

Heterocycles

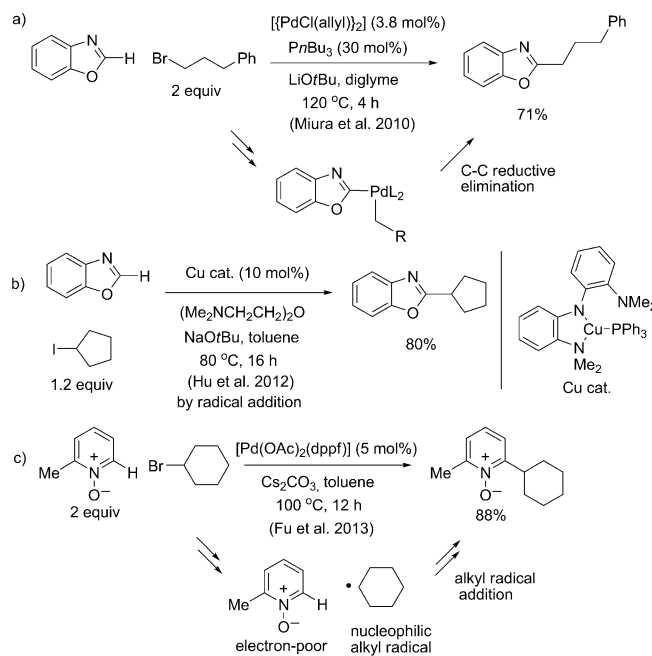
A General Palladium-Catalyzed Method for Alkylation of Heteroarenes Using Secondary and Tertiary Alkyl Halides**

Xiaojin Wu, Jessica Wei Ting See, Kai Xu, Hajime Hirao, Julien Roger, Jean-Cyrille Hierso, and Jianrong (Steve) Zhou*

Abstract: A general alkylation of heterocycles using a simple palladium catalyst is reported. Most classes of heterocycles, including indoles and pyridines, efficiently coupled with unactivated secondary and tertiary alkyl halides. An alkyl radical addition to neutral heteroarenes is most likely involved.

Alkylated heteroarenes are commonly used in medicines and materials. In recent years, transition-metal-catalyzed alkylations of heteroarenes^[1] have emerged as useful alternatives to Friedel–Crafts alkylation,^[2] Minisci-type radical additions,^[3] and metal-catalyzed hydroheteroarylation of olefins.^[4] Many metal-catalyzed alkylations using unactivated alkyl halides have focused on 1,3-azoles, which have rather acidic hydrogen atoms,^[5] and heterocycles carrying directing groups.^[6] Other families of heterocycles are less explored. Furthermore, secondary and tertiary alkyl halides have been rarely used.

In 2010, Miura et al. reported a palladium-catalyzed alkylation of 1,3-azoles and primary alkyl halides successfully coupled (Scheme 1a).^[5b] Mechanistically, the key C–C bond was formed through reductive elimination on palladium centers. Later, Hu et al. realized the copper-catalyzed coupling of 1,3-azoles with secondary alkyl halides and a radical pathway was deduced (Scheme 1b).^[7] Recently, Fu et al. successfully applied a palladium-catalyzed alkylation to pyridine N-oxides.^[8] Both secondary and tertiary alkyl halides were used, but only C2-substituted pyridine N-oxides reacted efficiently and C2-substituents were necessary to prevent double alkylation. The alkyl groups were introduced as radicals onto the electron-poor azines with low-lying LUMOs (Scheme 1c). Herein, we report a simple [Pd/dppp] catalyst which allows regioselective alkylation of various



Scheme 1. Metal-catalyzed alkylation of heterocycles with alkyl halides.

families of heteroarenes using secondary and tertiary alkyl halides.

Initially, we attempted a model transformation between 1,3-benzoxazole and cyclohexyl iodide by applying the reaction conditions described in Schemes 1a and c. Unfortunately, only 5% and 30% yields were obtained, respectively. Gratifyingly, a simple catalyst derived from [Pd(PPh₃)₄] and dppp catalyzed the model reaction in high yield (Table 1). The diphosphine dppp proved to be optimal among many added phosphines and gave 88% yield. When it was omitted, [Pd(PPh₃)₄] alone gave a much lower yield (entry 1). Other added bisphosphines (entries 3–9), monophosphines (entries 14–19), and an N-heterocyclic carbene, IMes (entry 20), were less effective. For example, dppf afforded only 56% yield in this reaction (entry 8). Our efforts to use other robust ferrocene-derived di-, tri-, and tetraphosphines, which were developed by Hierso et al. for palladium-catalyzed arylations, did not lead to further improvement (entries 10–13).^[9] If the molar ratio of the heterocycle and CyI was changed to 2:1, the yield decreased to 60%. For other reaction condition optimizations, see the Supporting Information.

The [Pd/dppp] catalyst was applied to couplings of 1,3-benzoxazole with various secondary and tertiary alkyl iodides

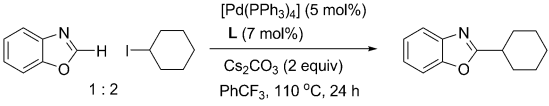
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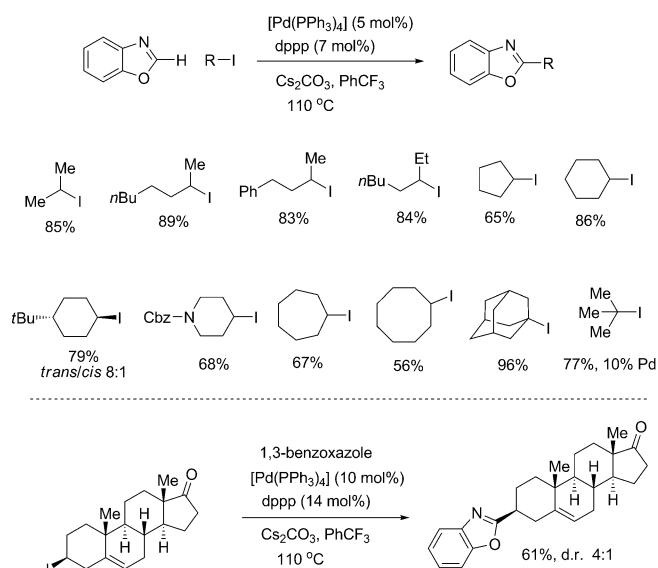
Table 1: Effect of supporting ligands in the model alkylation of 1,3-benzoxazole.^[a]

			
Entry	Added L	Conv. [%]	Conv. to product [%] ^[b]
1	none	58	32
2	dppp	97	88
3	dppe	97	63
4	dppb	93	70
5	XantPhos	76	57
6	DPEPhos	90	68
7	(R)-binap	76	70
8	dppf	79	56
9	dippf	94	56
10		96	69
11		82	50
12		87	42
13		70	20
14	PCy ₃	51	21
15	PtBu ₂ Me	82	52
16	PtBu ₃	63	33
17	P(<i>p</i> -MeOC ₆ H ₄) ₃	70	68
18	JohnPhos	89	65
19	SPhos	53	36
20	IMes	76	57

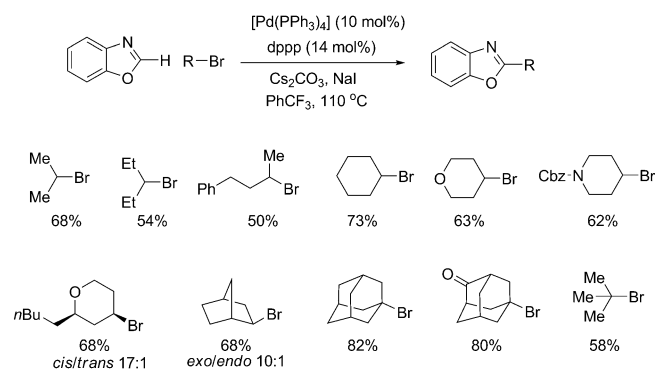
[a] Reactions were run on a 0.1 mmol scale. [b] Determined by GC analysis. binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl, dippf = 1,1'-bis(diisopropylphosphino)ferrocene, dppb = 1,4-bis(diphenylphosphino)butane, dppe = 1,2-bis(diphenylphosphino)ethane, DPEPhos = bis(2-diphenylphosphinophenyl)ether, dppp = 1,3-bis(diphenylphosphino)propane, IMes = 1,3-dimesityl-1,3-dihydro-2H-imidazol-2-ylidene, JohnPhos = 2-(di-*tert*-butylphosphino)biphenyl, SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, XantPhos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.

(Scheme 2). Both cyclic and acyclic halides reacted well. The reaction of CyI was scaled up to 10 mmol using a Schlenk manifold to afford 72 % yield. When an isomeric mixture of 4-*tert*-butylcyclohexyl iodide (*trans/cis* ratio: 2:1) was used, the *cis* isomer was preferentially consumed and the *trans* product was formed selectively with a *trans/cis* ratio of 8:1. Importantly, both 1-adamantyl and *tert*-butyl iodides gave good yields. 1,3-Benzoxazole also coupled diastereoselectively with an estrone-derived halide in a satisfactory yield.

The catalytic system was also successfully applied to couplings of secondary and tertiary alkyl bromides when two equivalents of NaI were used as an additive (Scheme 3).



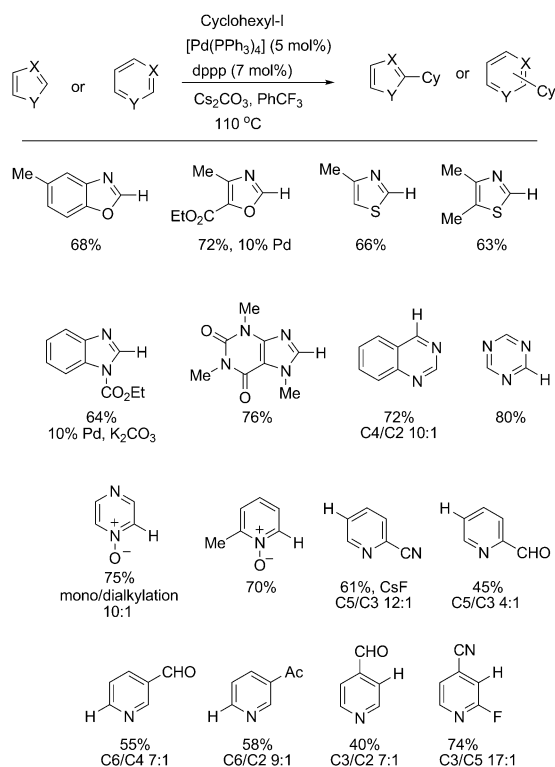
Scheme 2. Couplings of 1,3-benzoxazole and various alkyl iodides.



Scheme 3. Couplings of 1,3-benzoxazole and alkyl bromides (yields are those of the isolated products).

Without NaI, the yield was less than 10 % in the reaction with cyclohexyl bromide. When an isomeric mixture of 4-bromo-2-pentyltetrahydropyran (*trans/cis* ratio: 1:2) was used, the *trans* isomer was consumed faster and the coupling product was predominantly *cis* (*trans/cis* ratio: 1:17). In the reaction of *exo*-2-bromonorborene, the product was predominantly *exo*. A small amount of alkyl iodides were detected during palladium catalysis, which suggests that alkyl iodides were probably actual reactants.

This palladium-catalyzed alkylation can be applied to most major families of azacycles. Not only 1,3-azoles but also 6-membered azines can be alkylated (Scheme 4). 2-Methylpyridine *N*-oxide coupled efficiently. Without the C2 substituent, its reactivity decreased dramatically. Interestingly, our method can be used for regioselective alkylation of electron-deficient pyridines. The substrate scope of substituted pyridines and regioselectivity are very different from that of many existing metal-catalyzed alkylation procedures.^[10]



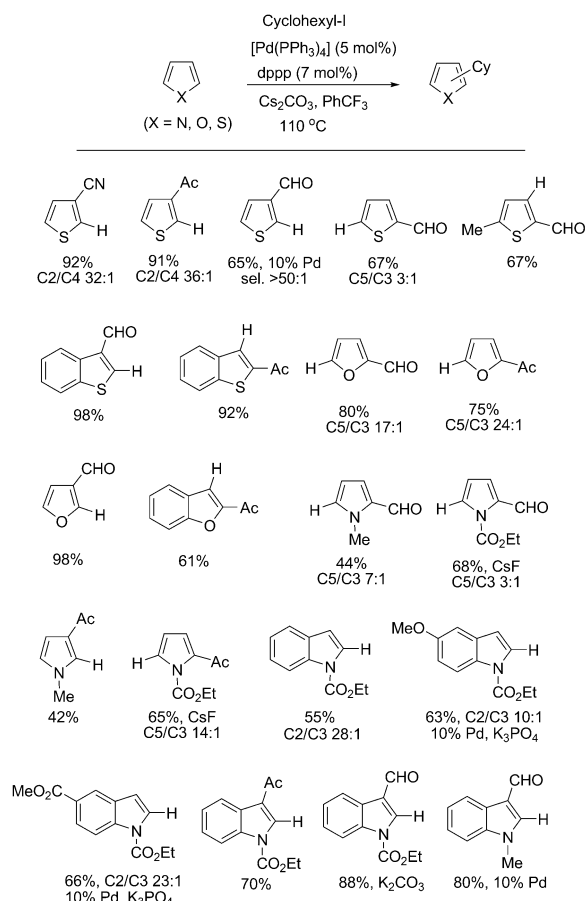
Scheme 4. Alkylation of five- and six-membered electron-poor azacycles with Cyl (yields are those of the isolated major isomers).

The alkylation procedure was also successfully applied to furans, thiophenes, pyrroles, and their benzoid-fused derivatives (Scheme 5). The presence of electron-withdrawing aldehydes, ketones, and nitriles were important for substrate activation and regiocontrol. Most notably, electron-rich and electron-neutral indoles bearing N-carbamate groups can also undergo C2-selective alkylation, which was quite rare in transition-metal-catalyzed alkylation of indoles.^[11] For example, Ackermann et al. reported some examples of nickel- and cobalt-catalyzed directed alkylation of indoles using secondary alkyl halides.^[12] However, in those examples, strong bases or Grignard reagents were used and sensitive polar groups such as aldehydes and ketones were not tolerated. Recently, Bach et al. also reported C2-selective alkylation of indoles and electron-deficient pyrroles using palladium and norbornene dual catalysis, but only primary alkyl halides were used.^[13]

The new procedure was applied to *tert*-alkylation of many families of heterocycles using 1-adamantyl iodide (Scheme 6). In the case of 3-cyanopyridine, the selectivity was switched from C6 to C4, probably because of the small size of the nitrile group. Notably, both electron-neutral and electron-rich indoles successfully coupled well.

In general, primary alkyl halides containing linear aliphatic chains were unsuccessful. The major side reaction was palladium-catalyzed elimination of alkyl halides to olefins.^[14] However, some branched primary alkyl halides still coupled in reasonable yields (Scheme 7).

Previously, alkyl radicals were implicated in other palladium-catalyzed C–C bond-forming reactions using alkyl



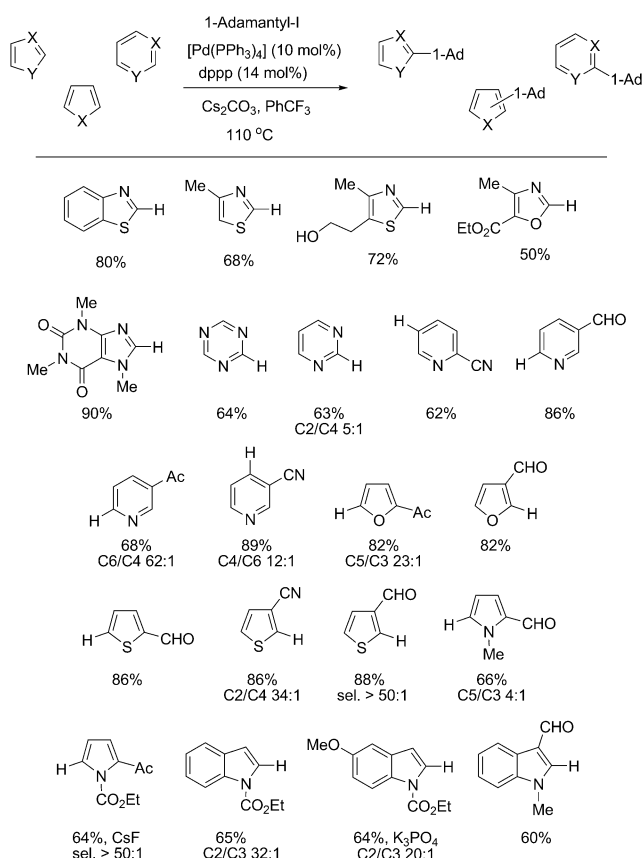
Scheme 5. Alkylation of furans, thiophenes, pyrroles, and their benzoid-fused derivatives with Cyl (yields are those of the isolated major isomers).

halides.^[8,15] Similarly under our reaction conditions, TEMPO trapped the cyclohexyl radical and formed *N*-cyclohexyl-TEMPO in significant amounts (Scheme 8a). In another experiment of indole *tert*-alkylation, the adamantyl radical was significantly reduced to adamantane in the presence of 1,4-cyclohexadiene, a good hydrogen-atom donor (Scheme 8b).

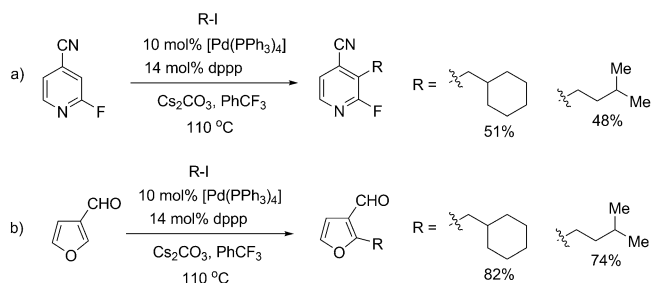
Further support for a radical pathway came from DFT calculations using the B3LYP functional with a 6-31 + G* basis set. The experimental values of regioselectivity corroborated closely the calculated enthalpy gap between two transition states of cyclohexyl radical addition to the major and minor sites of several heteroarenes (see the Supporting Information).

Therefore, we propose a possible catalytic cycle in Scheme 8c. It starts from single electron transfer from [(dppp)Pd⁰] to the alkyl halide to give an alkyl radical and [(dppp)Pd^IX].^[16] Radical addition to a heteroarene, back electron transfer to [(dppp)Pd^IX] and deprotonation furnishes the alkylated heteroarene.

In summary, we report a general alkylation of heterocycles using a simple [Pd/dppp] catalyst. Most topical classes of heterocycles, including indoles and pyridines, efficiently coupled with unactivated secondary and tertiary alkyl halides.



Scheme 6. Couplings of 1-adamantyl iodide and heterocycles (yields are those of the isolated major isomers).



Scheme 7. Palladium-catalyzed alkylation using primary alkyl halides.

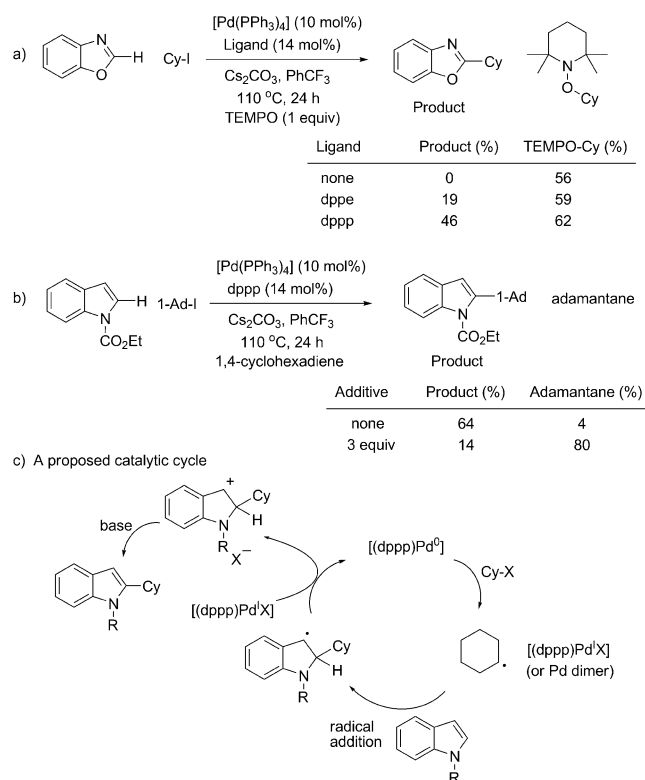
An alkyl radical addition to neutral heteroarenes is most likely involved.

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- [1] Recent reviews: a) L. Ackermann, *Chem. Commun.* **2010**, 46, 4866; b) X. L. Hu, *Chem. Sci.* **2011**, 2, 1867; P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, 112, 5879.
[2] a) M. Rueping, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2010**, 6, 6; b) R. Taylor, *Electrophilic Aromatic Substitution*, Wiley,



Scheme 8. Radical trapping and a possible catalytic cycle.

- Chichester, **1990**; c) G. A. Olah, *Friedel-Crafts Chemistry*, Wiley, New York, **1973**; d) recent use of metal halides or triflate precatalysts: M. Rueping, B. J. Nachtsheim, T. Scheidt, *Org. Lett.* **2006**, 8, 3717; e) I. Iovel, K. Mertins, J. Kischel, A. Zapf, M. Beller, *Angew. Chem. Int. Ed.* **2005**, 44, 3913; *Angew. Chem.* **2005**, 117, 3981; f) K. Mertins, I. Iovel, J. Kischel, A. Zapf, M. Beller, *Angew. Chem. Int. Ed.* **2005**, 44, 238; *Angew. Chem.* **2005**, 117, 242; g) Y.-P. Xiao, X.-Y. Liu, C.-M. Che, *J. Organomet. Chem.* **2009**, 694, 494.
[3] a) W. R. Bowman, J. M. D. Storey, *Chem. Soc. Rev.* **2007**, 36, 1803; b) K. S. K. Murthy, E. E. Knaus, *Drug Dev. Res.* **1999**, 46, 155; c) F. Minisci, E. Vismara, F. Fontana, *Heterocycles* **1989**, 28, 489; d) M. A. J. Dunston, *MedChemComm* **2011**, 2, 1135; recent examples: e) F. O'Hara, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2013**, 135, 12122; f) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, 492, 95; g) G. A. Molander, V. Colombel, V. A. Braz, *Org. Lett.* **2011**, 13, 1852.
[4] Examples: a) T. Andou, Y. Saga, H. Komai, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, 52, 3213; *Angew. Chem.* **2013**, 125, 3295; b) Y. Nakao, N. Kashihara, K. S. Kanyiva, T. Hiyama, *Angew. Chem. Int. Ed.* **2010**, 49, 4451; *Angew. Chem.* **2010**, 122, 4553; c) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, 41, 1013; d) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, 110, 624; e) Z. Ding, N. Yoshikai, *Angew. Chem. Int. Ed.* **2013**, 52, 8574; *Angew. Chem.* **2013**, 125, 8736; f) Y. Nakao, H. Idei, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2009**, 131, 15996; g) N. A. Foley, J. P. Lee, Z. Ke, T. B. Gunnoe, T. R. Cundari, *Acc. Chem. Res.* **2009**, 42, 585; h) C. S. Sevov, J. F. Hartwig, *J. Am. Chem. Soc.* **2013**, 135, 2116; i) C. Liu, C. F. Bender, X. Han, R. A. Widenhoefer, *Chem. Commun.* **2007**, 3607.

- [5] Alkylation using alkyl halides: a) P. Ren, I. Salihi, R. Scopelliti, X. Hu, *Org. Lett.* **2012**, *14*, 1748; b) T. Yao, K. Hirano, T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 12307; c) L. Ackermann, B. Punji, W. Song, *Adv. Synth. Catal.* **2011**, *353*, 3325; d) C. Verrier, C. Hoarau, F. Marsais, *Org. Biomol. Chem.* **2009**, *7*, 647; e) O. Vechorkin, V. Proust, X. Hu, *Angew. Chem. Int. Ed.* **2010**, *49*, 3061; *Angew. Chem.* **2010**, *122*, 3125. Alkylation using *N*-tosylhydrozones: f) X. Zhao, G. Wu, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2011**, *133*, 3296; g) T. Yao, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2012**, *51*, 775; *Angew. Chem.* **2012**, *124*, 799; h) W.-C. Lee, C.-H. Wang, Y.-H. Lin, W.-C. Shih, T.-G. Ong, *Org. Lett.* **2013**, *15*, 5358.
- [6] Examples: a) Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* **2013**, *135*, 5308; b) K. Gao, N. Yoshikai, *J. Am. Chem. Soc.* **2013**, *135*, 9279; c) L. Ilies, T. Matsubara, S. Ichikawa, S. Asako, E. Nakamura, *J. Am. Chem. Soc.* **2014**, *136*, 13126.
- [7] P. M. Perez Garcia, T. Di Franco, A. Orsino, P. Ren, X. Hu, *Org. Lett.* **2012**, *14*, 4286.
- [8] B. Xiao, Z.-J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 616.
- [9] a) D. Roy, S. Mom, M. Beaupérin, H. Doucet, J.-C. Hierso, *Angew. Chem. Int. Ed.* **2010**, *49*, 6650; *Angew. Chem.* **2010**, *122*, 6800; b) V. A. Zinovyeva, S. Mom, S. Fournier, C. H. Devillers, H. Cattey, H. Doucet, J.-C. Hierso, D. Lucas, *Inorg. Chem.* **2013**, *52*, 11923; c) J.-C. Hierso, M. Beaupérin, P. Meunier, *Eur. J. Inorg. Chem.* **2007**, 3767.
- [10] Examples: a) J. C. Lewis, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2007**, *129*, 5332; b) B.-T. Guan, Z. Hou, *J. Am. Chem. Soc.* **2011**, *133*, 18086; c) L. D. Tran, O. Daugulis, *Org. Lett.* **2010**, *12*, 4277; d) Y. Nakao, Y. Yamada, N. Kashiwara, T. Hiyama, *J. Am. Chem. Soc.* **2010**, *132*, 13666.
- [11] Nickel-catalyzed coupling of indoles and α -bromoesters: A. Nakatani, K. Hirano, T. Satoh, M. Miura, *Chem. Eur. J.* **2013**, *19*, 7691.
- [12] a) W. Song, S. Lackner, L. Ackermann, *Angew. Chem. Int. Ed.* **2014**, *53*, 2477; *Angew. Chem.* **2014**, *126*, 2510; b) B. Punji, W. Song, G. A. Shevchenko, L. Ackermann, *Chem. Eur. J.* **2013**, *19*, 10605.
- [13] a) L. Jiao, E. Herdtweck, T. Bach, *J. Am. Chem. Soc.* **2012**, *134*, 14563; b) L. Jiao, T. Bach, *Angew. Chem. Int. Ed.* **2013**, *52*, 6080; *Angew. Chem.* **2013**, *125*, 6196.
- [14] A. C. Bissember, A. Levina, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 14232.
- [15] Examples: a) Y. Zou, J. Zhou, *Chem. Commun.* **2014**, *50*, 3725; b) C. M. McMahon, E. J. Alexanian, *Angew. Chem. Int. Ed.* **2014**, *53*, 5974; *Angew. Chem.* **2014**, *126*, 6084; c) K. S. Bloome, R. L. McMahan, E. J. Alexanian, *J. Am. Chem. Soc.* **2011**, *133*, 20146; d) I. Ryu, S. Kreimerman, F. Araki, S. Nishitani, Y. Oderaotoshi, S. Minakata, M. Komatsu, *J. Am. Chem. Soc.* **2002**, *124*, 3812; e) T. Ishiyama, S. Abe, N. Miyaura, A. Suzuki, *Chem. Lett.* **1992**, *21*, 691; f) G. Manolikakes, P. Knochel, *Angew. Chem. Int. Ed.* **2009**, *48*, 205; *Angew. Chem.* **2009**, *121*, 211; g) H. Liu, Z. Qiao, X. Jiang, *Org. Biomol. Chem.* **2012**, *10*, 7274; h) S. Sumino, A. Fusano, T. Fukuyama, I. Ryu, *Acc. Chem. Res.* **2014**, *47*, 1563; i) B. M. Monks, S. P. Cook, *Angew. Chem. Int. Ed.* **2013**, *52*, 14214; *Angew. Chem.* **2013**, *125*, 14464; j) S. Bräse, B. Waegell, A. de Meijere, *Synthesis* **1998**, 148.
- [16] Early mechanistic studies: A. V. Kramer, J. A. Osborn, *J. Am. Chem. Soc.* **1974**, *96*, 7832.

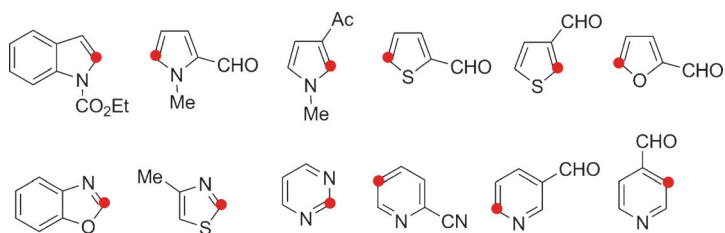
Communications



Heterocycles

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A General Palladium-Catalyzed Method
for Alkylation of Heteroarenes Using
Secondary and Tertiary Alkyl Halides



A radical way: The title reaction has been realized for many unactivated alkyl halides and a variety of heteroarenes (see picture; red dots denote the point of alkylation with secondary and tertiary

alkyl halides). Preliminary mechanistic studies indicate that the palladium catalyst initiates an alkyl radical addition to heterocycles.