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Sulfoximine Assisted Pd(II)-Catalyzed Bromination and Chlorination of Primary β-C(sp^3)–H Bond

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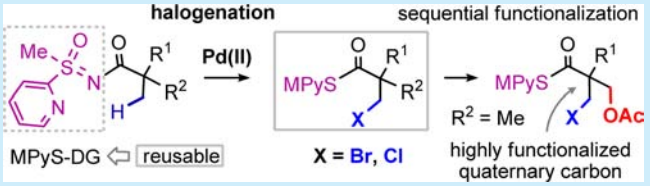
Supporting Information

ABSTRACT: *S*-Methyl-*S*-2-pyridyl-sulfoximine (MPyS) directed bromination and chlorination of the 1°-β-C(sp^3)–H bond of MPyS-N-amides is realized under the influence of N-Br/Cl-phthalimides and a Pd(II)-catalyst. The sequential halogenation and acetoxylation of α-dimethyl MPyS-N-amides constructs highly functionalized α-trisubstituted aliphatic acid derivatives. The MPyS directing group is cleaved from the halogenated products and recovered.

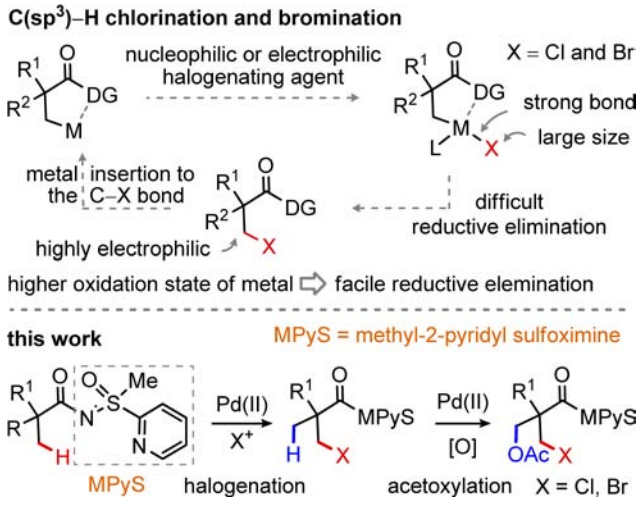


Direct functionalization of the remote unactivated C(sp^3)–H bond through C–H activation has a profound impact in organic chemistry. Of note, the installation of a halogen into a C(sp^3)–H bond creates a haloalkane, a versatile motif amenable to a variety of functional group transformations, synthetically useful reactions,[1] and the total synthesis of natural products.[2] Common functional groups (olefin, –OH, –CO_2H and its analogues)[3] are readily transformed into halogenated alkanes, while radical reactions of unreactive alkanes generate non-selective haloalkanes under harsh reaction conditions.[4] In contrast, a directing group (DG) can control the regioselectivity of the transition-metal-catalyzed activation[5] and halogenation of remote C(sp^3)–H bonds, allowing direct access to haloalkanes.[6,7] Interestingly, prefunctionalization of the substrate is not required for this method, which broadens its scope and synthetic utility. Therefore, this method offers opportunities for late-stage induction of a halogen into an aliphatic chain, consequently promoting the efficient synthesis of complex molecules.[8]

The Pd(II)-catalyzed oxazoline-directed di-iodination and asymmetric monoiodination of 1°-C(sp^3)–H bonds is exemplary and extensive,[6a−c] while C(sp^3)–Cl bond formation is limited to benzylic C–H bonds of 8-methyl quinoline, 1°-C(sp^3)–H bonds of *N*-methoxy amide and 2-*tert*-butylpyridine.[6d−f] Despite significant advances in direct C–H halogenation, the bromination and chlorination of aliphatic C–H bonds through regioselective activation of remote C(sp^3)–H bonds remains underdeveloped, reinforcing the inherent difficulties associated with these transformations. The specific challenges for effective bromination/chlorination of C(sp^3)–H bonds are the reductive elimination leading to C–halogen(X) bond formation,[9] the likelihood of metal insertion into the C–X bond,[10] and the facile nucleophilic displacement of the C–X bond (Scheme 1). The concurrent participation of a Pd(II)/Pd(IV) species would facilitate reductive elimination and minimize oxidative insertion of the Pd species into the newly formed C–X bond of the haloalkane.

Recently, we demonstrated a Pd(II)-catalyzed 1°-β-C(sp^3)–H bond acetoxylation of methyl-2-pyridylsulfoximine (MPyS)-N-amides at rt.[11] Despite the challenges involved in the C(sp^3)–H bond halogenation, herein, we showcase the installation of Br/Cl-groups into the 1°-C(sp^3)–H bond and sequential functionalization of two β-C(sp^3)–H bonds by halogenation and acetoxylation of MPyS-N-amides with the help of MPyS-DG in the presence of a Pd-catalyst.

Scheme 1. Challenges of C(sp^3)–H Halogenation and the Current Work



The investigation was initiated exposing *N*-[2,2-dimethylpropanoyl]-*S*-methyl-*S*-2-pyridylsulfoximine (**2a**) to Pd-catalysts, brominating/chlorinating agents, and solvents; the results are summarized in Table 1.[12] The reaction between **2a** and NBS (**Br-1**) in Pd(OAc)$_2$ in AcOH at 60 °C for 15 h led to β-C(sp^3)–H bromination product **3a** (14%, crude ^{1}H NMR) and 36% of the C(sp^3)-acetoxylation compound (entry 1),[12] as the reductive eliminations linked to the formation of C–O and C–Br bonds are comparable.[9d] This preliminary result thus provoked finding

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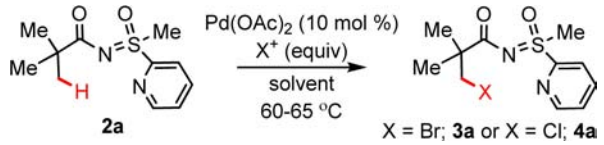
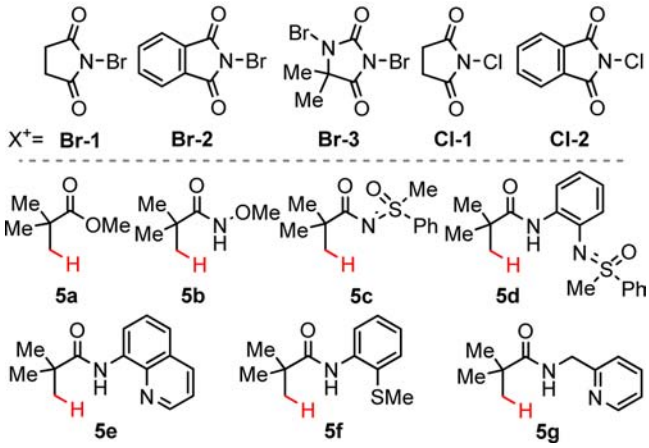
Table 1. Optimization of Reaction Parameters[a]



entry	X^+ (equiv)	additive (equiv)	solvent	yield(%)[b] 3a/4a
1	Br-1 (1.2)	-	AcOH	14[c]
2	Br-1 (1.2)	-	DCE	34
3	Br-1 (1.2)	AcOH (1)	DCE	44
4	Br-1 (1.2)	PivOH (1)	DCE	38
5	Br-1 (1.2)	*i*-$PrCO_2H$ (1)	DCE	36
6	Br-1 (1.5)	AcOH (1)	DCE	50
7	Br-1 (2.0)	AcOH (1)	DCE	43
8	Br-2 (1.5)	AcOH (1)	DCE	58
9	Br-3 (1.5)	AcOH (1)	DCE	24
10	**Br-2 (1.5)**	**AcOH (2.5)**	**DCE**	**65**
11	Br-2 (1.5)	AcOH (5.0)	DCE	52
12	Cl-1 (1.5)	AcOH (2.5)	DCE	37
13	Cl-2 (1.5)	AcOH (2.5)	DCE	58
14	**Cl-2 (1.5)**	**AcOH (2.5)**	**DCE**	**66**[d]
15	-	-	DCE	-[e]



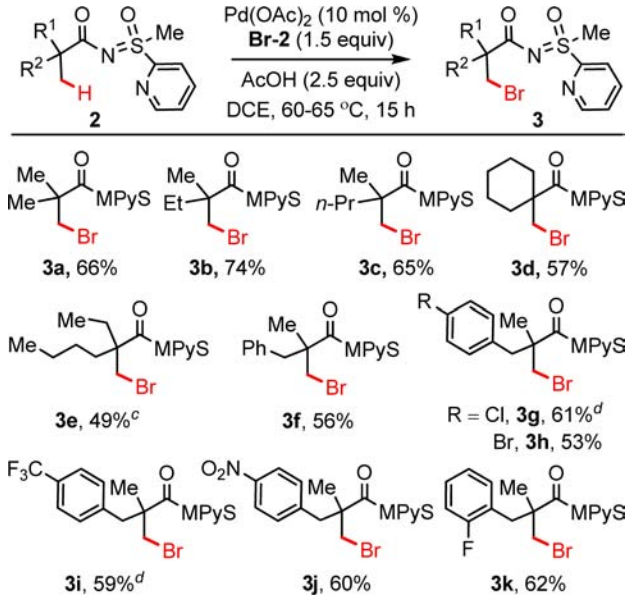
[a]Reactions were carried out with **2a** (50 mg, 0.21 mmol) and X^+ (1.0–2.0 equiv) for 15 h. [b]Isolated yield. [c]36% acetoxylated product was observed. [d]15 mol % of catalyst was used. [e]1.5 equiv of $CuCl_2$ and 2.0 equiv of AgOAc were used, and the reaction was performed at 100 °C.

optimized conditions for the efficient conversion of **2a** to **3a**. Interestingly, the reaction in $ClCH_2CH_2Cl$ (DCE) produced 34% of **3a** (entry 2).

Among other Pd(II) salts screened, $Pd(OAc)_2$ was found to be the best; the reaction did not proceed in the absence of a catalyst.[12] Other solvents CH_2Cl_2, $CHCl_3$, CCl_4, THF, and DMF were inferior.[12] Surprisingly, addition of AcOH (1.0 equiv) enhanced the yield of **3a** to 44% (entry 3), whereas PivOH or $^tPrCO_2H$ were moderate (entries 4 and 5). The use of 1.5 equiv of NBS is better over 2.0 equiv of NBS (entries 6 and 7). To our delight, reaction of **2a** with *N*-bromophthalimide (**Br-2**; NBP) led to 58% of **3a** (entry 8), whereas 1,3-dibromo-5,5-dimethyl-imidazolidine-2,4-dione (**Br-3**) was ineffective (entry 9). Gratifyingly, **3a** (65%) was isolated with AcOH (2.5 equiv) (entry 10); use of 5.0 equiv AcOH yielded a lower amount of **3a** (entry 11). Having the optimized conditions for the $C(sp^3)$–H bromination in hand, we next focused on the C–H chlorination of **2a**. As anticipated, *N*-chlorophthalimide (**Cl-2**; NCP) worked better than *N*-chlorosuccinimide (**Cl-1**; NCS) under the catalytic conditions in entry 10, affording 58% of **4a** (entries 12 and 13). The use of $Pd(OAc)_2$ (15 mol %) led to **4a** (66%) (entry 14). To our disappointment, chlorination of **2a** under Yu's conditions ($CuCl_2$ and AgOAc) did not succeed (entry 15).[6d,12] In addition, none of the notable mono- **5a–c** and bicoordinated **5d–g** DGs were found to be competent (Table 1).[12,13]

The optimized conditions (entry 10, Table 1) are utilized to assess the scope and limitations of the unprecedented β-$C(sp^3)$–H bromination of MPyS-N-amides (Scheme 2).

Scheme 2. Bromination of β-$C(sp^3)$–H Bonds of Amides[a,b]



[a]Reaction conditions: **2** (0.3 mmol), $Pd(OAc)_2$ (10 mol %), **Br-2** (0.45 mmol), AcOH (2.5 equiv), DCE (3.0 mL) at 60–65 °C. [b]Isolated yields. [c]0.25 mmol of **2e** was used. [d]Reaction was continued for 18 h.

The α-dialkyl and 2-methylcyclohexyl substituted MPyS-N-amides **2a–e** were successfully reacted with **Br-2** to exclusively provide the corresponding 1°-β-CH_2–Br products **3a–e** in moderate to good yields. The brominating agent **Br-2** did not even affect the reactive benzyl C–H bond, suggesting non-occurrence of the radical intermediate.[14] The Br-moiety especially inserted into the 1°-β-C–H bond affording **3f** in 56% yield. The halo and other functional groups (Cl, Br, CF_3, and NO_2) on the aryl moiety in **2g–j** did not affect the reaction outcome and survived; good yields of the desired products **3g–j** were isolated. The *ortho*-F-substituted **2k** was no exception delivering **3k** in 62% yield. In contrast, the electron-rich aryl moiety in MPyS-N-amides underwent electrophilic brominations.[12]

We next explored the generality of chlorination on α-disubstituted MPyS-N-amides under the optimized conditions shown in entry 14, Table 1 (Scheme 3). A series of 1°-β-CH_2–Cl products **4a–e** were readily synthesized from the α-methylalkyl bearing aliphatic acid derivatives in good yields. The chlorination on the additional β-CH_3 moiety in **4a** was sluggish; however, the reaction at 80 °C allowed formation of 42% of β,β'-dichloro compound **4d**. As anticipated, the reagents used for chlorination did not affect the benzylic C–H bonds; a variety of chlorinated

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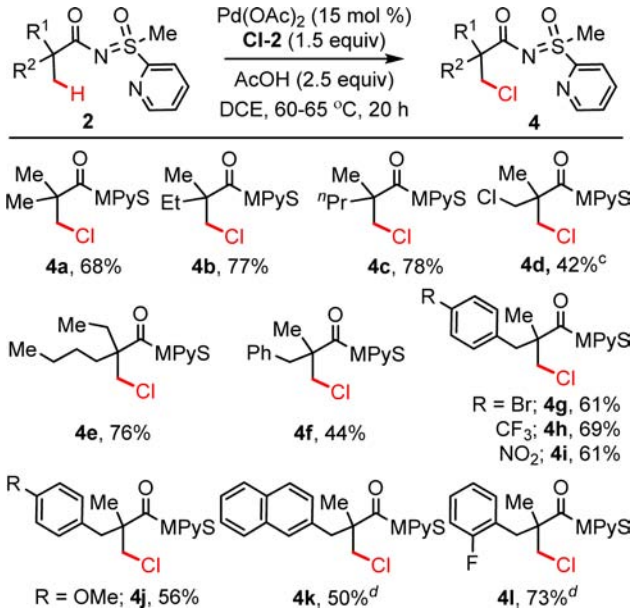
Scheme 3. Chlorination of β-C(sp^3)−H Bonds of Amides[a,b]

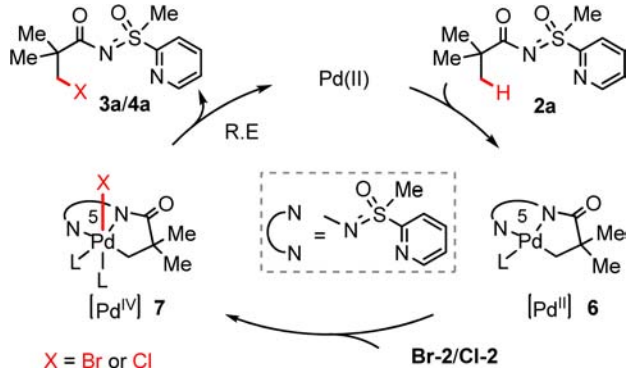


[a]Reaction conditions: **2** (0.3 mmol), $Pd(OAc)_2$ (15 mol %), **Cl-2** (0.45 mmol), AcOH (2.5 equiv), DCE (3.0 mL) at 60−65 °C. [b]Isolated yields. [c]Reaction was heated at 80 °C. [d]Reaction was continued for 24 h.

products **4f−i** having Br, CF_3, or NO_2 functional groups on arenes were synthesized. To our surprise, the electron-rich *p*-OMe aryl and β-naphthyl moieties are inert to electrophilic chlorination, affording the desired **4j** and **4k** in moderate yields. The chlorination of *o*-fluoro benzyl α-dimethyl substituted amide gave **4l** in 73% yield. The α-mono-/unsubstituted MPyS-N-amides did not undergo halogenation, suggesting the requirement of dialkyls adjacent to the DG due to the Thorpe−Ingold effect;[12,15] even the molecule having three methelyne groups ($-CH_2-$) failed to provide the corresponding halogenated product.[12]

Although the mechanistic details are yet to be established, we presumed the participation of Pd^{II} and Pd^{IV} species in this halogenation reaction (Scheme 4).[16] The chelation of pyridine

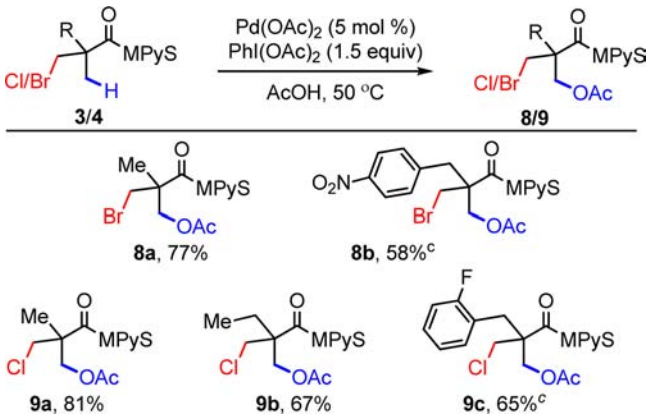
Scheme 4. Proposed Catalytic Cycle



and the sulfoximine N-atom to the Pd^{II} species followed by activation of the C(sp^3)−H of MPyS-N-amide produces [5,5]-fused bicyclic cyclopalladated intermediate **6**. The oxidation of the Pd^{II} species with NXP delivers Pd^{IV} species **7**.[16] Finally, reductive elimination of **7** leads to the halogenated product **3/4**. The role of AcOH in this reaction presumably is to help regenerate the active catalyst by replacing the phthalimide ligand on Pd(II).

The twofold C−H functionalizations are appealing, as it introduces identical or different functional groups in the molecule.[17] Consequently, induction of different functional groups on two 1°-β-C(sp^3)−H bonds in 2,2-dimethyl carboxylic acid would infuse creating a highly functionalized quaternary carbon center. The remarkable ability of MPyS-DG assisted multiple functionalizations was thus probed executing the formation of unprecedented C−Br/Cl and C−O moieties on two β-C(sp^3)−H bonds (Scheme 5).[11] Gratifyingly, acetoxylation

Scheme 5. Sequential Double C−H Activation[a,b]

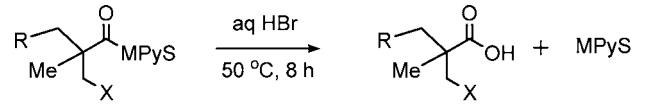


[a]Reaction conditions: **3** or **4** (0.25 mmol), $Pd(OAc)_2$ (5.0 mol %), $PhI(OAc)_2$ (0.37 mmol), AcOH (1.0 mL) at 50 °C. [b]Isolated yields. [c]Reaction was carried out with 0.20 mmol of **3j** and **4l**.

of bromo-compounds **3a** and **3j** or alkyl chlorides **4a−b** and **4l** with $Pd(OAc)_2$ and $PhI(OAc)_2$ in AcOH independently produced **8a−b** and **9a−c**, respectively (Scheme 5), *displaying the effectiveness of multiple C−H activations with the aid of a single DG*.[17,18]

Finally, hydrolysis of the halogenated products with aqueous HBr readily cleaves the MPyS-DG. Thus, the desired β-halo carboxylic acids **10** (82%) and **11** (85%) were obtained from **3b** and **4a**, respectively, with the recovery of an appreciable amount of MPyS (Scheme 6).[19]

Scheme 6. Recovery of MPyS Directing Group



The utility of the alkyl-bromo-group in **3b** is demonstrated through nucleophilic azide displacement followed by [3 + 2] cycloaddition with phenyl acetylene for the fabrication of triazole **12** (eq 1).[12,20]

In conclusion, a novel MPyS-directing-group-assisted bromination and chlorination of 1°-β-C(sp^3)−H bonds of aliphatic acid derivatives is demonstrated for the first time. The unprecedented halogenation and acetoxylation sequence on two β-CH_3 moieties provides access to highly functionalized quaternary carbon centers bearing carboxylic acids. We believe

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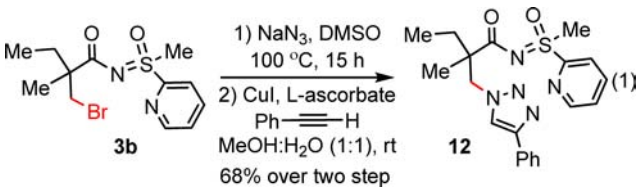

these preliminary results will find broad synthetic utility and boost the development of novel methods for creating C−halogen moieties in the unactivated remote C(sp^3)−H bonds.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ DEDICATION

Dedicated to Professor H. Ila on the occasion of her 70th birthday.

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■ REFERENCES

(1) (a) *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Dekker: New York, 1996. (b) Crampton, M. R. In *Organic Reaction Mechanism*; Knipe, A. J., Eds.; Wiley: New York, 2007. (c) *Metal Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (d) *Topics in Organometallic Chemistry: Palladium in Organic Synthesis*; Tsuji, J., Ed.; Springer: New York, 2005; pp 85−108. (e) Dudnik, A. S.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 10693.

(2) (a) Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Tsodikova, S. G.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3364. (b) Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141.

(3) (a) Johnson, R. G.; Ingham, R. K. *Chem. Rev.* **1956**, *56*, 219. (b) Kochi, J. K. *J. Am. Chem. Soc.* **1965**, *87*, 2500. (c) Roberts, I.; Kimball, G. E. *J. Am. Chem. Soc.* **1937**, *59*, 947. (d) Li, Z.; Crosignani, S.; Linclau, B. *Tetrahedron Lett.* **2003**, *44*, 8143.

(4) Skell, P. S.; Traynham, J. G. *Acc. Chem. Res.* **1984**, *17*, 160.

(5) For reviews on sp^3 C−H functionalization, see: (a) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (b) Li, H.; Lia, B. J.; Shi, Z. *J. Catal. Sci. Technol.* **2011**, *1*, 191. (c) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (f) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439.

(6) (a) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (b) Giri, R.; Chen, X.; Hao, X.-S.; Li, J.-J.; Liang, J.; Fan, Z.-P.; Yu, J.-Q. *Tetrahedron: Asymmetry* **2005**, *16*, 3502. (c) Giri, R.; Wasa, M.; Brazzano, S. P.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 5685. (d) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (e) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483. (f) Stowers, K. J.; Kubota, A.; Sanford, M. S. *Chem. Sci.* **2012**, *3*, 3192.

(7) For selected examples of sp^2 C−H halogenation, see: (a) Sun, X.; Shan, G.; Sun, Y.; Rao, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4440. (b) Schröder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 8298. (c) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 5524. (d) Kakiuchi, F.; Kochi, T.; Mutsutani, H.; Kobayashi, N.; Urano, S.; Sato, M.; Nishiyama, S.; Tanabe, T. *J. Am. Chem. Soc.* **2009**, *131*, 11310. (e) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 5215. (f) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523. (g) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416.

(8) For sp^3 C−H functionalization in organic synthesis, see: (a) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (b) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976 and references cited therein.

(9) (a) Wheelaghan, O. R.; Ortuño, M. A.; Díez, J.; Garrido, S. E. G.; Maya, C.; Lledós, A.; Conejero, S. *J. Am. Chem. Soc.* **2012**, *134*, 15261. (b) Crosby, S. H.; Thomas, H. R.; Clarkson, G. J.; Rourke, J. P. *Chem. Commun.* **2012**, *48*, 5775. (c) Kaspi, A. W.; Goldberg, I.; Vigalok, A. *J. Am. Chem. Soc.* **2010**, *132*, 10626. (d) Oloo, W.; Zavalij, P. Y.; Zhang, J.; Khaskin, E.; Vedernikov, A. N. *J. Am. Chem. Soc.* **2010**, *132*, 14400. (e) Frech, C. M.; Milstein, D. *J. Am. Chem. Soc.* **2006**, *128*, 12434. (f) Goldberg, K. I.; Yan, J. Y.; Winter, E. L. *J. Am. Chem. Soc.* **1994**, *116*, 1573.

(10) (a) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 1533. (b) Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83.

(11) (a) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2012**, *14*, 3724. (b) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2014**, *16*, 968.

(12) For more details, see the Supporting Information.

(13) The exact role of bidentate MPyS-DG for the C(sp^3)−H halogenation is not known. Both the N-atoms in MPyS-DG are sp^2-hybridized, while other bidentate DGs in **5d−g** possess one sp^2-N-atom. Although the strong binding affinity of N-atoms in **5d−g** successfully activates the C(sp^3)−H bond, it presumably hampers the ready reductive elimination under the optimized conditions. Whereas the weak coordination of the sulfoximine N(sp^2)-atom to metal facilitates reductive elimination.

(14) Djerassi, C. *Chem. Rev.* **1948**, *43*, 271.

(15) (a) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2014**, *136*, 1789. (b) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898. (c) Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030.

(16) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142.

(17) (a) Li, S.; Chen, G.; Feng, C.-G.; Gong, W.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 5267. (b) Sarkar, D.; Melkonyan, F. S.; Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 10800.

(18) The acetoxylation of **3a** under Yu's conditions [$Pd(OAc)_2$ (5 mol %), MeCOOOtBu (2.0 equiv), Ac_2O at 65 °C for 24 h] produces **8a** in 40% yield; see: 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.

(19) (a) Ihara, H.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 7502. (b) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. (c) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518.

(20) Kappe, C. O.; Eycken, E. V. *Chem. Soc. Rev.* **2010**, *39*, 1280.