

Accepted Article

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Visible-Light-Driven Pd-Catalyzed Radical Alkylation of C—H Bonds with General Unactivated Alkyl Bromides

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Dedicated to the 150th Anniversary of the Gesellschaft Deutscher Chemiker (GDCh)

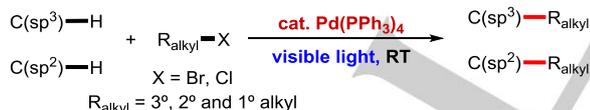
Abstract: Herein, we report a novel visible-light photoredox system with Pd(PPh₃)₄ as the sole catalyst to realize the first direct cross-coupling of C(sp³)—H bonds in *N*-aryl tetrahydroisoquinolines with general unactivated alkyl bromides. Moreover, intra- and intermolecular alkylations of hetero-arenes were also developed under mild reaction conditions. A variety of tertiary, secondary and primary alkyl bromides undergo such reactions to generate C(sp³)—C(sp³) and C(sp²)—C(sp³) bonds in moderate to excellent yields. These redox-neutral reactions feature broad substrate scope (>60 examples), good functional group tolerance and facile generation of quaternary centers. Mechanistic studies indicate that the simple Pd-complex acts as the visible-light photocatalyst and radicals are involved in the process.

Over the past decades, visible-light photoredox catalysis has emerged as a useful tool to realize novel organic transformations under mild conditions.^[1] Beside organic dyes,^[2] Ru- and Ir-complexes, chemists have applied many other transition metal complexes as photocatalysts in organic synthesis (Scheme 1, A).^[3,4] Although palladium catalysts have been widely used in cross-coupling reactions^[5] and limited photophysical properties have been well studied,^[6] the use of a simple and commercially available palladium complex without any exogenous photosensitizer in the visible-light photoredox procedure has been less investigated.^[7,8]

A) Visible-light photocatalysts in organic synthesis



B) Simple Pd-complex as the catalyst in photoredox process (this work)

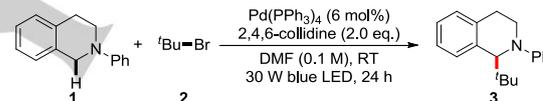


Scheme 1. Visible-light photocatalysis.

Pd-catalyzed direct transformations of C—H bonds are highly useful and attractive methods in organic chemistry.^[9] Although significant progress has been achieved, Pd-catalyzed C—H functionalization with unactivated alkyl halides, especially tertiary ones, lags behind due to the challenges associated with

sluggish oxidative addition and reductive elimination as well as the competitive side reactions, such as β -H elimination and protonation of the resulting alkylpalladium intermediates.^[10] Recently, great breakthrough has been realized that Fu, Zhou, and Alexanian independently realized Pd-catalyzed radical alkylation of (hetero)arenes with unactivated alkyl halides.^[11,12] Pd-catalyzed alkylation of C(sp³)—H bonds with unactivated tertiary and secondary alkyl halides, however, remains unexplored. We wondered whether it was possible to resolve such challenges by introducing visible light as an energy source to activate the Pd-catalyst and facilitate the radical cross-couplings. Herein, we report the discovery of a unique visible-light photoredox system with Pd(PPh₃)₄ as sole catalyst to realize the first general cross-coupling of C(sp³)—H bonds in *N*-aryl tetrahydroisoquinolines with unactivated alkyl halides (Scheme 1, B). Moreover, alkylation of (hetero)aryl C(sp²)—H bonds was also realized under mild reaction conditions.

Table 1: Screening the reaction conditions.^[a]



entry	variation from the standard conditions	yield (%) ^[b]
1	None	98 (90)
2	PdCl ₂ (PPh ₃) ₂ as catalyst	89
3	PdBr ₂ (PPh ₃) ₂ as catalyst	94 (87)
4	Pd(OAc) ₂ as catalyst	trace
5	Pd ₂ (dba) ₃ as catalyst	N.D.
6	Pd ₂ (dba) ₃ , 10 mol% PPh ₃	62
7	no light	N.D.
8	no Pd(PPh ₃) ₄	N.D.
9	110 °C, without light	N.D.

[a] **1** (0.2 mmol), **2** (0.3 mmol), Pd(PPh₃)₄ (6 mol%), 2,4,6-collidine (0.4 mmol) in *N,N*-dimethyl formamide (DMF) (2 mL) at room temperature (20 °C) for 24 h under irradiation with 30 W blue LED. [b] GC yields. The isolated yield is given in parentheses. LED = light-emitting diode. N.D. = Not detected.

With this hypothesis in mind, we started to investigate the reaction of 2-phenyl-1,2,3,4-tetrahydroisoquinoline **1**^[13] and *tert*-butylbromide **2**, in which the catalytic formation of new quaternary centers^[14] would be achieved. After screening a lot of parameters (Please see more details in SI), we were happy to get the desired product **3** in 90% isolated yield with Pd(PPh₃)₄ as catalyst in the absence of any extra photoinitiators (Table 1, entry 1). Control experiments demonstrated that phosphorus ligand, Pd-catalyst and visible-light irradiation were indispensable for the reaction (Table 1, entries 2-8. See more details in Table S2 and Figure S14 in SI). Importantly, thermal reaction without light delivered no product (Table 1, entry 9).

On the basis of these observations, we evaluated the generality of this reaction with a range of unactivated tertiary alkyl bromides (Table 2, A). A wide set of other sterically hindered *tert*-alkyl bromides were conveniently converted into the desired products in good to excellent yields, indicating the high versatility of this catalytic system. Notably, these congested

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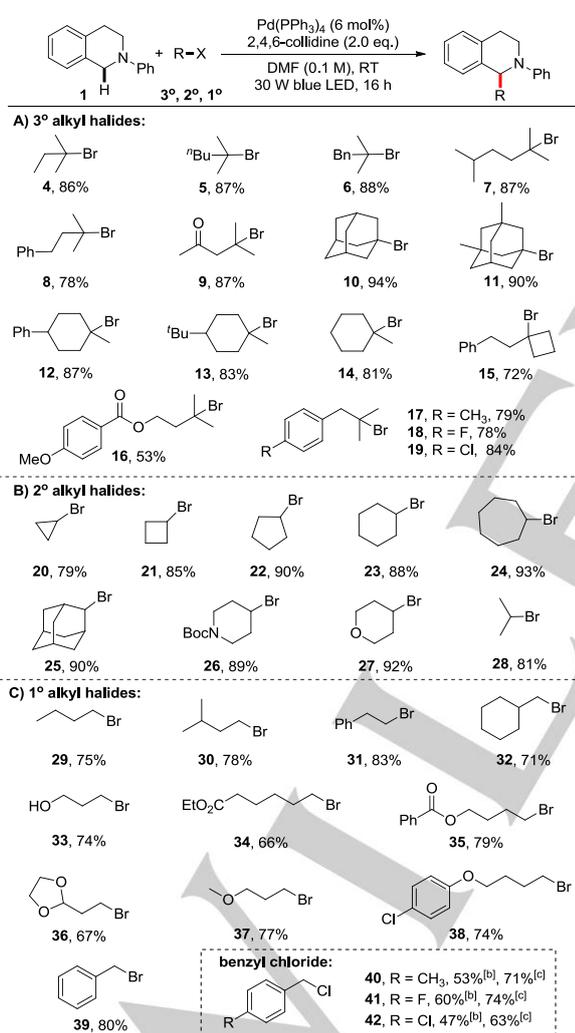
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quaternary centers were generated efficiently with no detection of isomerization products via this photoredox strategy. Moreover, carbonyl-containing functional groups (**9** and **16**) survived the reaction conditions without complications.

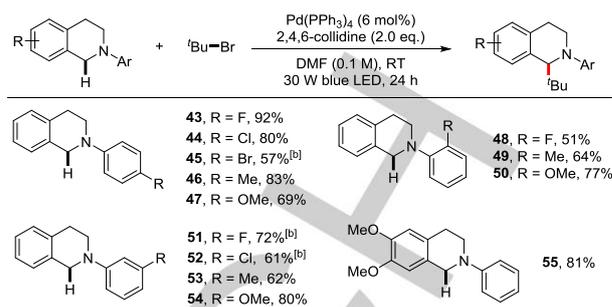
In addition to tertiary alkyl bromides, various unactivated secondary and primary alkyl bromides were also examined (Table 2, B and C). For example, the secondary alkyl bromides (**20–28**), including cyclic and acyclic ones, all reacted smoothly. Moreover, a variety of unactivated primary alkyl bromides also worked well (**29–42**). Notably, LiBr was helpful to promote the reactions of benzyl chlorides, indicating that benzyl bromides are key players in this reaction (**40–42**). This reaction tolerated many kinds of functional groups, including alcohol (**33**), ester (**34** and **35**), ether (**36** and **37**), chloro (**38** and **42**) and fluoro (**41**), which may be beneficial for subsequent transformations.

Table 2: Direct α -alkylation of amines with alkyl halides.^[a]



[a] The standard reaction conditions (Table 1, entry 1). Isolated yields are reported. [b] 48 h. [c] LiBr (1.5 eq.) was added, 48 h.

Table 3: Substrate scope of *N*-aryl tetrahydroisoquinolines.^[a]

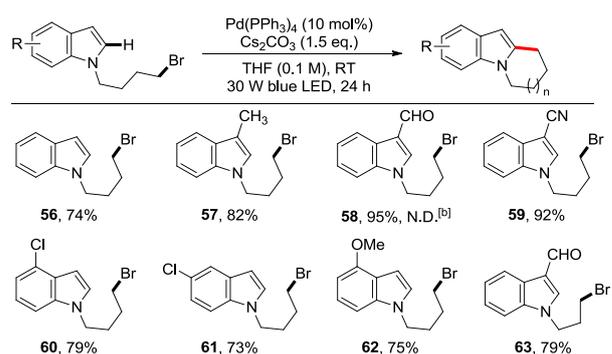


[a] The standard reaction conditions (Table 1, entry 1). Isolated yields are reported. [b] 48 h.

The catalytic system appears to be general with a variety of *N*-aryl tetrahydroisoquinolines (Table 3). The benzene rings on the nitrogen atom bearing fluoro, chloro, bromo, as well as methoxyl at the *ortho*, *meta*, and *para* positions can successfully give the corresponding alkylation products (**43–54**) in moderate to excellent yields. The substituent on the benzene ring of tetrahydroisoquinoline can be varied, as demonstrated by the selective *tert*-butylation of **55** in 81% yield. However, alternative benzyl amines show no reactivity in this transformation (Please see more details in SI).

Considering the high importance of functionalization of heteroarenes, we further applied this catalytic system toward the intramolecular alkylation of indoles under mild reaction conditions. With minor alterations of base and solvent, such cyclization proceeded efficiently to generate the desired products in good to excellent yields (Table 4). The electronic nature of the substituents on the indole ring has little effect on the transformation with slight preference for electron-withdrawing groups at C-3 position (**57–63**). This method offers a mild and safe alternative to indole functionalization avoiding the use of organostannanes or ultraviolet light.^[15]

Table 4: Indole functionalization via intramolecular cyclization.^[a]

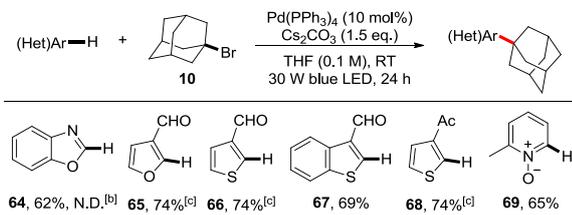


[a] *N*-alkylindole (0.2 mmol), Pd(PPh₃)₄ (10 mol%), Cs₂CO₃ (0.3 mmol) in THF (2 mL) at room temperature (20 °C) for 24 h under irradiation with 30 W blue LED. Isolated yields are reported. [b] Without light or without Pd(PPh₃)₄.

Moreover, this photoredox protocol can also be applied to the intermolecular C–H alkylation of heteroarenes (Table 5). Benzoxazole (**64**), furan (**65**), thiophenes (**66–68**), and 2-methylpyridine *N*-oxide (**69**) all can be alkylated well with **10**, delivering the desired products containing otherwise difficult to obtain quaternary centers. In all of these cases, C2-selective alkylated

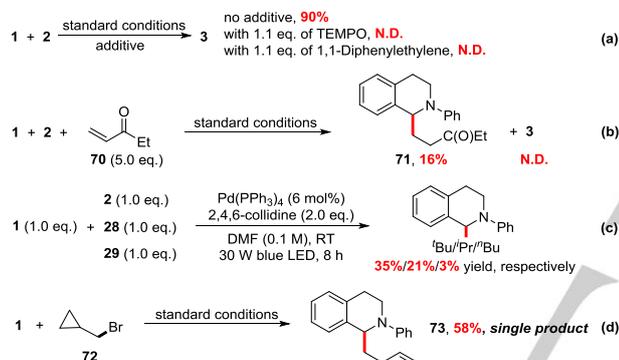
products were obtained. Notably, electron-withdrawing functional groups were important for the reactivity and regioselectivity.

Table 5: Coupling of 1-adamantyl bromide and heterocycles.^[a]



[a] Heterocycles (0.4 mmol), **10** (0.2 mmol), Pd(PPh₃)₄ (10 mol%), Cs₂CO₃ (0.3 mmol) in THF (2 mL) at room temperature (20 °C) for 24 h under irradiation with 30 W blue LED, unless otherwise noted. Isolated yields are reported. [b] Without light or without Pd(PPh₃)₄. [c] 48 h.

To gain more insight into this alkylation reaction, mechanistic studies were conducted with radical trapping experiments, competing reactions and radical clock reactions (Scheme 2, Please see SI for details), which all indicated that this reaction proceeded through a radical-type mechanism.



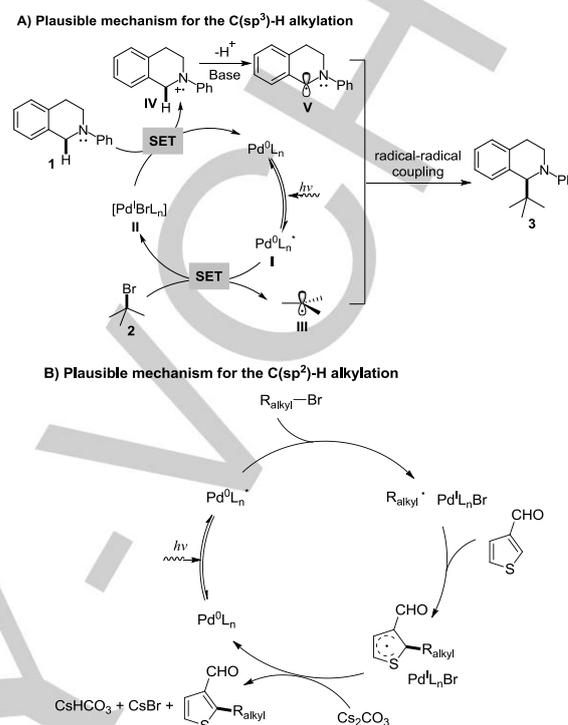
Scheme 2. Selected mechanistic studies

In order to verify that the Pd(0) catalyst is the photoabsorbing species, photophysical behaviors including absorption and emission spectra were performed (Please see SI for more details). As shown in Figure S5-S10 of SI, fluorescence quenching experiments and Stern-Volmer studies indicate that the alkyl bromide quenches the excited state of Pd(PPh₃)₄, where it presumably engages in single electron transfer (SET) with the excited Pd(0) complex.^[7]

Based on the obtained results and previous reports,^[11,12] we propose the following mechanism with **1** and **2** as the substrates (Scheme 3A). Under visible-light irradiation, the active Pd(0)-complex undergoes SET with **2** to provide *tert*-butyl radical **III** and Pd-complex **II**, which further reacts with **1** to afford a radical cation **IV** and regenerate Pd(0)-complex.^[16] The generated **IV** undergoes deprotonation in the presence of base to give an α -amino radical **V**, which undergoes radical-radical coupling with **III** to afford the desired product **3**^[8c]. At this stage, we could not exclude other pathways for this catalysis.

Based on previous reports,^[11,12] our mechanistic hypothesis for the alkylation of heterocycles is shown in Scheme 3B. It starts from the SET from the excited Pd⁰L_n* to the alkyl halide, forming an alkyl radical and Pd^IL_nBr complex.^[7] The carbon-centered radical then adds to the heteroarene to generate an cyclic alkyl radical intermediate, followed by SET, deprotonation

and rearomatization to give the alkylated heteroarene, as well as regeneration of the Pd(0) catalyst. Further mechanistic studies and applications of such Pd-complexes in visible-light photocatalysis are underway in our laboratory.



Scheme 3. Possible mechanism.

In conclusion, we have developed a unique and general visible-light-driven Pd-catalyzed process to realize the efficient radical alkylation of C–H bonds with general alkyl halides under mild reaction conditions. A variety of unactivated alkyl bromides, including tertiary, secondary and primary ones, could undergo such reactions to selectively generate C(sp³)–C(sp³) and C(sp²)–C(sp³) bonds in moderate to excellent yields. These redox-neutral reactions feature broad substrate scope (>60 examples), good functional group tolerance, as well as facile construction of quaternary centers. Key for the success of this photochemistry is the disclose of simple and commercially available Pd(PPh₃)₄ as the sole catalyst.

Acknowledgements

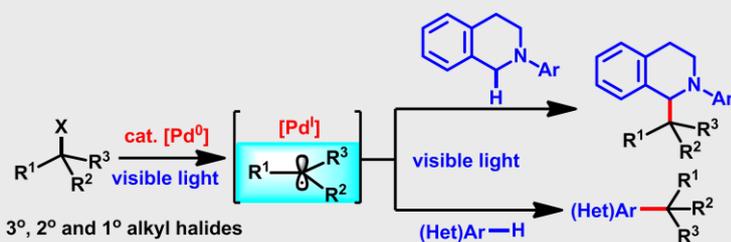
Financial support is provided by the National Natural Science Foundation of China (21772129), the “973” Project from the MOST of China (2015CB856600), the “1000-Youth Talents Plan”, and the Fundamental Research Funds for the Central Universities. We also thank Prof. Oliver Reiser, Prof. Aiwen Lei, Prof. Li-Zhu Wu, Prof. Wen-Jing Xiao, Prof. Yi-Yun Chen, Prof. Di Wu and Prof. Jason J. Churma (Sichuan University) for invaluable help.

Keywords: visible-light photoredox • C–H transformation • palladium catalysis • unactivated alkyl halides • radical

- [1] For recent reviews, see: a) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322; b) J. Xuan, L.-Q. Lu, J.-R. Chen, W.-J. Xiao, *Eur. J. Org. Chem.* **2013**, *2013*, 6755; c) M. N. Hopkinson, B. Sahoo, J. L. Li, F. Glorius, *Chem. Eur. J.* **2014**, *20*, 3874; d) E. Meggers, *Chem. Commun.* **2015**, *51*, 3290; e) D. C. Fabry, M. Rueping, *Acc. Chem. Res.* **2016**, *49*, 1969; f) Y.-Y. Gui, L. Sun, Z.-P. Lu, D.-G. Yu, *Org. Chem. Front.* **2016**, *3*, 522; g) M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* **2016**, *81*, 6898; h) K. L. Skubi, T. R. Blum, T. P. Yoon, *Chem. Rev.* **2016**, *116*, 10035; i) B. König, *Eur. J. Org. Chem.* **2017**, *2017*, 1979.
- [2] For recent reviews, see: a) D. Ravelli, M. Fagnoni, A. Albini, *Chem. Soc. Rev.* **2013**, *42*, 97; b) D. P. Hari, B. König, *Chem. Commun.* **2014**, *50*, 6688; c) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075.
- [3] For leading reviews with Cu-complexes or Au-complex as photocatalysts, see: a) S. Paria, O. Reiser, *ChemCatChem* **2014**, *6*, 2477; b) A. C. Hernandez-Perez, S. K. Collins, *Acc. Chem. Res.* **2016**, *49*, 1557; c) O. Reiser, *Acc. Chem. Res.* **2016**, *49*, 1990; d) J. Xie, H. Jin, A. S. K. Hashmi, *Chem. Soc. Rev.* **2017**, *46*, 5193.
- [4] For selected examples of Au, Pt, Co, Fe-complexes as photocatalysts, see: a) L. M. Kreis, S. Krautwald, N. Pfeiffer, R. E. Martin, E. M. Carreira, *Org. Lett.* **2013**, *15*, 1634; b) J.-J. Zhong, Q.-Y. Meng, G.-X. Wang, Q. Liu, B. Chen, K. Feng, C.-H. Tung, L.-Z. Wu, *Chem. Eur. J.* **2013**, *19*, 6443; c) C.-J. Wu, J.-J. Zhong, Q.-Y. Meng, T. Lei, X.-W. Gao, C.-H. Tung, L.-Z. Wu, *Org. Lett.* **2015**, *17*, 884; d) J. Xie, S. Shi, T. Zhang, N. Mehrkens, M. Rudolph, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2015**, *54*, 6046; e) J. Zhang, D. Campolo, F. Dumur, P. Xiao, J. P. Fouassier, D. Gigmes, J. Lalevée, *ChemCatChem* **2016**, *8*, 2227; f) L. Huang, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2016**, *55*, 4808.
- [5] A. de Meijere, S. Bräse, M. Oestreich, *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley-VCH, Weinheim, 2014.
- [6] For related reports, see: a) J. V. Caspar, *J. Am. Chem. Soc.* **1985**, *107*, 6718; b) P. D. Harvey, H. B. Gray, *J. Am. Chem. Soc.* **1988**, *110*, 2145; c) T. Ishiyama, A. Suzuki, *Tetrahedron Lett.* **1991**, *32*, 6923; d) T. Tsubomura, A. Ishikura, K. Hoshino, H. Narita, K. Sakai, *Chem. Lett.* **1997**, *26*, 1171; e) E. Ye, H. Tan, S. Li, W. Y. Fan, *Angew. Chem. Int. Ed.* **2006**, *45*, 1120; f) G. Imperato, B. König, *ChemSusChem* **2008**, *1*, 993; g) M. A. Fredricks, M. Drees, K. Köhler, *ChemCatChem* **2010**, *2*, 1467; h) W.-P. To, Y. Liu, T.-C. Lau, C.-M. Che, *Chem. Eur. J.* **2013**, *19*, 5654. i) S. Sumino, A. Fusano, T. Fukuyama, I. Ryu, *Acc. Chem. Res.* **2014**, *47*, 1563. j) S. Sumino, T. Ui, I. Ryu, *Org. Chem. Front.* **2015**, *2*, 1085. k) S. Sumino, I. Ryu, *Org. Lett.* **2016**, *18*, 52.
- [7] During the revision of this manuscript, two elegant visible light-induced palladium-catalyzed radical transformations of alkyl halides were reported, see: a) D. Kurandina, M. Parasram, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2017**, DOI: 10.1002/anie.201706554; b) M. Parasram, P. Chuentragool, Y. Wang, Y. Shi, V. Gevorgyan, *J. Am. Chem. Soc.* **2017**, DOI: 10.1021/jacs.7b08459.
- [8] For selected Pd-catalyzed process employing exogenous photosensitizers with visible light irradiation, see: a) D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18566; b) J. Zoller, D. C. Fabry, M. A. Ronge, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 13264; c) J. Xuan, T.-T. Zeng, Z.-J. Feng, Q.-H. Deng, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, H. Alper, *Angew. Chem. Int. Ed.* **2015**, *54*, 1625; d) S. Choi, T. Chatterjee, W. J. Choi, Y. You, E. J. Cho, *ACS Catal.* **2015**, *5*, 4796; e) W.-M. Cheng, R. Shang, H.-Z. Yu, Y. Fu, *Chem. Eur. J.* **2015**, *21*, 13191; f) N. Xu, P. Li, Z. Xie, L. Wang, *Chem. Eur. J.* **2016**, *22*, 2236.
- [9] For selected reviews, see: a) B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949; b) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; d) J. Roger, A. L. Gottumukkala, H. Doucet, *ChemCatChem* **2010**, *2*, 20; e) G. He, B. Wang, W. A. Nack, G. Chen, *Acc. Chem. Res.* **2016**, *49*, 635; f) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev.* **2017**, *117*, 8754.
- [10] For selected reviews, see: a) A. C. Frisch, M. Beller, *Angew. Chem. Int. Ed.* **2005**, *44*, 674; b) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417; c) N. Kambe, T. Iwasaki, J. Terao, *Chem. Soc. Rev.* **2011**, *40*, 4937; d) E. Geist, A. Kirschning, T. Schmidt, *Nat. Prod. Rep.* **2014**, *31*, 441; e) W. Zhang, J. Dai, H. Xu, *Chin. J. Org. Chem.* **2015**, *35*, 1820; f) J. Choi, G. C. Fu, *Science* **2017**, *356*, eaaf7230.
- [11] For selected reviews, see: a) T. Tsubomura, K. Sakai, *Coord. Chem. Rev.* **1998**, *171*, 107; b) ref 6j; c) Q. Liu, X. Dong, J. Li, J. Xiao, Y. Dong, H. Liu, *ACS Catal.* **2015**, *5*, 6111; d) W.-J. Zhou, Y. Zhang, G. Cao, H. Liu, D.-G. Yu, *Chin. J. Org. Chem.* **2017**, *37*, 1322.
- [12] a) B. Xiao, Z. J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 616; b) X. Wu, J. W. T. See, K. Xu, H. Hirao, J. Roger, J.-C. Hierso, J. Zhou, *Angew. Chem. Int. Ed.* **2014**, *53*, 13573; c) A. R. O. Venning, P. T. Bohan, E. J. Alexanian, *J. Am. Chem. Soc.* **2015**, *137*, 3731; d) A. R. O. Venning, M. R. Kwiatkowski, J. E. R. Peña, B. C. Lainhart, A. A. Guruparan, E. J. Alexanian, *J. Am. Chem. Soc.* **2017**, *139*, 11595.
- [13] For photochemistry of tetrahydroisoquinolines, see: a) H. Bartling, A. Eisenhofer, B. König, R. M. Gschwind, *J. Am. Chem. Soc.* **2016**, *138*, 11860; b) Q. Yang, L. Zhang, C. Ye, S. Luo, L.-Z. Wu, C.-H. Tung, *Angew. Chem. Int. Ed.* **2017**, *56*, 3694 and reference therein.
- [14] B. Wang, Y. Q. Tu, *Acc. Chem. Res.* **2011**, *44*, 1207.
- [15] a) F. Aldabbagh, W. R. Bowman, E. Mann, *Tetrahedron Lett.* **1997**, *38*, 7937; b) S. J. Kaldas, A. Cannillo, T. McCallum, L. Barriault, *Org. Lett.* **2015**, *17*, 2864.
- [16] As the putative Pd(I)-complex, which may in equilibrium with Pd(II) complex via disproportionation, can easily oxidize the alkyl radical to carbocation (ref 12b), we speculate that it can also oxidize electron-rich nitrogen atom to radical cation. Please see more details in SI.

Prof. Dr. W.-J. Zhou, G.-M. Cao, G. Shen, X.-Y. Zhu, Dr. Y.-Y. Gui, J.-H. Ye, L. Sun, L.-L. Liao, Dr. J. Li, Prof. Dr. D.-G. Yu*

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+ Redox-neutral + Broad substrate scope + Efficient + Mild reaction condition
+ General + Good FGs tolerance + Green + Inter- and intra molecular

Pd, just do it! A novel visible-light photoredox system with Pd(PPh₃)₄ as the sole catalyst is disclosed to realize the direct alkylation of C—H bonds with general unactivated alkyl bromides under mild reaction conditions. These redox-neutral reactions feature high yields, broad substrate scope (>60 examples), facile generation of quaternary centers and good functional group tolerance.