# Silver-Catalyzed C(sp³)−H Chlorination

Jun Ozawa[†] and Motomu Kanai*[,†,‡]

[†]Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
[‡]JST, ERATO, Kanai Life Science Catalysis Project, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

S *Supporting Information*

ABSTRACT: A silver-catalyzed chlorination of benzylic, tertiary, and secondary C(sp³)−H bonds was developed. The reaction proceeded with as low as 0.2 mol % catalyst loading at room temperature under air atmosphere with synthetically useful functional group compatibility. The regioselectivity and reactivity tendencies suggest that the chlorination proceeded through a radical pathway, but an intermediate alkylsilver species cannot be ruled out.
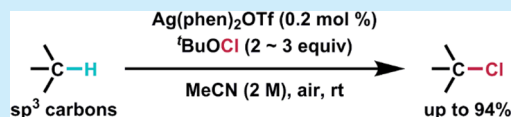
Organic halides are synthetically versatile and frequently used in a variety of functional group transformations and C−C bond formations. Direct C−H halogenation is an efficient and straightforward route to organic halides; nevertheless, C−H halogenation methods widely applicable to the synthesis of complex molecules are limited.[1] Direct halogenation of unactivated C(sp³)−H bonds is especially difficult. Electrophilic and radical C(sp³)−H halogenations using *N*-halosuccinimide without the use of any catalysts are common for benzylic, allylic, and activated C(sp³)−H bonds but generally require relatively harsh reaction conditions (high temperature, acidic/basic, or UV irradiation).[2] Despite the potential difficulties controlling the site-selectivity for radical halogenation of aliphatic substrates, Alexanian recently reported unique halogenation reagents that achieve site-selective C(sp³)−H halogenation under mild, visible light-irradiation conditions.[3]

Transition metal-catalyzed C(sp³)−H halogenation could overcome the potential drawbacks of conventional halogenation reactions. Shilov originally reported Pt-catalyzed, methyl group-selective C(sp³)−H chlorination of simple alkanes,[4] and Sanford recently extended the substrate scope to aliphatic amines.[5] Those reactions proceeded at high temperature (>100 °C) and were not applicable to starting materials containing C(sp²)−H bonds.[6] Directing group-assisted C(sp³)−H halogenations were reported by Yu (iodination),[7] Sanford (chlorination),[8] Sahoo (chlorination and bromination),[9] and Rao (chlorination, bromination, and iodination),[10] where the β-position of the oxazolines or amides was selectively activated by Cu or Pd catalysts. Hill[11] and Groves[12] reported Mn porphyrin-catalyzed C(sp³)−H chlorination and bromination, but the yields were generally not high. Therefore, there remains room to develop a synthetically useful catalytic C(sp³)−H halogenation. Here, we report a Ag-catalyzed C(sp³)−H chlorination at benzylic, tertiary, and secondary positions. The reaction was operationally simple and promoted by a small amount of the catalyst with high functional group compatibility at room temperature under air.

Our preliminary investigation of metal-catalyzed C(sp³)−H halogenation revealed that C(sp³)−H chlorination of isoamyl benzoate (**1a**) was catalyzed by Ag(phen)₂OTf at room
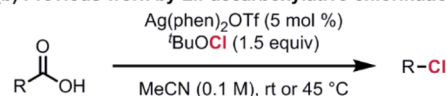
temperature using *tert*-butyl hypochlorite (*ᵗ*BuOCl) as an oxidant to give **2a** in moderate yield (Scheme 1a). No *tert*-

Scheme 1. Initial Results
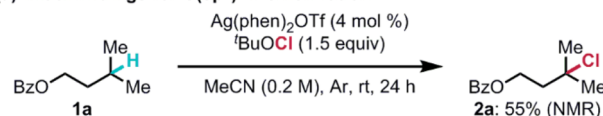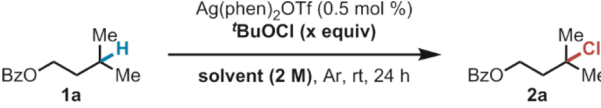
butoxylation was observed in ¹H NMR and MS analysis of the crude mixture. To our surprise, the reaction conditions were almost identical to those for decarboxylative chlorination reported by Li (Scheme 1b).[13] That report, however, did not describe C(sp³)−H chlorination. Considering the broader applicability of C−H activation reactions compared with decarboxylative reactions, as well as the synthetic utilities of the product alkyl chlorides,[14] we began intensive optimization studies of the reaction conditions for this novel activation mode.

The optimization results are summarized in Table 1 (see Supporting Information (SI) for details). Catalyst screening revealed that Ag salts bearing bipyridine-type ligands had acceptable reactivity, yielding up to 78% of **2a** when using 0.5 mol % AgOTf phenanthroline catalyst (Table 1, entry 1). Ligands were essential for high product yield (entries 2 vs 1, 3, and 4). MeCN was the best solvent (entries 1 and 5−9) probably because Ag(phen)₂OTf did not dissolve well in the other solvents. Water did not interfere with the chlorination process (entries 1 vs 8 and 9). Oxidants other than *ᵗ*BuOCl were not efficient (entries 10 and 11). An increased amount of

## Table 1. Screening of the Reaction Conditions[a]

entry	[t]BuOCl (equiv)	solvent	yield (%)[b]	rsm (%)[b]
1	2	dist. MeCN	78	21
2[c]	2	dist. MeCN	12	87
3[d]	2	dist. MeCN	60	39
4[e]	2	dist. MeCN	69	30
5	2	dry EtOAc	50	44
6	2	dry CH₂Cl₂	37	43
7	2	dry CHCl₃	27	58
8	2	MeCN/water (1:1)	79	12
9	2	MeCN[f]	76	23
10	2 equiv NCS	MeCN[f]	0	
11	2 equiv NaOCl	MeCN[f]	3	96
12	3	MeCN[f]	84	11
13	4	MeCN[f]	87	11
14[g]	2	MeCN[f]	64	35
15[h]	2	MeCN[f]	76	23
16[i]	2	MeCN[f]	80	19
17[i]	3	MeCN[f]	92	7

[a]The reactions were performed using 0.2 mmol **1a**. [b]NMR yield of **2a** and recovered starting material (rsm) using 1,1,2,2-tetrachloroethane as an internal standard. [c]AgOTf (1 mol %) was used as catalyst. [d]Ag(bpy)OTf (1 mol %) was used as catalyst. [e]Ag(bpy)₂OTf (1 mol %) was used as catalyst. [f]Neither distilled nor anhydrous. [g]Under an oxygen atmosphere (1 atm). [h]Under air (1 atm). [i]Forty-eight hour reaction. phen: 1,10-phenanthroline; bpy: 2,2′-bipyridyl; NCS: N-chlorosuccinimide.

[t]BuOCl (entries 9 vs 12 and 13) and a prolonged reaction time (entries 9 vs 16; 12 vs 17) improved the yield. Finally, we performed the reaction under O₂ atmosphere or air (entries 9 vs 14 and 15). No C(sp³)−O bond formation was observed in any of the three entries, however, and the yields did not differ significantly between the reactions under Ar and air. Thus, special care to prevent air and water contamination is not necessary for this C(sp³)−H chlorination reaction. Overall, the conditions in entry 17 were found to be the best.

Under the optimized conditions using 0.2 mol % catalyst, we investigated the substrate scope (Scheme 2). Benzylic, tertiary, and secondary C(sp³)−H bonds were chlorinated in moderate to high yield. Slight modifications of the reaction conditions were necessary for benzylic chlorination: use of anhydrous MeCN and 2 equiv [t]BuOCl minimized undesired hydrolysis of the product and the dichlorination byproduct, respectively (see SI for details). Various esters (**2a−2d**, **2g**, **2n**, **2p**, **2s−2u**), a bromo functionality (**2e**, **2j**), nitriles (**2f**, **2i**, **2q**), a nitro group (**2h**), a carboxylic acid (**2l**), a phthalimide (**2m**, **2p**), a ketone (**2k**, **2o**, **2v**), and a mesyl group (**2r**) were tolerated under the chlorination conditions. Regioisomers were generated when there were two or more C(sp³)−H bonds sufficiently reactive to give C(sp³)−Cl bonds (**2c**, **2c′**). δ-Chlorination was slightly favored over γ-chlorination (γ/δ = 1:1.7), suggesting that the relative reactivity of C(sp³)−H bonds is influenced by the electronic characteristics. This tendency was also evident in the reactions of **1b** and **1m**. According to Li et al.,[13] decarboxylative chlorination scarcely occurred from primary carboxylic acids at room temperature. This is consistent with the result of **2l**, where tertiary C−H chlorination proceeded in high yield from nonprotected carboxylic acid **1l**. Because of the mild reaction

Scheme 2. Substrate Scope[a]
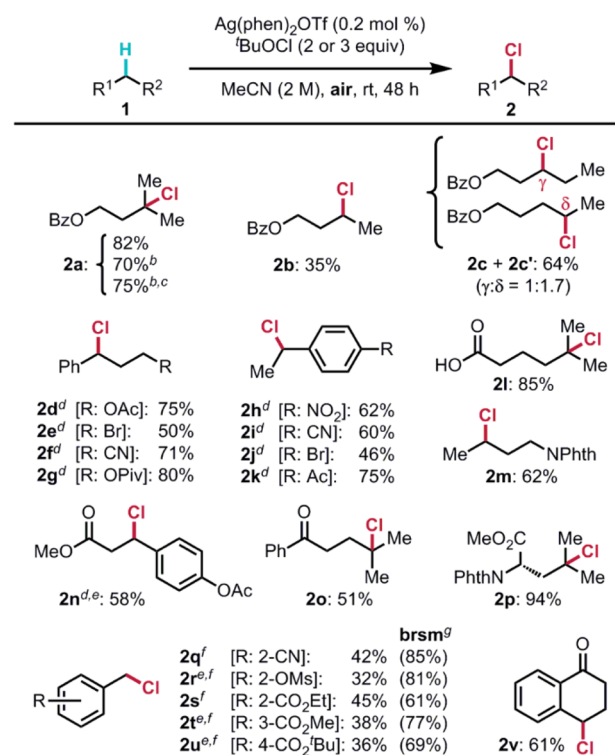
[a]General reaction conditions: **1** (2 mmol, 1 equiv), Ag(phen)₂OTf (0.004 mmol), and [t]BuOCl (6 mmol) in MeCN (1 mL) at room temperature. Product **2** was isolated by silica gel column chromatography. [b]Five millimolar (1 g) of **1a** was used. [c]Catalyst was prepared by mixing AgOTf (0.01 mmol) and 1,10-phenanthroline (0.02 mmol) in situ. [d]Anhydrous MeCN and 2 equiv of [t]BuOCl were used under Ar. [e]Scale of 0.2 mmol. [f]Anhydrous MeCN was used under Ar. [g]Yield based on recovered starting material (brsm) in parentheses, calculated from NMR of the crude mixture. Phth: phthaloyl; brsm: based on recovered starting material.
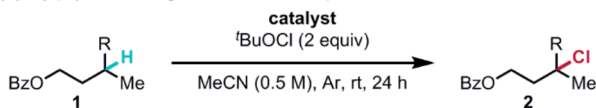
conditions, β-halo carbonyl compound **2n** was obtained in synthetically useful yield despite the easy decomposition of **2n** into the corresponding α,β-unsaturated carbonyl compound via an E1cB mechanism. Product **2v** could tautomerize to 1-naphthol after eliminating HCl, but such undesirable decomposition was not detected. Benzylic C(sp³)−H chlorination of toluene derivatives also proceeded (**2q−2u**), although in only moderate yield. C(sp³)−H chlorination of allylic/propargylic compounds and ethers was not successful under those conditions, giving complicated mixtures of products.[15] Additionally, substrates containing nucleophilic aromatic rings, such as anisole derivatives, furnished electrophilic aromatic substitution to give aryl chlorides.[16]

Gram-scale C(sp³)−H chlorination proceeded with a yield similar to that of a smaller-scale reaction (Scheme 2, **2a**, second row), indicating that the reaction was scalable. Additionally, a comparable yield was obtained when the catalyst was prepared by mixing AgOTf and 1,10-phenanthroline in the reaction mixture instead of preparing Ag(phen)₂OTf in advance (Scheme 2, **2a**, third row).

For insight to be gained into the reaction mechanism, the following experiments were conducted. First, the reaction was applied to enantiomerically pure **1w** containing a chiral tertiary stereogenic center (Scheme 3a). The corresponding chlorination product **2w** was obtained as a racemic form, suggesting

B

Scheme 3. Mechanistic Insight into C(sp³)–H Chlorination[a]

(a) Application to optically active substrate

1w
(Ar = p-NO₂-C₆H₄)

2w, *racemic*
27% (2 steps
after Me esterification)
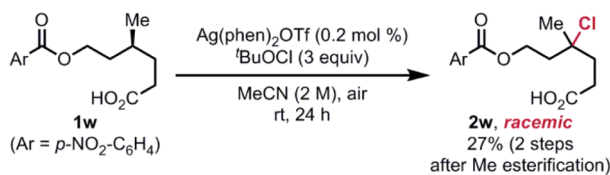
(b) C(sp³)–H cleavage via free radical process

catalyst
^{t}BuOCl (2 equiv)

MeCN (0.5 M), Ar, rt, 24 h

entry	catalyst (mol %)	yield (%)[a]	rsm (%)[a]	
1	Ag(phen)₂OTf (0.5)	78	21	
2	NHPI (25)	30	69	R = Me (1a)
3	white LED	34	57	
4	Ag(phen)₂OTf (0.5)	41	45	
5	NHPI (25)	4	96	R = H (1b)
6	white LED	21	75	

[a]NMR yield and rsm using 1,1,2,2-tetrachloroethane as an internal standard. NHPI: N-hydroxyphthalimide

that the reaction could proceed through a tertiary carbon radical intermediate. Next, we examined whether a free *tert*-butoxy radical was an active species for the C(sp³)–H cleavage step (Scheme 3b). We tried a combination of ^{t}BuOCl and N-hydroxyphthalimide (NHPI)[2c] or photoirradiation in the presence of ^{t}BuOCl,[17] conditions known to generate the *tert*-butoxy radical. The yields of 2a or 2b were much lower than those under standard reaction conditions (Scheme 3b, entries 1 vs 2 and 3; 4 vs 5 and 6). These results imply that the free *tert*-butoxy radical is not involved in this C(sp³)–H chlorination process. Radical clock experiments resulted in a complicated reaction mixture, providing no meaningful conclusion.

On the basis of the experimental results described above and the proposed mechanism for decarboxylative chlorination by Li,[13] a plausible catalytic cycle is depicted in Figure 1. First, Ag(phen)₂OTf and ^{t}BuOCl (2:1) react to form dinuclear
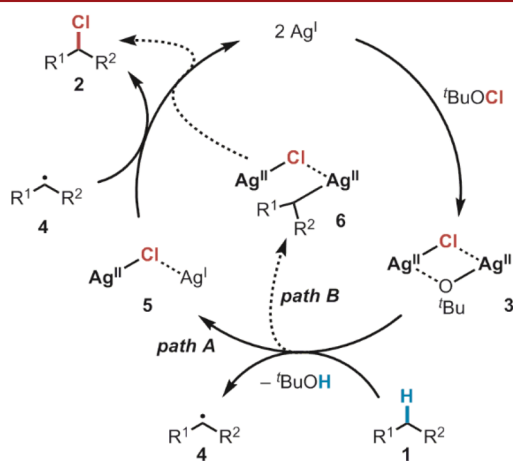

Figure 1. Proposed reaction mechanism.

Ag(II) complex 3. The color of the reaction mixture turned brown by the addition of ^{t}BuOCl to a solution containing Ag(phen)₂OTf, which is the same color reported for Ag(II) dinuclear complexes.[13,18,19] After homolytic cleavage of the Ag–O^{t}Bu bond, the *tert*-butoxy radical abstracts a H atom from a C(sp³)–H bond of substrate 1 to produce carbon radical 4. Finally, 4 traps a Cl atom from complex 5 to give chlorinated product 2, and Ag(I) is regenerated to close the catalytic cycle (path A). The Cl-transfer process from 5 to carbon radical 4 should be very fast because the O₂ trap of the carbon radical was not observed even in an oxygen atmosphere.[20] As an alternative pathway, alkylsilver 6 is generated after C(sp³)–H cleavage in 1 by 3, from which alkyl chloride product 2 is eliminated and Ag(I) regenerates (path B). Alkylsilver compounds are generally highly unstable but could be stable at room temperature with the help of ligands.[21] Additionally, alkylsilver compounds exhibited similar characteristics to alkyl radicals: they decomposed in the presence of radical scavengers such as O₂, I₂, and thiols,[22] and readily epimerized at room temperature.[22] Therefore, generation of alkylsilver intermediate 6 cannot be excluded by the experimental results shown in Scheme 3. The use of ligands such as 1,10-phenanthroline and 2,2′-bipyridyl will likely facilitate the formation of reactive dinuclear complex 3 and 5 or 6, leading to successful C(sp³)–H chlorination.

In conclusion, a Ag(phen)₂OTf-catalyzed C(sp³)–H chlorination reaction was developed. Benzylic, tertiary, and secondary C(sp³)–H bonds were chlorinated under mild conditions and with synthetically useful functional group tolerance using as low as 0.2 mol % catalyst. The features of the reaction enable simple and easy operation on both the small and large scale. On the basis of this method, we are currently studying a catalyst-controlled site-selective C(sp³)–H chlorination.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00367.

> General experimental procedure, optimization of the reaction conditions, and characterization of the products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kanai@mol.f.u-tokyo.ac.jp.

ORCID ⓘ

Motomu Kanai: 0000-0003-1977-7648

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) For selected examples of C–H halogenation in total synthesis, see: (a) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824–828. (b) Iwasa, E.; Hamashima, Y.; Fujishiro, S.; Higuchi, E.; Ito, A.; Yoshida, M.; Sodeoka, M. *J. Am. Chem. Soc.* **2010**, *132*, 4078–4079. (c) Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2014**, *136*, 17750–17756. (d) Hong, B.; Li, C.; Wang, Z.; Chen, J.; Li, H.;

Lei, X. *J. Am. Chem. Soc.* **2015**, *137*, 11946−11949. (e) Fox, J. C.; Gilligan, R. E.; Pitts, A. K.; Bennett, H. R.; Gaunt, M. J. *Chem. Sci.* **2016**, *7*, 2706−2710.

(2) For selected examples, see: (a) Fokin, A. A.; Lauenstein, O.; Gunchenko, P. A.; Schreiner, P. R. *J. Am. Chem. Soc.* **2001**, *123*, 1842−1847. (b) Jiang, X.; Shen, M.; Tang, Y.; Li, C. *Tetrahedron Lett.* **2005**, *46*, 487−489. (c) Zhuk, T. S.; Gunchenko, P. A.; Korovai, Ya.; Yu; Schreiner, P. R.; Fokin, A. A. *Theor. Exp. Chem.* **2008**, *44*, 48−53. (d) Kundu, R.; Ball, Z. T. *Org. Lett.* **2010**, *12*, 2460−2463. (e) Kee, C. W.; Chan, K. M.; Wong, M. W.; Tan, C.-H. *Asian J. Org. Chem.* **2014**, *3*, 536−544.

(3) (a) Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. *J. Am. Chem. Soc.* **2014**, *136*, 14389−14392. (b) Quinn, R. K.; Könst, Z. A.; Michalak, S. E.; Schmidt, Y.; Szklarski, A. R.; Flores, A. R.; Nam, S.; Horne, D. A.; Vanderwal, C. D.; Alexanian, E. J. *J. Am. Chem. Soc.* **2016**, *138*, 696−702.

(4) (a) Gol'dshlger, N. F.; Tyabin, M. B.; Shilov, A. E.; Shteinman, A. A. *Zh. Fiz. Khim.* **1969**, *43*, 2174. (b) Shilov, A. E.; Shteinman, A. A. *Coord. Chem. Rev.* **1977**, *24*, 97−143. (c) Kao, L.-C.; Sen, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1242−1243. (d) Fekl, U.; Goldberg, K. I. *Adv. Inorg. Chem.* **2003**, *54*, 259−320. (e) Lersch, M.; Tilset, M. *Chem. Rev.* **2005**, *105*, 2471−2526.

(5) Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 12796−12799.

(6) (a) Jones, W. D.; Feher, F. J. *J. Am. Chem. Soc.* **1984**, *106*, 1650−1663. (b) Buchanan, J. M.; Stryker, J. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 1537−1550. (c) Nolan, S. P.; Hoff, C. D.; Stoutland, P. O.; Newman, L. J.; Buchanan, J. M.; Bergman, R. G.; Yang, G. K.; Peters, K. S. *J. Am. Chem. Soc.* **1987**, *109*, 3143−3145. (d) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879−2932. (e) Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2009.

(7) (a) Giri, R.; Chen, X.; Hao, X.-S.; Li, J.-J.; Liang, J.; Fan, Z.-P.; Yu, J.-Q. *Tetrahedron: Asymmetry* **2005**, *16*, 3502−3505. (b) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112−2115. (c) Giri, R.; Wasa, M.; Breazzano, S. P.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 5685−5688.

(8) (a) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483−11498. (b) Stowers, K. J.; Kubota, A.; Sanford, M. S. *Chem. Sci.* **2012**, *3*, 3192−3195.

(9) Rit, R. K.; Yadav, M. R.; Ghosh, K.; Shankar, M.; Sahoo, A. K. *Org. Lett.* **2014**, *16*, 5258−5261.

(10) Yang, X.; Sun, Y.; Sun, T.-y.; Rao, Y. *Chem. Commun.* **2016**, *52*, 6423−6426.

(11) Hill, C. L.; Smegal, J. A.; Henly, T. J. *J. Org. Chem.* **1983**, *48*, 3277−3281.

(12) (a) Liu, W.; Groves, J. T. *J. Am. Chem. Soc.* **2010**, *132*, 12847−12849. (b) Liu, W.; Groves, J. T. *Acc. Chem. Res.* **2015**, *48*, 1727−1735.

(13) Wang, Z.; Zhu, L.; Yin, F.; Su, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 4258−4263.

(14) (a) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945−1947. (b) Nishimoto, Y.; Saito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2009**, *65*, 5462−5471. (c) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428−429. (d) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7442−7445. (e) Gong, T.-J.; Jiang, Y.-Y.; Fu, Y. *Chin. Chem. Lett.* **2014**, *25*, 397−400. (f) Li, Z.; Sun, H.-M.; Shen, Q. *Org. Biomol. Chem.* **2016**, *14*, 3314−3321. (g) Atack, T. C.; Cook, S. P. *J. Am. Chem. Soc.* **2016**, *138*, 6139−6142. (h) Börjesson, M.; Moragas, T.; Martin, R. *J. Am. Chem. Soc.* **2016**, *138*, 7504−7507.

(15) Unsuitable substrates are summarized in the SI.

(16) Electrophilic aromatic substitution proceeded, along with the C(sp³)−H chlorination, in the case of substrates containing electron-rich aromatic groups (see the below scheme). This aromatic substitution proceeded in the absence of the Ag catalyst.
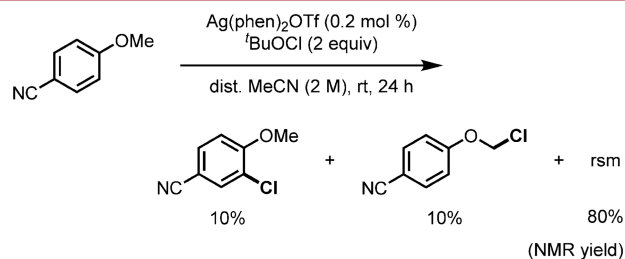
(17) Walling, C.; Jacknow, B. B. *J. Am. Chem. Soc.* **1960**, *82*, 6108−6112.

(18) Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202−16203.

(19) The reaction color did not change under ligandless conditions, where the product yield was low (Table 1, entry 2).

(20) Both chloride radical ($CuCl_2$) and O_2 are reported to react very rapidly with carbon radicals ($k \approx 10^9$). See (a) $CuCl_2$: Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 856−865. (b) O_2: Marchaj, A.; Kelley, D. G.; Bakac, A.; Espenson, J. H. *J. Phys. Chem.* **1991**, *95*, 4440−4441.

(21) Butylsilver is reported to decompose at −60 °C, but 3-(dimethylamino)propylsilver is stable up to 15 °C. See Westmijze, H.; Kleijn, H.; Vermeer, P. *J. Organomet. Chem.* **1979**, *172*, 377−383.

(22) Whitesides, G. M.; Bergbreiter, D. E.; Kendall, P. E. *J. Am. Chem. Soc.* **1974**, *96*, 2806−2813.