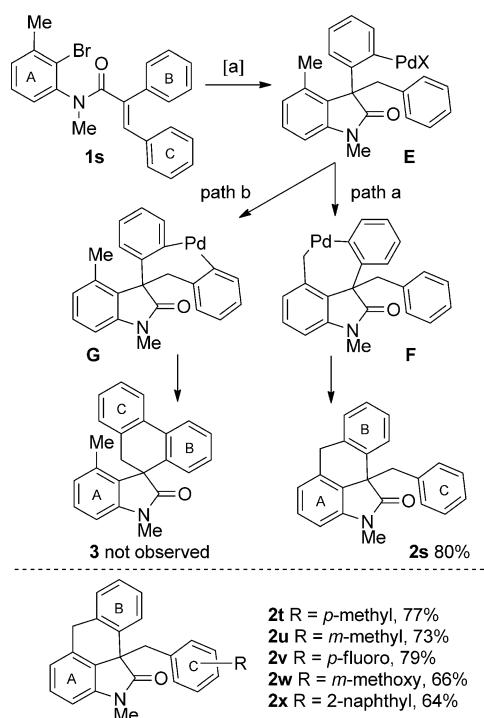


Scheme 3. Reaction scope: varying the α-aryl unit (ring B). [a] Standard reaction conditions are detailed in Scheme 2. Yields are those for the isolated product. [b] Only the major regioisomer is represented. The ratio was determined by ¹H NMR analysis of the crude reaction mixture. [c] Used 0.2 equiv of Pd(OAc)₂.

outcome of the reaction and provided tetracyclic [3,4]-fused oxindoles (**2j–m**) in excellent yields. Two regioisomers could be produced in the case of *meta*-substituted substrates. However, regioselectivity was found to be substituent-dependant. With a *meta*-methyl substituent, the cyclization occurred preferentially at the less hindered position to afford **2n** in excellent yield and regioselectivity (**2n/2n'** = 92:8). Similarly, the β-naphthal-substituted substrate afforded **2o** as a major product. In contrast, with substrates having a *meta*-oxygen substituent, the regioselectivity changed, thus leading to the more hindered tetracyclic compound **2p** as the major product (**2p/2p'** = 95:5). The increased acidity of the *ortho* C(sp²)–H in conjunction with the chelating effect of the oxygen atom could account for the change in regioselectivity. The 3,5-difluorophenyl substrate was compatible with the reaction conditions and afforded **2q** in 83 % yield. However,

substitution at *ortho*-position is detrimental to the reaction (**2r**), most probably because of the steric hindrance.

To further explore the generality of the present domino process, the α,β -disubstituted acrylamide derivative **1s** was submitted to our standard reaction conditions (Scheme 4).

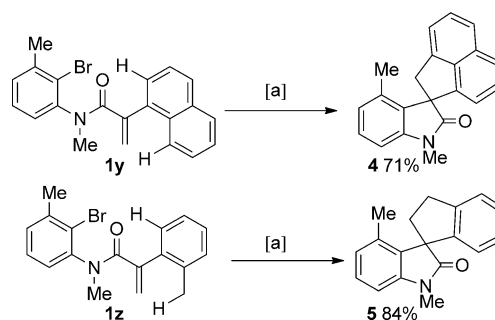


Scheme 4. Chemoselective activation of C(sp³)-H over C(sp²)-H: synthesis of 3-benzyl substituted [3,4]-fused oxindoles. [a] Standard reaction conditions are detailed in Scheme 2. Yields are those for the isolated product.

Mechanistically, the intermediate **E**, generated by intramolecular carbopalladation and 1,4-palladium migration, could activate either the neighboring C4 methyl C(sp³)-H (path a) or the aromatic C(sp²)-H (path b), thus leading to the formation of the [3,4]-fused tetracycle **2s** and spirooxindole **3**, respectively. In both cases seven-membered palladacycles (**F** and **G**) are formed. Interestingly, **2s** was formed exclusively (80 %) at the expense of **3**. These results are surprising since activation of C(sp²)-H bonds (path b) are generally favored over C(sp³)-H bonds (path a).^[21] This unusual chemoselectivity pattern turned out to be general under our reaction conditions. As shown in Scheme 4, [3,4]-fused tetracycles (**2t–x**) were formed exclusively from the corresponding anilides regardless of the electronic property of the substituent in the aromatic ring (ring C).

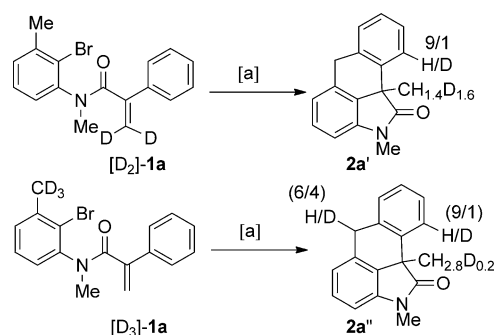
However, when substrates allowed the reaction going through a six-membered palladacycle intermediate, reductive elimination prevailed over the alternative 1,4-palladium migration process. As shown in Scheme 5, **1y** and **1z** were converted into the corresponding spirocycles **4** and **5** by C(sp²)-H and C(sp³)-H bond activations, respectively.^[22]

Significant deuterium loss and deuterium scrambling were observed when the deuterated substrates [D₂]-**1a** and [D₃]-**1a**



Scheme 5. Direct C-H activation prevailed over 1,4-palladium migration. [a] Standard reaction conditions as detailed in Scheme 2. Yields are those for the isolated product.

were subjected to the standard reaction conditions (Scheme 6). These results clearly indicated that both 1,4-palladium migration and C(sp³)-H activation were reversible.^[23] The partial deuterium loss can be explained by proton exchange between palladium(II) intermediates (**B** and **D**,



Scheme 6. Isotope-labeling experiments. [a] Standard reaction conditions as detailed in Scheme 2.

Scheme 1) and the reaction media. These observations made the kinetic studies very difficult and inconclusive (for additional kinetic isotope effect studies, see the Supporting Information).^[24]

In conclusion, we developed a novel palladium(0)-catalyzed carbopalladation/1,4-palladium shift by a C(sp²)-H bond activation/C(sp³)-H bond activation/C-C bond-forming process. The C(sp³)-H activation went through a rare seven-membered palladacycle intermediate which occurred chemoselectively in the presence of a competitive C(sp²)-H bond. The reaction allows an efficient synthesis of tetracyclic [3,4]-fused oxindoles in high yields from simple starting materials. Preliminary mechanistic studies demonstrated the reversibility of both the 1,4-palladium migration and C(sp³)-H activation processes under the reaction conditions.

Experimental Section

N-(2-Bromo-3-methylphenyl)-*N*-methyl-2-phenylacrylamide (**1a-Br**; 20.0 mg, 0.061 mmol, 1.0 equiv) was charged into a tube equipped with a stirring bar and was introduced into a nitrogen filled glovebox. Pd(OAc)₂ (1.4 mg, 0.006 mmol, 0.1 equiv), PCy₃·HBF₄ (4.5 mg,

0.012 mmol, 0.2 equiv), and CsOPiv (28.7 mg, 0.122 mmol, 2.0 equiv) were added, followed by degassed *N,N*-dimethylacetamide (1.6 mL, *c* = 0.1M) and *N,N*-diethylaniline (20.0 μ L, 0.122 mmol, 2.0 equiv). The resulting mixture was stirred for 3 min at room temperature and then overnight in a preheated oil bath at 140 °C. The reaction mixture was partitioned between ethyl acetate and aqueous HCl solution (1.0N). The aqueous layer was extracted with ethyl acetate and the combined organic extracts were washed with water, aqueous NaOH solution (1.0N), and brine, and then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 95:5) to afford 2,10b-dimethyl-6,10b-dihydronaphtho[1,2,3-*cd*]indol-1(2*H*)-one **2a** (12.7 mg, 84%).

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- [1] Recent reviews: a) A. Millemaggi, R. J. K. Taylor, *Eur. J. Org. Chem.* **2010**, 4527–4547; b) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, 352, 1381–1407.
- [2] a) K. Stratmann, R. E. Moore, R. Bonjouklian, J. B. Deeter, G. M. L. Patterson, S. Shaffer, C. D. Smith, T. A. Smitka, *J. Am. Chem. Soc.* **1994**, *116*, 9935–9942; b) C. Kikuchi, T. Ando, T. Watanabe, H. Nagaso, M. Okuno, T. Hiranuma, M. Koyama, *J. Med. Chem.* **2002**, *45*, 2197–2206; c) M. Tsuda, T. Mugishi, K. Komatsu, T. Sone, M. Tanaka, Y. Mikami, M. Hirai, Y. Ohzumi, J. Kobayashi, *Tetrahedron* **2003**, *59*, 3227–3230.
- [3] a) J. Li, N. Wang, C. Li, X. Jia, *Org. Lett.* **2012**, *14*, 4994–4997; b) D. D. Schwarzer, P. J. Gritsch, T. Gaich, *Angew. Chem.* **2012**, *124*, 11682–11684; *Angew. Chem. Int. Ed.* **2012**, *51*, 11514–11516; c) S. Bhunia, S. Ghosh, D. Dey, A. Bisai, *Org. Lett.* **2013**, *15*, 2426–2429; [3,4]-fused cyclic indoles: d) S. P. Breazano, Y. B. Poudel, D. L. Boger, *J. Am. Chem. Soc.* **2013**, *135*, 1600–1606; e) D. Shan, Y. Gao, Y. Jia, *Angew. Chem.* **2013**, *125*, 5002–5005; *Angew. Chem. Int. Ed.* **2013**, *52*, 4902–4905.
- [4] “C–H Activation”: *Topics in Current Chemistry*, Vol. 292 (Eds.: J.-Q. Yu, Z.-J. Shi), Springer, Berlin, **2010**.
- [5] a) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902–4911; b) H. Li, B.-J. Li, Z.-J. Shi, *Catal. Sci. Technol.* **2011**, *1*, 191–206. C–H functionalization in natural product synthesis, see: c) L. McMur-ray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885–1898; d) W. R. Gutekunst, P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976–1991; e) D. Y.-K. Chen, S. W. Youn, *Chem. Eur. J.* **2012**, *18*, 9452–9474; f) D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118–1126.
- [6] Selected recent examples of palladium(0)-catalyzed C(sp³)–H activation: a) O. Baudoin, A. Herrbach, F. Gueritte, *Angew. Chem.* **2003**, *115*, 5914–5918; *Angew. Chem. Int. Ed.* **2003**, *42*, 5736–5740; b) C.-G. Dong, Q.-S. Hu, *Angew. Chem.* **2006**, *118*, 2347–2350; *Angew. Chem. Int. Ed.* **2006**, *45*, 2289–2292; c) M. Lafrance, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 14570–14571; d) T. Watanabe, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2008**, *10*, 1759–1762; e) A. Salcedo, L. Neuville, J. Zhu, *J. Org. Chem.* **2008**, *73*, 3600–3603; f) M. Wasa, K. M. Engle, J. Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 9886–9887; g) S. Rousseaux, M. Davi, J. Sofack-Kreutzer, C. Pierre, C. E. Kefalidis, E. Clot, K. Fagnou, O. Baudoin, *J. Am. Chem. Soc.* **2010**, *132*, 10706–10716; h) J. Pan, M. Su, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 8806–8810; *Angew. Chem. Int. Ed.* **2011**, *50*, 8647–8651; i) S. Rousseaux, B. Liégault, K. Fagnou, *Chem. Sci.* **2012**, *3*, 244–248.
- [7] For palladium(II)-catalyzed C(sp³)–H activation, see: a) B. Liégault, K. Fagnou, *Organometallics* **2008**, *27*, 4841–4843; b) J. J. Neumann, S. Rakshit, T. Dröge, F. Glorius, *Angew. Chem.* **2009**, *121*, 7024–7027; *Angew. Chem. Int. Ed.* **2009**, *48*, 6892–6895; c) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3680–3681; d) E. J. Yoo, M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 17378–17380; e) K. J. Stowers, K. C. Fortner, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 6541–6544; f) P. Novák, A. Correa, J. Gallardo-Donaire, R. Martin, *Angew. Chem.* **2011**, *123*, 12444–12447; *Angew. Chem. Int. Ed.* **2011**, *50*, 12236–12239; g) Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 12984–12986; h) G. He, G. Chen, *Angew. Chem.* **2011**, *123*, 5298–5302; *Angew. Chem. Int. Ed.* **2011**, *50*, 5192–5196; i) E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 7–10; j) A. Iglesias, R. Alvarez, A. R. de Lera, K. Muñiz, *Angew. Chem.* **2012**, *124*, 2268–2271; *Angew. Chem. Int. Ed.* **2012**, *51*, 2225–2228.
- [8] Enantioselective C(sp³)–H functionalization. Palladium(II)-catalyzed: a) B.-F. Shi, N. Maugel, Y.-H. Zhang, J.-Q. Yu, *Angew. Chem.* **2008**, *120*, 4960–4964; *Angew. Chem. Int. Ed.* **2008**, *47*, 4882–4886; b) M. Wasa, K. M. Engle, D. W. Lin, E. J. Yoo, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 19598–19601; Palladium(0)-catalyzed: c) M. Nakanishi, D. Katayev, C. Besnard, E. P. Kündig, *Angew. Chem.* **2011**, *123*, 7576–7579; *Angew. Chem. Int. Ed.* **2011**, *50*, 7438–7441; d) S. Anas, A. Cordi, H. B. Kagan, *Chem. Commun.* **2011**, *47*, 11483–11485; e) T. Saget, S. Lemouzy, N. Cramer, *Angew. Chem.* **2012**, *124*, 2281–2285; *Angew. Chem. Int. Ed.* **2012**, *51*, 2238–2242; f) D. Katayev, M. Nakanishi, T. Bürgi, E. P. Kündig, *Chem. Sci.* **2012**, *3*, 1422–1425; g) N. Martin, C. Pierre, M. Davi, R. Jazzer, O. Baudoin, *Chem. Eur. J.* **2012**, *18*, 4480–4484; For a review, see: h) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242–3272.
- [9] a) G. Cuny, M. Bois-Choussy, J. Zhu, *Angew. Chem.* **2003**, *115*, 4922–4925; *Angew. Chem. Int. Ed.* **2003**, *42*, 4774–4777; b) A. Pinto, L. Neuville, J. Zhu, *Angew. Chem.* **2007**, *119*, 3355–3359; *Angew. Chem. Int. Ed.* **2007**, *46*, 3291–3295; c) A. Salcedo, L. Neuville, C. Rondot, P. Retailleau, J. Zhu, *Org. Lett.* **2008**, *10*, 857–860; d) T. Gerfaud, L. Neuville, J. Zhu, *Angew. Chem.* **2009**, *121*, 580–585; *Angew. Chem. Int. Ed.* **2009**, *48*, 572–577; e) A. Pinto, L. Neuville, J. Zhu, *Tetrahedron Lett.* **2009**, *50*, 3602–3605; f) S. Jaegli, W. Erb, P. Retailleau, J.-P. Vors, L. Neuville, J. Zhu, *Chem. Eur. J.* **2010**, *16*, 5863–5867; g) S. Jaegli, J. Dufour, H.-L. Wei, T. Piou, X.-H. Duan, J.-P. Vors, L. Neuville, J. Zhu, *Org. Lett.* **2010**, *12*, 4498–4501; h) T. Piou, L. Neuville, J. Zhu, *Org. Lett.* **2012**, *14*, 3760–3763; i) T. Piou, L. Neuville, J. Zhu, *Tetrahedron* **2013**, *69*, 4415–4420.
- [10] T. Piou, L. Neuville, J. Zhu, *Angew. Chem.* **2012**, *124*, 11729–11733; *Angew. Chem. Int. Ed.* **2012**, *51*, 11561–11565.
- [11] For reviews on palladium migration, see: a) S. Ma, Z. Gu, *Angew. Chem.* **2005**, *117*, 7680–7685; *Angew. Chem. Int. Ed.* **2005**, *44*, 7512–7517; b) F. Shi, R. C. Larock, *Top. Curr. Chem.* **2010**, *292*, 123–164; c) For a recent example involving 1,7-palladium migration, see: J. Zhou, J. He, B. Wang, W. Yang, H. Ren, *J. Am. Chem. Soc.* **2011**, *133*, 6868–6870.
- [12] a) R. F. Heck, *J. Organomet. Chem.* **1972**, *37*, 389–396; b) J. Cámpora, J. A. López, P. Palma, P. Valerga, E. Spillner, E. Carmona, *Angew. Chem.* **1999**, *111*, 199–203; *Angew. Chem. Int. Ed.* **1999**, *38*, 147–151; c) G. Karig, M.-T. Moon, N. Thasana, T. Gallagher, *Org. Lett.* **2002**, *4*, 3115–3118; d) Q. Huang, A. Fazio, G. Dai, M. A. Campo, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 7460–7461; e) O. René, D. Lapointe, K. Fagnou, *Org. Lett.* **2009**, *11*, 4560–4563; f) Z. Lu, C. Hu, J. Guo, J. Li, Y. Cui, Y. Jia, *Org. Lett.* **2010**, *12*, 480–483.
- [13] For reviews on the Catellani reaction, see: a) M. Catellani, *Synlett* **2003**, 298–313; b) M. Catellani, E. Motti, N. Della Ca', *Acc. Chem. Res.* **2008**, *41*, 1512–1522; c) A. Martins, B. Mariampillai, M. Lautens, *Top. Curr. Chem.* **2010**, *292*, 1–33; d) R. Ferraccioli, *Synthesis* **2013**, 581–591.

- [14] a) M. A. Campo, R. C. Larock, *J. Am. Chem. Soc.* **2002**, *124*, 14326–14327; b) M. A. Campo, H. Zhang, T. Yao, A. Ibdah, R. D. McCulla, Q. Huang, J. Zhao, W. S. Jenks, R. C. Larock, *J. Am. Chem. Soc.* **2007**, *129*, 6298–6307.
- [15] a) G. Dyker, *Angew. Chem.* **1992**, *104*, 1079–1081; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1023–1025; b) H. Ren, P. Knochel, *Angew. Chem.* **2006**, *118*, 3541–3544; *Angew. Chem. Int. Ed.* **2006**, *45*, 3462–3465; c) T. Saget, N. Cramer, *Angew. Chem.* **2012**, *124*, 13014–13017; *Angew. Chem. Int. Ed.* **2012**, *51*, 12842–12845.
- [16] M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J.-L. Peglion, E. Clot, O. Baudoin, *J. Am. Chem. Soc.* **2008**, *130*, 15157–15166.
- [17] For details, see the Supporting information. The substrate **1a** was synthesized in two steps starting from the commercially available 2-bromo-3-methylaniline and 2-phenylacrylic acid.
- [18] M. Lafrance, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497.
- [19] Structure of **2a** was confirmed by X-ray analysis. See the Supporting information.
- [20] Phenanthridine, see: a) L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581–590; b) F. Bonnaterre, M. Bois-Choussy, J. Zhu, *Beilstein J. Org. Chem.* **2008**, *4*, 1–6; Carbazoles, see: c) D. E. Ames, D. Bull, *Tetrahedron* **1982**, *38*, 383–387.
- [21] To the best of our knowledge, there were only two examples reported in the literature: a) L.-C. Campeau, D. J. Schipper, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3266–3267; b) C. Tsukano, M. Okuno, Y. Takemoto, *Angew. Chem.* **2012**, *124*, 2817–2820; *Angew. Chem. Int. Ed.* **2012**, *51*, 2763–2766.
- [22] Compounds of type **1z** lacking the *ortho* methyl group failed to undergo spirocyclization (Ref. [10]). We are examining this divergency in detail.
- [23] a) J. Zhao, M. A. Campo, R. C. Larock, *Angew. Chem.* **2005**, *117*, 1907–1909; *Angew. Chem. Int. Ed.* **2005**, *44*, 1873–1875; b) A. Mota, A. Dedieu, C. Bour, J. Suffert, *J. Am. Chem. Soc.* **2005**, *127*, 7171–7182.
- [24] E. M. Simmons, J. F. Hartwig, *Angew. Chem.* **2012**, *124*, 3120–3126; *Angew. Chem. Int. Ed.* **2012**, *51*, 3066–3072.