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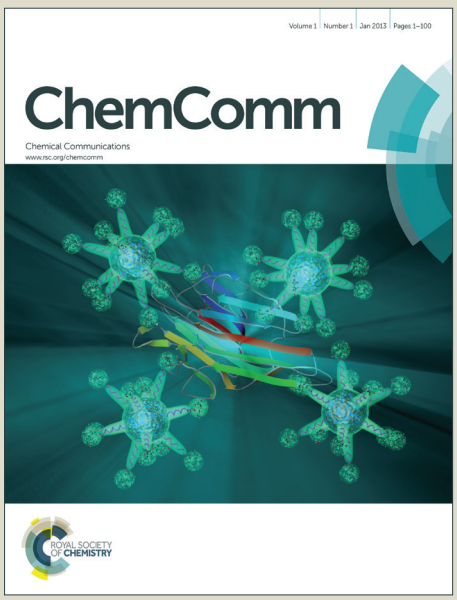

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Rhodium(III)-Catalyzed Cyanation of Vinylic C-H Bonds: *N*-Cyano-*N*-Phenyl-*p*-Toluenesulfonamide as Cyanation Reagent

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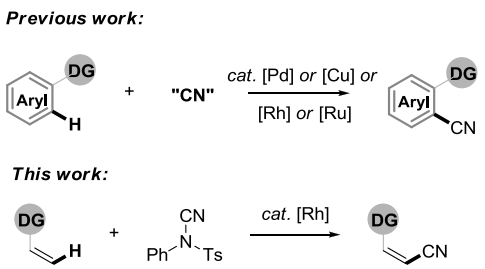
Rh(III)-catalyzed directed vinylic C-H cyanation reaction has been developed as a practical method for the synthesis of alkenyl nitriles. *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS), a user-friendly cyanation reagent, was used in the transformation. Both acrylamides and ketoximes can be employed in the new C-H cyanation process.

Nitriles are versatile building blocks in the synthesis of natural products and pharmaceuticals.[1] Moreover, nitriles can be easily transformed to a series of functional groups, such as amines, aldehydes, amidines, tetrazoles, and amides.[2] As a result, the methods to build the R-CN bonds have been intensively studied in synthetic organic chemistry. The early synthetic efforts for the preparation of organonitriles included two traditional methods such as the Sandmeyer reaction and Rosenmund−von Braun reaction.[3] Recently, a variety of protocols on the basis of transition metal-catalyzed cyanation of halides, pseudohalides and metallic reagents have been developed.[4] In contrast, direct cyanation through C-H bond functionalization is more attractive due to the conciseness of the synthetic route without pre-functionalization (Scheme 1).[5-8] For instance, Yu, Chang and Jiao respectively reported Cu- or Pd-catalyzed C-H cyanation of arenes.[7] Notwithstanding these pioneering examples involving C-H cyanation of arenes under the assistance of various directing groups, few examples have been reported to access alkenyl-nitriles via C-H bond cleavage.[8] The alkenylnitrile is highly versatile and widely represented in important dyes, herbicides and natural products.[9]

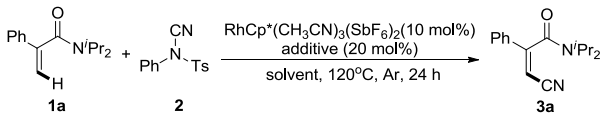


Scheme 1. Transition Metal-Catalyzed C-H Cyanation.

Recently we reported a Rh(III)-catalyzed directed arene C-H cyanation using *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) as the cyanation source.[10] Rhodium(III)-catalyzed C-H reaction has been proved to be a good complement to other transition metals in terms of substrate scope and functional group compatibility.[10-12] This result led us to attempt the direct cyanation of vinylic C-H bonds. Here in, we describe a highly efficient and selective Rh(III)-catalyzed direct intermolecular C-H cyanation of acrylamides and ketoximes using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide.

Initially, we chose N,N-diisopropyl-2-phenylacrylamide (**1a**) and *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (**2,** NCTS) as model substrates to screen the reaction conditions. When **1a** (0.1 mmol) and **2** (0.2 mmol) was treated with $RhCp^*(CH_3CN)_3(SbF_6)_2$ (5 mol%) in DCE at 120°C for 24 h, we were disappointed to find that we failed to obtain any desired product **3a** (entry 1, Table 1). Fortunately, when catalytic amount of base NaOAc (20 mol%) to the reaction, we got desired product **3a** in 80% yield (entry 3). The acid HOPiv completely suppressed the reaction (entry 4). To further improve the yield, the combination of NaOAc and Ag_2CO_3 improved the yield to 88% (entry 5). Subsequently, we investigated the effect of the solvent on the cyanation reaction. Reduced yields were gained in other solvents, such as toluene and 1,4-dioxane (entry 6, 7). The combination of $[RhCp^*Cl_2]_2$ and $AgSbF_6$ displayed similar reactivity to catalyze the C-H cyanation reaction (entry 8). Additionally, we carried out a control experiment (entry 9) that showed the present reaction does not proceed smoothly when $[Ru(p\text{-cymene})Cl_2]_2$ replaced Rh(III) catalyst. No product was obtained in the absence of Rh catalyst (entry 10).

Table 1. Optimization of the reaction conditions[a]

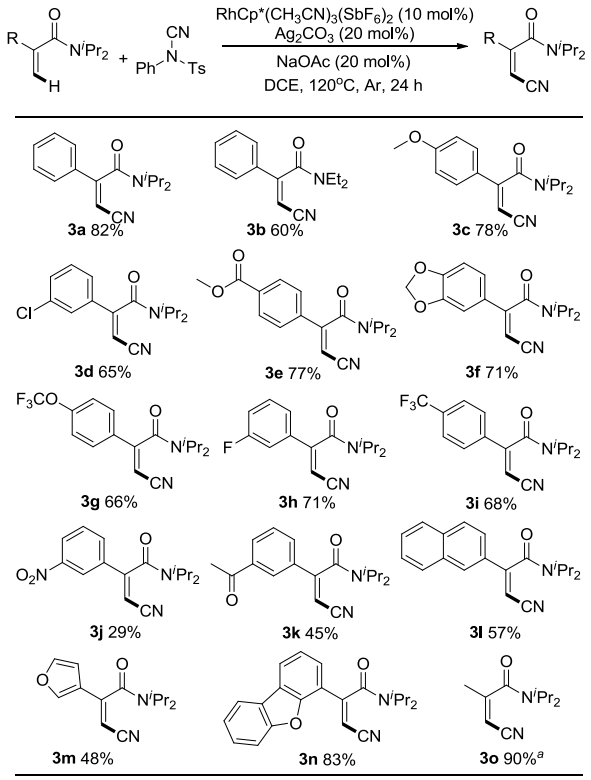


entry	Additive[f]	Solvent	Yield (%)[b]
1	—	DCE	trace
2	$NaHCO_3$	DCE	58
3	NaOAc	DCE	80
4	HOPiv	DCE	trace
5	NaOAc+$AgCO_3$	DCE	**88(82)**
6	NaOAc+$AgCO_3$	Toluene	67
7	NaOAc+$AgCO_3$	dioxane	75
8[c]	NaOAc+$AgCO_3$	DCE	85
9[d]	NaOAc+$AgCO_3$	DCE	15
10[e]	NaOAc+$AgCO_3$	DCE	0

[a] Reaction conditionsc: acrylamide **1a** (0.1 mmol), **2** (0.2 mmol), $RhCp^*(CH_3CN)_3(SbF_6)_2$ (10 mol%), additive (20 mol%), solvent (0.5 ml), 120°C, Ar. [b] Determined by GC analysis. The yield in parenthesis is isolated yield. [c] Using $[RhCp^*Cl_2]_2$ (5 mol%) and $AgSbF_6$ (20 mol%) as catalyst. [d] Using $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%) and $AgSbF_6$ (20 mol%) as

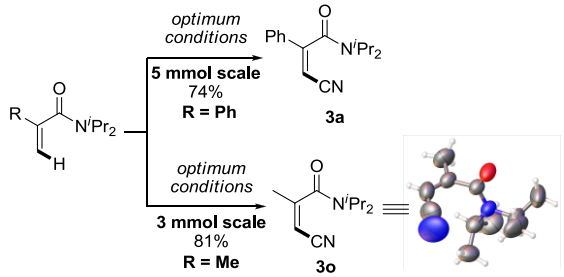
catalyst.[e] Without RhCp*$(CH_3CN)_3(SbF_6)_2$. [f] Using NaOAc (20 mol%) and $AgCO_3$ (20 mol%) when both of them were used.

Table 2. Scope of Substituted Vinylamides



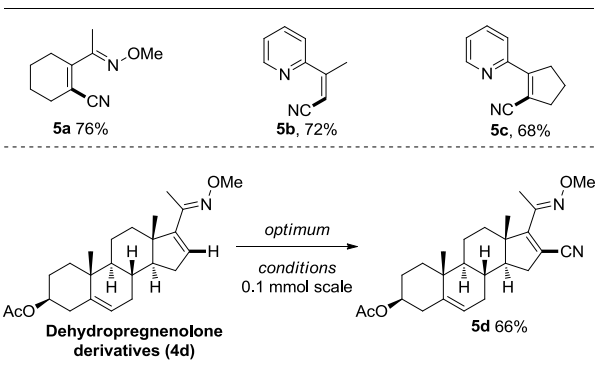
[a] Condition :$[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), $NaHCO_3$ (20 mol%), DCE, 120°C, Ar, 24 h. Isolated yields.

With the optimized reaction conditions in hand (*$[RhCp^*(CH_3CN)_3](SbF_6)_2$, Ag_2CO_3, NaOAc in DCE at 120 ℃ for 24 h*), a variety of acrylamides were examined to test the scope of the reaction (Table 2). when N,N-diethylamide derivative replaced **1a**, the reaction gave a moderate yield. Both electron-donating and withdrawing groups could be tolerated in this reaction. For electron-donating groups, 4-OMe and 4,5-OCH_2O derivatives gave isolated yields of 78% (**3c**) and 71% (**3f**). Electron withdrawing groups, such as 4-COOMe, 3-NO_2, 3-Ac can also proceed in the reaction **(3e, 3j, 3k**). Moreover, the aryl-Cl groups were well compatible with the Rh-catalyzed C-H cyanation processes, which made additional functionalization possible at this position (**3d**). Pharmaceutically interesting fluorinated, trifluoromethylated and trifluoromethoxylated derivatives were also cyanated effectively under the optimized conditions (**3h, 3i, 3g**). To our delight, heterocycles which are important block in the drug synthesis were also be tolerated in the cyanation reaction. Furan and dibenzofuran derivatives were transformed into the corresponding alkenylnitriles in 48% and 83% yield (**3m**, **3n**). Importantly, 2-methacrylamide was also converted effectively with the modificatory condition (**3o**) and the conformation of product was confirmed by X-ray analysis (Scheme 2). To prove the utility of the new strategy, we performed the C-H cyanation reaction on a preparative scale. Under the optimum reaction conditions, we were able to prepare **3a** and **3o** in slightly reduced yield (Scheme 2).



Scheme 2. Scaled-up C-H cyanation reaction.

To explore the scope of the Rh-catalyzed C-H cyanation process with regards to other directing groups, we tested *O*-methyl oximes and pyridines (Scheme 3). It was found that both of *O*-methyl oximes and pyridines can be used in the reaction to generate the desired cyanated products in good yields. This finding is synthetically valuable because the *O*-methyl oximes are derived from the ketone groups. Furthermore, we tested the application of the new C-H cyanation reaction to complex bioactive molecules. When dehydropregnenolone derivatives was treated with the Rh-catalyzed C-H cyanation process, we successfully obtained cyanated products in 66% isolated yield (Scheme 3). Our result indicated that the new C-H cyanation process may be useful for rapid generation of the derivatives of bioactive compounds.



[a] Conditions: as conditions in Table 1, entry 5.

Scheme 3. Cyanation of ketone oximes and pyridines.[a]

On the basis of previous reports on rhodium-catalyzed C-H activation reacted with an unsaturated system, we proposed the following mechanism[13] for the Rh-catalyzed C-H cyanation reaction: Firstly, the Rh(III) catalyst reacted with the substrate **1a** through C-H activation step to generate a rhodacycle(III) intermediate **I**. Secondly, intermediate **I** was coordinated with NCTS followed by insertion of the C≡N moiety into the C-Rh(III) bond to produce **II**. Finally, elimination of a tosyl aniline-coordinated Rh(III) complex from **II** took place to generate the target product **3a**. The Rh(III) complex then went back to the catalytic cycle.

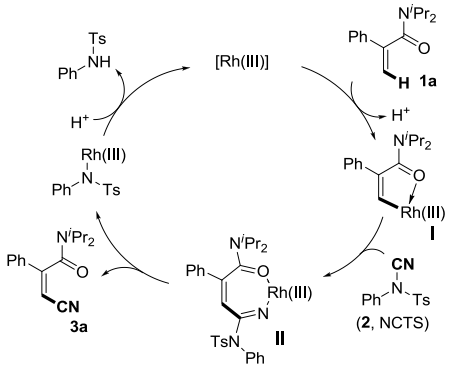


Figure 1. Proposed Mechanism.

In summary, we have developed a practical Rh-catalyzed C-H activation with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide for the synthesis of alkenyl nitriles. The reaction tolerated a variety of synthetically important functional groups (e.g. aryl-Cl, heterocycles). Both acrylamides and ketoximes can be employed as directing group in the new C-H cyanation process. Further exploration of the synthetic utilities of this chemistry and in-depth mechanistic study are currently in progress.

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Author Contributions

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Notes and references

1 (a) A. Kleemann, J. Engel, B.Kutscher, D. Reichert, *Pharmaceutical Substances: Syntheses, Patents, Applications, 4th ed*., Thieme, Stuttgart, 2001; (b) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.*, 2010, **53**, 7902; (c) R. C. Larock, *Comprehensive Organic Transformations: A Guide to Fucntional Group Preparations*, VCH, New York, 1989.

2 (a) R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; John Wiley & Sons: New York, 1999; (b) Z. Rappoport, *Chemistry of the Cyano Group*; John Wiley & Sons: London, 1970.

3 (a) T. Sandmeyer, *Ber. Dtsch. Chem. Ges*. 1884, **17**, 1633; (b) C. Galli, *Chem. Rev.* 1988, **88**, 765; (c) J. Lindley, *Tetrahedron* 1984, **40**, 1433.

4 For reviews: (a) P. Anbarasan, T. Schareina, M. Beller, *Chem. Soc. Rev.* 2011, **40**, 5049; (b) J. Kim, H. J. Kim, S. Chang, *Angew. Chem. Int. Ed.*, 2012, **51**, 11948; (c) S. Ding, N. Jiao, *Angew. Chem., Int. Ed.* 2012, **51**, 9226; For selected examples: (d) P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.*, 2011, **50**, 519; (e) M. Sundermeier, S. Mutyala, A. Zapf, A. Spannenberg, M. Beller, *J. Organomet. Chem.*, 2003, **684**, 50; (f) G. Kaupp, J. Schmeyers, J. Boy, *Chem. Eur. J.*, 1998, **4**, 2467; (g) G.-Y. Zhang, J.-T. Yu, M.-L. Hu, J. Cheng, *J. Org. Chem.*, 2013, **78**, 2710; (h) N. Sato, Q. Yue, *Tetrahedron*, 2003, **59**, 5831; (i) Z. Jiang, Q. Huang, S. Chen, L. Long, X. Zhou, *Adv. Synth. Catal.*, 2012, **354**, 589; (j) F.-H. Luo, C. Chu, C.-H. Cheng, *Organometallics*, 1998, **17**, 1025; (k) S. Goswami, A. Manna, A. K. Maity, S. Paul, A. K. Das, M. K. Das, P. Saha, C. K. Quah, H.-K. Fun, *Dalton trans.*, **2013**, 42, 12844.

5 Selected reviews on other C-H functionalizations : (a) I. A. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.*, 2010, **110**, 890; (b) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem., Int. Ed.*, 2011, **50**, 11062; (c) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.*, 2011, **40**, 1857; (d) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* 2012, **45**, 788.

6 (a) Z. Shu, W. Ji, X. Wang, Y. Zhou, Y. Zhang, J. Wang, Angew. Chem., Int. Ed., 2014, **53**, 2186; (b) X. Jia, D. Yang, S. Zhang, J, Cheng, *Org. Lett.*, 2009, **11**, 4716; (c) G. Yang, C. Kuang, Y. Zhang, J. Wang, *Org. let.*, 2010, **12**, 1052; (d) H.-Q, Do, O. Daugulis, *Org. Lett.*, 2010, **12**, 2517; (e) K. Okamoto, M. Watanabe, M. Murai, R. Hatao, K. Ohe, *Chem. Commun.*, 2012, **48**, 3127; (f) X. Ren, J. Chen, F. Chen, J. Cheng, *Chem. Commun.*, 2011, **47**, 6725; (g) J. Peng, J. Zhao, Z. Hu, D. Liang, J. Huang, Q. Huang, Q. Zhu, *Org. Lett.*, 2012, **14**, 4966; (h) S. Xu, X. Huang, X. Hong, B. Xu, *Org. Lett.*, 2012, **14**, 4614; (i) B. Liu, J. Wang, B. Zhang, Y. Sun, L. Wang, J. Chen, J. Cheng, *Chem. Commun.*, 2014, **50**, 2315; (j) J. Jin, Q. Wan, P. Lu, Y. Wang, *Chem. Commun.*, 2012, **48**, 9933; (k) G. Zhang, Y. Xia, G. Cheng, D. Liu, R. Wang, *Org. Lett.*, 2014, **16**, 656.

7 (a) X. Chen, X.-S. Hao, C.E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790; (b)J. kim, S. Chang, *J. Am. Chem. Soc.*, 2010, **132**, 10272; (c) J. Kim, J. Choi, K. Shin, S. Chang, *J. Am. Chem. Soc.*, 2012, **134**, 2528; (d) J. Kim, H. Kim, S. Chang, *Org. Lett.*, 2012, **14**, 3924; (e) S. Ding, N. Jiao, *J. Am. Chem. Soc.*, 2012, **133**, 12374.

8 X. Hong, H. Wang, G. Qian, Q. Tan, B. Xu, *J. Org. Chem.*, 2014, **79**, 3228.

9 (a) M. An, A. Sarker, D.-C. Jung, J.-D. *Hong*, *Bull. Korean Chem. Soc.*, 2011, **32**, 2083; (b) F. F. Fleming, *Nat. Prod. Rep.*, 1999, **16**, 596; (c) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.*, 2010, **53**, 7902; (d) C. Qin, N. Jiao, *J. Am. Chem. Soc*., 2010, **132**, 15893; (e) M. Alterman, A. Hallberg, *J. Org. Chem.*, 2000, **65**, 7984; (f) T. Oishi, K.Yamaguchi, N. Mizuno, *Angew. Chem., Int. Ed.*, 2009, **48**, 6286; (g) K. Ishihara, Y. Furuya, H. Yamamoto, *Angew. Chem., Int. Ed.* 2002, **41**, 2983; (h) K. Yamaguchi, H. Fujiwara, Y. Ogasawara, M. Kotani, N. Mizuno, *Angew. Chem., Int. Ed.*, 2007, **46**, 3922; (i) J. Xu, L. Zhang, N.Jiao, *Org. Lett.* 2010, **12**, 2888; (j) Y. Nakao, A. Yada, S. Ebata, T. J. Hiyama, *J. Am. Chem. Soc*., 2007, **129**, 2428.

10 (a) T.-J. Gong, B. Xiao, W.-M. Cheng, W. Su, J. Xu, Z.-J. Liu, L. Liu, Y. Fu, J. Am. Chem. Soc., 2013, **135**, 10636; (b) T.-J. Gong, B. Xiao, Z.-J. Liu, J. Wan, J. Xu, D.-F. Luo, Y. Fu, L. Liu, Org. Lett., 2011, **13**, 3235; (c) T.-J. Gong, W. Su, Z.-J. Zhao, W.-M. Cheng, B. Xiao, Y. Fu, Org. Lett., 2014, **16**, 330; (d) Y. Yang, S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2014, **53**, 8677; (e) Y. Yang, Y, Zhang, J. Wang, *Org. Lett.*, 2011, **13**, 5608; (f) M. Chaitanya, D. Yadagiri, P. Anbarasan, *Org. Lett.*, 2013, **15**, 4960; (g) W. Liu, L. Ackermann, *Chem. Commun.*, 2012, **50**, 1878.

11 For reviews, see: (a) T. Satoh, M. Miura, *Chem. Eur. J.*, 2010, **16**, 11212; (b) D. A. Colby, A. S. Tsai, R. G. Bergman, J.A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814; (c) F. W. Patureau, J. Wencel-Delord, F. Glorius, *Aldrichimica Acta*, 2012, **45**, 31; (d) G. Song, F. Wang, X. Li, *Chem. Soc. Rev*., 2012, **41**, 3651; (e) C. Zhu, R. Wang, J. R. Falck, *Chem.-Asian J.* 2012, **7**, 1502; (f) N. Kuhl, N. Schröder, F. Glorius, *Adv. Synth. Catal.*, 2014, **356**, 1443.

12 For selected recent examples of Rh^{III}-catalyzed C−H founctionalization with alkenes: (a) K. Ueura, T. Satoh, M. Miura, *Org. Lett.*, 2007, **9**, 1407; (b) F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* 2010, **132**, 9982; (c) H. Li, Y. Li, X.-S. Zhang, K. Chen, X. Wang, Z.-J. Shi, *J. Am. Chem. Soc.*, 2011, **133**, 15244; (d) K. Graczyk, W. Ma, L. Ackermann, *Org. Lett.*, 2012, **14**, 4110; (e) C. Wang, H. Chen, Z. Wang, J. Chen, Y. Huang, *Angew. Chem., Int. Ed.*, 2012, **51**, 7242; (f) B. Liu, Y. Fan, Y. Gao, C. Sun, C. Xu, J. Zhu, *J. Am. Chem. Soc*., 2013, **135**, 468; (g) T. K. Hyster, L. Knörr, T. R. Ward, T. Rovis, T. *Science*, 2012, **338**, 500; (h) B. Ye, N. Cramer, *Science*, 2012, **338**, 504; (i) W. Zhen, F. Wang, M. Zhao, Z. Du, X. Li, *Angew. Chem., Int. Ed.*, 2012, **51**, 11819; with alyknes: (j) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 18326; (k) H. Wang, C. Grohmann, C. Nimphius, F. Glorius, *J. Am. Chem. Soc.*, 2012, **134**, 19592; (l) J. Jayakumar, K. Parthasarathy,

C.-H. Cheng, *Angew. Chem., Int. Ed.*, 2012, **51**, 197; (m) D. Wang, F. Wang, G. Song, X. Li, *Angew. Chem., Int. Ed.* 2012, **51**, 12348; (n) Z. Shi, C. Grohmann, F. Glorius, *Angew. Chem., Int. Ed.* 2013, **52**, 5393; with CO, imines, aldehydes: (o) K. D. Hesp, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.*, 2011, **133**, 11430; (p) Y. Li, B.-J. Li, W.-H Wang, W.-P. Huang, X.-S. Zhang, K. Chen, Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2011, **50**, 2115; with bromination and iodination: (q) N. Schröder, J. Wencel-Delord, F. Glorius, *J. Am. Chem. Soc.*, 2012, **134**, 8298; with electrophilic amination reagent: (r) J. Y. Kim, S. H. Park, J. Ryu, S. H. Cho, S. H. Kim, S. Chang, *J. Am. Chem. Soc.*, 2012, **134**, 9110; (s) D.-G. Yu, M. Suri, F. Glorius, *J. Am. Chem. Soc.*, 2013, **135**, 8802; with diazo compounds: (t) W.-W. Chan, S.-F. Lo, Z. Zhou, W.-Y. Yu, *J. Am. Chem. Soc.*, 2012, **134**, 13565; (u) T. K. Hyster, K. E. Ruhl, T. Rovis, *J. Am. Chem. Soc.*, 2013, **135**, 5364; (v) Z. Shi, D. C. Koester, M. Boultadakis-Arapinis, F. Glorius, *J. Am. Chem. Soc.*, 2013, ***135***, 12204.

13 We conducted deuterium exchange experiments and found C-H activation process is reversible, see the supporting information.