

Cite this: *Chem. Sci.*, 2018, 9, 100Received 25th October 2017
Accepted 18th November 2017

DOI: 10.1039/c7sc04611a

rsc.li/chemical-science

Site-selective bromination of sp^3 C–H bonds†Shyam Sathyamoorthi,^a Shibdas Banerjee,^b J. Du Bois,^{*a} Noah Z. Burns^{*a} and Richard N. Zare^{*a}

A method for converting sp^3 C–H to C–Br bonds using an *N*-methyl sulfamate directing group is described. The reaction employs $Rh_2(oct)_4$ and a mixture of NaBr and NaOCl and is performed in aqueous solution open to air. For all sulfamates examined, oxidation occurs with high selectivity at the γ -carbon, affording a uniquely predictable method for C–H bond halogenation. Results from a series of mechanistic experiments suggest that substrate oxidation likely proceeds by a radical chain process. Initial formation of an *N*-halogenated sulfamate followed by Rh-mediated homolysis generates an N-centered radical, which serves as the active oxidant.

Introduction

Oxidation of a specific sp^3 C–H bond in a complex molecule remains an outstanding challenge in reaction methods development.^{1–3} While several protocols for the selective conversion of sp^3 C–H centers to C–N and C–O bonds are now available,^{4–16} fewer methods for the synthesis of C–halogen bonds^{17–36} have been described despite the fact that molecules bearing halogen functional groups are prevalent in nature. In addition, as alkyl halides are versatile precursors for a variety of synthetic transformations, including cross-coupling, substitution, elimination, and the installation of boron-, silicon-, nitrogen-, and oxygen-based groups, methods for accessing these types of materials have value in synthesis.^{37–41} Here, we describe a reaction protocol for the site-selective bromination of sp^3 C–H bonds using an *N*-methyl sulfamate directing group. This auxiliary is facile to install on 1° and 2° alcohol derivatives and can be removed through nucleophilic displacement. Mechanistic studies suggest that the reaction proceeds through an N-centered radical, reminiscent of the Hoffman–Löffler–Freitag amine synthesis.^{42–55} With all sulfamates tested, oxidation occurs preferentially at the γ -carbon, offering a predictable and precise method for oxidative C–H bond halogenation under mild reaction conditions.

Results and discussion

Initial optimization of conditions for alkylbromide formation was performed with isopentyl methylsulfamate **1**, a simple,

unfunctionalized substrate with a single tertiary C–H bond. A variety of transition metal salts were tested in conjunction with 3 equivalents each of NaBr and NaOCl, a reagent combination known to generate hypobromite *in situ* and used previously for the oxidative cyclization of sulfamate esters.⁵⁶ While little to no reaction ensued in the presence of catalytic Mn^{3+} , Co^{2+} , Cu^{2+} ,

Table 1 Evaluating reaction conditions for directed C–H bromination

Entry	Catalyst	Solvent ^a	[2]/[1] ^b
1	(<i>R,R</i>)-Mn-Jacobsen (5%)	CH ₂ Cl ₂	RSM
2	Co(OAc) ₂ ·4H ₂ O (5%)	CH ₂ Cl ₂	1/8
3	CuBr ₂ (5%)	CH ₂ Cl ₂	1/8
4	Ni(OAc) ₂ ·4H ₂ O (5%)	CH ₂ Cl ₂	RSM
5	Rh₂(oct)₄ (5%)	CH₂Cl₂	4/1
6	Rh ₂ (O ₂ C ^t Bu) ₄ (5%)	CH ₂ Cl ₂	2/1
7	Rh₂(O₂CCPh₃)₄ (5%)	CH₂Cl₂	4/1
8	Rh ₂ (OAc) ₄ (5%)	CH ₂ Cl ₂	1/5
9	Na ₄ Rh ₂ (CO ₃) ₄ (5%)	CH ₂ Cl ₂	1/7
10	None	CH ₂ Cl ₂	1/4
11	None ^c	CH ₂ Cl ₂	RSM
12	Rh ₂ (oct) ₄ (5%)	CH ₂ Cl ₂ ^d	1/3
13	Rh ₂ (oct) ₄ (5%)	CH ₂ Cl ₂ ^e	1/2 ^f
14	Rh ₂ (oct) ₄ (5%)	iPrOAc	1/2
15	Rh ₂ (oct) ₄ (5%)	Benzene	1/2

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7sc04611a

^a All reactions were performed in a biphasic solvent mixture with the indicated solvent and an equivalent volume of saturated aqueous Na₂HPO₄ unless otherwise noted. ^b Product ratio determined by ¹H NMR integration, see ESI for details. ^c Reaction flask wrapped in foil. ^d Reaction performed with no added co-solvent. ^e Reaction conducted with an equivalent volume of deionized H₂O. ^f A small amount of the corresponding chloride product is also formed. RSM = recovered starting material.



Table 2 Oxidative halogenation of *N*-methyl sulfamate derivatives

$ \begin{array}{c} \text{R}_1 \text{---} \text{CH}_2 \text{---} \text{CH}(\text{R}_2) \text{---} \text{OSO}_2\text{NHMe} \\ \xrightarrow[\text{aq Na}_2\text{HPO}_4/\text{CH}_2\text{Cl}_2]{\text{Rh}_2(\text{oct})_4 (5 \text{ mol } \%), \text{NaOCl} (3 \text{ equiv}), \text{NaBr} (3 \text{ equiv})} \\ \text{R}_1 \text{---} \text{CH}_2 \text{---} \text{C}(\text{Br})(\text{R}_2) \text{---} \text{OSO}_2\text{NHMe} \end{array} $			
entry	substrate	product	yield (%) ^a
1			R = Me 61 = Et 75 (45) ^b
2			50 ^c
3			R = Et 70 = ^t Bu 76 = 4- ⁱ PrBn 64
4			71 ^d
5			75 ^e
6			61
7			52 ^f
8			65
9			60 Ar = <i>p</i> -BrC ₆ H ₄
10			27
11			80 ^e
12			72 ^g (40) ^h racemic

^a Isolated product yield unless otherwise indicated. ^b Reaction performed with 0.1 mol% Rh₂(oct)₄. ^c Yield estimated by ¹H NMR integration using an internal standard. ^d Product isolated as a 1 : 1 mixture of diastereomers. ^e Product isolated as a mixture of diastereomers, ratio undetermined. ^f Product yield estimated by ¹H NMR integration using an internal standard. Chromatography on SiO₂ facilitates bromide elimination, see Fig. S1 for details. ^g Product isolated as a racemic mixture, see Fig. S2 for details. ^h Yield of corresponding chloride product obtained from a reaction performed without NaBr.

and Ni²⁺ (Table 1, entries 1–4), switching to Rh₂(oct)₄ (Table 1, entry 5) afforded a marked increase in conversion to brominated product **2**. The choice of dirhodium complex had a clear influence on reaction performance, as catalysts bearing hydrophobic ligands such as octanoate or triphenylacetate (Table 1, entries 5–7) out-performed others tested (Table 1, entries 8, 9), likely owing to the greater solubility of these complexes in dichloromethane. In the complete absence of transition metal, conversion to product still occurred (Table 1, entry 10) in a process that appears to be promoted by ambient light (Table 1, entry 11).

A 1 : 1 biphasic mixture of CH₂Cl₂/saturated aqueous Na₂HPO₄ was found to be the optimal solvent combination (Table 1, entry 5). In neat CH₂Cl₂, conversion to product was significantly reduced, and in unbuffered water with CH₂Cl₂ a mixture of both brominated and chlorinated products was obtained (Table 1, entries 12 and 13). Using organic co-solvents other than CH₂Cl₂ was similarly deleterious to reaction performance (Table 1, entries 14 and 15).

A range of structurally diverse *N*-methyl sulfamates has been prepared by condensation of the corresponding 1° and 2° alcohols with ClSO₂NHMe and subjected to the optimized halogenation protocol (Table 2). Oxidation of both tertiary and benzylic C–H bonds is possible in moderate to good yields, even with Rh₂(oct)₄ loadings as low as 0.1 mol% (entry 2). Different functional groups, including alkyl and benzyl esters, epoxides, trichloroethylsulfamate-protected aziridines, and silylated alcohols, are compatible with these conditions (Table 2, entries 3–6). For all substrates examined, C–H bond oxidation occurs nearly exclusively at the γ-carbon. This finding compares favorably with other directed C–H halogenation methods, which afford mixtures of constitutional isomers.^{15,20} The directed nature of this process is further highlighted in entries 8, 9, and 10. Each of these substrates furnishes the product of γ-C–H bond bromination despite possessing an activated benzylic C–H center. Positional selectivity is also noted in entries 11 and 12. Experiments with the latter substrate show that oxidation of an optically active 3° C–H bond gives racemic alkylbromide, a result consistent with the formation of a carbon-centered radical intermediate (*vide infra*). In addition, we have found that the absence of NaBr leads to generation of the corresponding chlorinated product (entry 12), albeit in reduced yield. All told, this new protocol offers an efficient, predictable, operationally simple method for C–H bond functionalization.

Displacement of the *N*-methyl alkoxy sulfonyl auxiliary can be achieved in a single-flask, two-step protocol that involves initial *N*-carbamoylation with Boc₂O followed by an S_N2 reaction (Scheme 1). The *N*-acylated sulfamate undergoes smooth reaction with nucleophiles such as N₃[−] and I[−] to give the corresponding alkylazide and alkyl iodide products, respectively. This method for excising the sulfamate directing group should add to the overall utility of the C–H halogenation process.

Previous work exploring the use of NaBr/NaOCl for the synthesis of [1,2,3]-oxathiazinane-2,2-dioxide heterocycles⁵⁶ suggested the formation of an *N*-halogenated species as a first step in the reaction pathway. In accord with this hypothesis, we



In a reaction mixture containing **5** and Rh₂(oct)₄, the red color ascribed to the mixed-valent dirhodium species persists

To test for a radical chain mechanism, a 1 : 1 mixture of brominated sulfamate **5** and chlorinated sulfamate **10** was stirred with catalytic Rh₂(oct)₄. ESI-MS analysis of the reaction mixture at 2 h revealed brominated products **2** and **6** and chlorinated products **11** and **12** (Fig. 2 and S5†). Such a product distribution lends strong support to our mechanistic scheme, as only an intermolecular collision between intermediates derived from **5** and **10** could lead to cross-halogenated products **2** and **12**.

As a final piece of mechanistic insight, a kinetic isotope effect (KIE) of $[P_H]/[P_D] = 3$ (Scheme 4 and Fig. S6†) has been measured in a competition experiment between protio- and

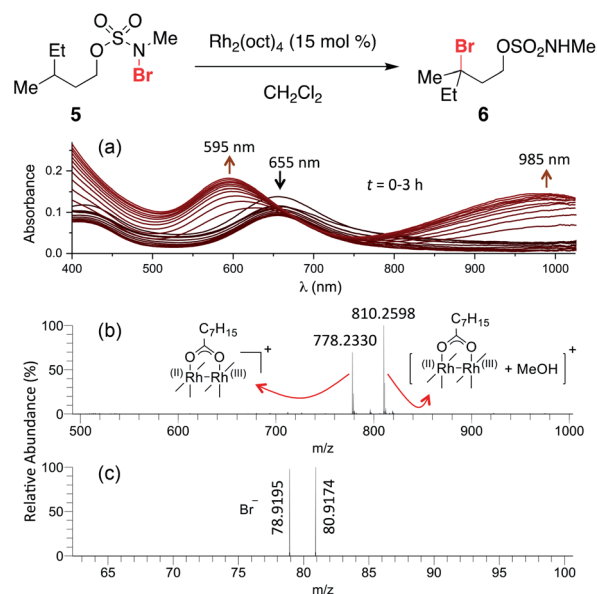
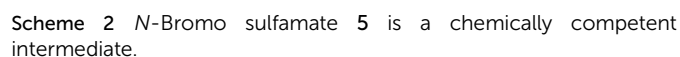
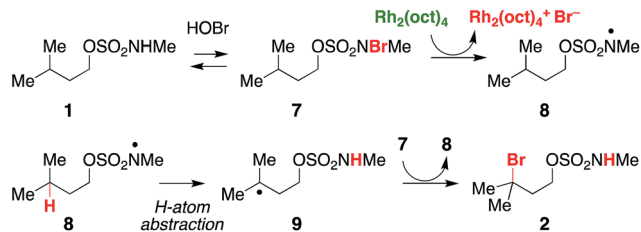


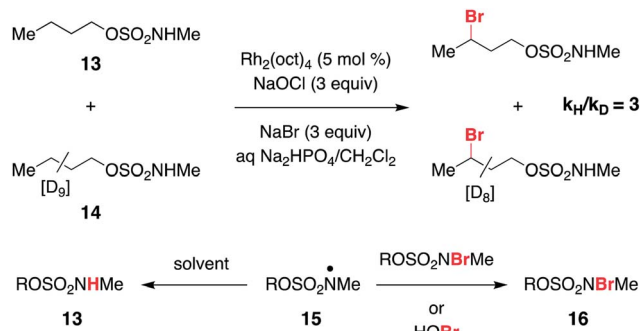
Fig. 1 (a) Continuous UV/vis spectrophotometric monitoring of the reaction of **5** shows an absorption spectrum characteristic of the conversion of a dinuclear $\text{Rh}^{2+}/\text{Rh}^{2+}$ complex ($\lambda_{\text{max}} = 418 \text{ nm}$ and 655 nm) to a $\text{Rh}^{2+}/\text{Rh}^{3+}$ complex ($\lambda_{\text{max}} = 595 \text{ nm}$ and 985 nm). High-resolution ESI-MS detected ion signals of (b) $\text{Rh}^{2+}/\text{Rh}^{3+}$ complex in positive ion mode, and (c) Br^- in negative ion mode; see ESI† for experimental details.



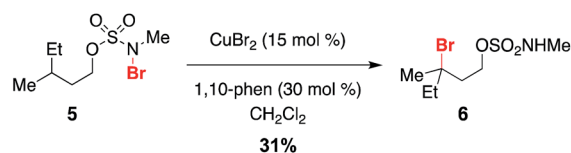
Scheme 3 A proposed radical-chain transfer process for C–H bromination.

deutero-sulfamate substrates, **13** and **14**. This result suggests that N-centered radical formation is not a committed, irreversible step. Reactions of **15** with a second N-halogenated sulfamate (or HOBr) to form **16** or with solvent to regenerate **13** are possible pathways that apparently compete with intramolecular γ -C–H abstraction, thus giving rise to a non-unitary KIE value in the competition experiment.⁵⁹

Given a radical chain mechanism for C–H halogenation, it is possible that metal complexes other than $\text{Rh}_2(\text{Oct})_4$ could serve as initiators. We have found that treatment of **5** with a combination of 15 mol% CuBr_2 and 1,10-phenanthroline forms the tertiary bromide product **6** in 31% yield (Scheme 5 and Fig. S7†).⁶⁰ While the efficiency of this reaction is lower than that with $\text{Rh}_2(\text{Oct})_4$ (Scheme 2), formation of **6** suggests that, at least in principle, new reaction manifolds utilizing first-row transition metals can be optimized for the oxidative halogenation of sp^3 C–H bonds.



Scheme 4 KIE study suggests reversibility of N-centered radical formation.



Scheme 5 CuBr_2 /phenanthroline as an alternate metal complex for reaction initiation.

Conclusions

A method for site-selective bromination of sp^3 C–H bonds using N-methyl sulfamate substrates is presented. Following halogenation, the sulfamate directing group can be displaced with nucleophiles to generate value-added alkylbromide products. The scope and predictability of this oxidation reaction distinguish these findings. UV/visible spectroscopy, ESI-MS analysis, and substrate probe experiments implicate a radical chain mechanism for C–H halogenation, initiated by $\text{Rh}_2(\text{Oct})_4$. Further exploration of sulfamate directing groups in C–H functionalization catalysis is warranted and should lead to high-precision methods for modifying sp^3 carbon centers.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Will Keown for assisting with UV/visible measurements. This work has been supported by the NSF under the CCI Center for Selective C–H Functionalization (CHE-1205646) and by the Air Force Office of Scientific Research through Basic Research Initiative grant (AFOSR FA9550-16-1-0113).

Notes and references

- 1 T. Newhouse and P. S. Baran, *Angew. Chem., Int. Ed.*, 2011, **50**, 3362–3374.
- 2 J. B. C. Mack, J. D. Gipson, J. Du Bois and M. S. Sigman, *J. Am. Chem. Soc.*, 2017, **139**, 9503–9506.

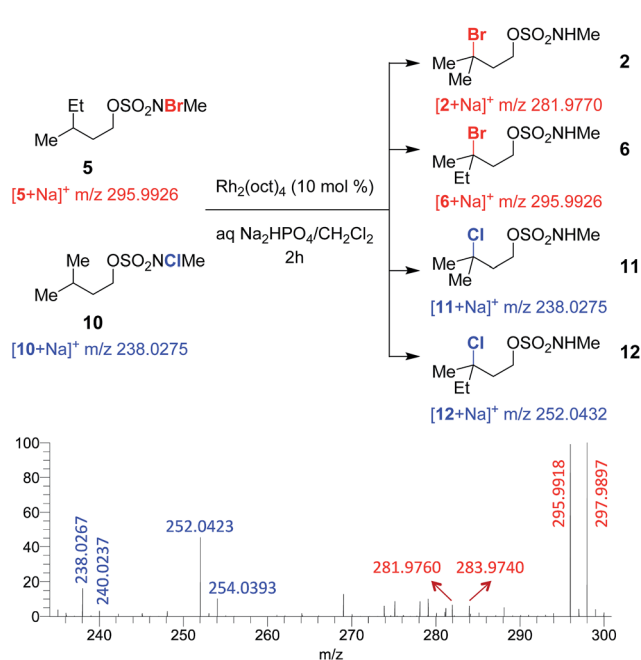


Fig. 2 High-resolution ESI-MS analysis shows that cross-halogenated products form in a competition experiment between bromosulfamate **5** and chlorosulfamate **10**. Experimental m/z values (in the spectrum) agree well with the theoretical m/z values (underneath the chemical structures).



- 3 M. C. White, *Science*, 2012, **335**, 807–809.
- 4 A. Company, J. Lloret, L. Gómez and M. Costas, in *Alkane C–H Activation by Single-Site Metal Catalysis*, ed. P. J. Pérez, Springer Netherlands, Dordrecht, 2012, pp. 143–228, DOI: 10.1007/978-90-481-3698-8_5.
- 5 J. L. Roizen, M. E. Harvey and J. Du Bois, *Acc. Chem. Res.*, 2012, **45**, 911–922.
- 6 S. Sathyamoorthi and J. Du Bois, *Org. Lett.*, 2016, **18**, 6308–6311.
- 7 S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936–946.
- 8 R. T. Gephart and T. H. Warren, *Organometallics*, 2012, **31**, 7728–7752.
- 9 E. A. Wappes, S. C. Fosu, T. C. Chopko and D. A. Nagib, *Angew. Chem., Int. Ed.*, 2016, **55**, 9974–9978.
- 10 E. A. Wappes, K. M. Nakafuku and D. A. Nagib, *J. Am. Chem. Soc.*, 2017, **139**, 10204–10207.
- 11 B. J. Stokes and T. G. Driver, *Eur. J. Org. Chem.*, 2011, 4071–4088.
- 12 G. Dequierez, V. Pons and P. Dauban, *Angew. Chem., Int. Ed.*, 2012, **51**, 7384–7395.
- 13 L. Gómez, I. Garcia-Bosch, A. Company, J. Benet-Buchholz, A. Polo, X. Sala, X. Ribas and M. Costas, *Angew. Chem., Int. Ed.*, 2009, **48**, 5720–5723.
- 14 C. Kim, K. Chen, J. Kim and L. Que, *J. Am. Chem. Soc.*, 1997, **119**, 5964–5965.
- 15 T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krska, *Chem. Soc. Rev.*, 2016, **45**, 546–576.
- 16 J. F. Hartwig, *J. Am. Chem. Soc.*, 2016, **138**, 2–24.
- 17 C. L. Hill, J. A. Smegal and T. J. Henly, *J. Org. Chem.*, 1983, **48**, 3277–3281.
- 18 X. Yang, Y. Sun, T. Sun and Y. Rao, *Chem. Commun.*, 2016, **52**, 6423–6426.
- 19 R. K. Rit, M. R. Yadav, K. Ghosh, M. Shankar and A. K. Sahoo, *Org. Lett.*, 2014, **16**, 5258–5261.
- 20 R.-Y. Zhu, T. G. Saint-Denis, Y. Shao, J. He, J. D. Sieber, C. H. Senanayake and J.-Q. Yu, *J. Am. Chem. Soc.*, 2017, **139**, 5724–5727.
- 21 A. E. Shilov and A. A. Shteinman, *Coord. Chem. Rev.*, 1977, **24**, 97–143.
- 22 R. K. Quinn, Z. A. Konst, S. E. Michalak, Y. Schmidt, A. R. Szklarski, A. R. Flores, S. Nam, D. A. Horne, C. D. Vanderwal and E. J. Alexanian, *J. Am. Chem. Soc.*, 2016, **138**, 696–702.
- 23 G. I. Nikishin, E. I. Troyansky and M. I. Lazareva, *Tetrahedron Lett.*, 1985, **26**, 3743–3744.
- 24 J. Ozawa and M. Kanai, *Org. Lett.*, 2017, **19**, 1430–1433.
- 25 W. Liu and J. T. Groves, *J. Am. Chem. Soc.*, 2010, **132**, 12847–12849.
- 26 R. Kundu and Z. T. Ball, *Org. Lett.*, 2010, **12**, 2460–2463.
- 27 K. Chen, J. M. Richter and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 7247–7249.
- 28 T. Liu, M. C. Myers and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2017, **56**, 306–309.
- 29 Q. Qin and S. Yu, *Org. Lett.*, 2015, **17**, 1894–1897.
- 30 L. R. Reddy, B. V. S. Reddy and E. J. Corey, *Org. Lett.*, 2006, **8**, 2819–2821.
- 31 (a) G. W. Gribble, in *Naturally Occurring Organohalogen Compounds – A Comprehensive Update*, ed. G. W. Gribble, Springer Vienna, Vienna, 2010, pp. 9–348; (b) B. Gál, C. Bucher and N. Z. Burns, *Mar. Drugs*, 2016, **14**, 206.
- 32 K. Chen and P. S. Baran, *Nature*, 2009, **459**, 824–828.
- 33 J. Richers, M. Heilmann, M. Drees and K. Tiefenbacher, *Org. Lett.*, 2016, **18**, 6472–6475.
- 34 L. Han, J.-B. Xia, L. You and C. Chen, *Tetrahedron*, 2017, **73**, 3696–3701.
- 35 H.-Y. Xiong, D. Cahard, X. Pannecoucke and T. Besset, *Eur. J. Org. Chem.*, 2016, 3625–3630.
- 36 D. Kalyani, A. R. Dick, W. Q. Anani and M. S. Sanford, *Tetrahedron*, 2006, **62**, 11483–11498.
- 37 A. S. Dudnik and G. C. Fu, *J. Am. Chem. Soc.*, 2012, **134**, 10693–10697.
- 38 S. L. Zultanski and G. C. Fu, *J. Am. Chem. Soc.*, 2013, **135**, 624–627.
- 39 X. Wang, S. Wang, W. Xue and H. Gong, *J. Am. Chem. Soc.*, 2015, **137**, 11562–11565.
- 40 C. K. Chu, Y. Liang and G. C. Fu, *J. Am. Chem. Soc.*, 2016, **138**, 6404–6407.
- 41 D. M. Peacock, C. B. Roos and J. F. Hartwig, *ACS Cent. Sci.*, 2016, **2**, 647–652.
- 42 M. E. Wolff, *Chem. Rev.*, 1963, **63**, 55–64.
- 43 C. Betancor, J. I. Concepcion, R. Hernandez, J. A. Salazar and E. Suarez, *J. Org. Chem.*, 1983, **48**, 4430–4432.
- 44 C. Q. O'Broin, P. Fernández, C. Martínez and K. Muñoz, *Org. Lett.*, 2016, **18**, 436–439.
- 45 J. C. K. Chu and T. Rovis, *Nature*, 2016, **539**, 272–275.
- 46 G. J. Choi, Q. Zhu, D. C. Miller, C. J. Gu and R. R. Knowles, *Nature*, 2016, **539**, 268–271.
- 47 D. H. R. Barton, A. L. J. Beckwith and A. Goosen, *J. Chem. Soc.*, 1965, 181–190.
- 48 A. W. Hofmann, *Ber. Dtsch. Chem. Ges.*, 1879, **12**, 984–990.
- 49 K. Löffler and C. Freytag, *Ber. Dtsch. Chem. Ges.*, 1909, **42**, 3427–3431.
- 50 G. Majetich and K. Wheless, *Tetrahedron*, 1995, **51**, 7095–7129.
- 51 C. Martínez and K. Muñoz, *Angew. Chem., Int. Ed.*, 2015, **54**, 8287–8291.
- 52 P. Becker, T. Duhamel, C. J. Stein, M. Reiher and K. Muñoz, *Angew. Chem., Int. Ed.*, 2017, **56**, 8004–8008.
- 53 R. Fan, D. Pu, F. Wen and J. Wu, *J. Org. Chem.*, 2007, **72**, 8994–8997.
- 54 D. Šakić and H. Zipse, *Adv. Synth. Catal.*, 2016, **358**, 3983–3991.
- 55 M. A. Short, J. M. Blackburn and J. L. Roizen, *Angew. Chem., Int. Ed.*, 2017, DOI: 10.1002/anie.201710322.
- 56 D. N. Zalatan and J. Du Bois, *Synlett*, 2009, 143–146.
- 57 C. R. Wilson and H. Taube, *Inorg. Chem.*, 1975, **14**, 2276–2279.
- 58 D. N. Zalatan and J. Du Bois, *J. Am. Chem. Soc.*, 2009, **131**, 7558–7559.
- 59 E. M. Simmons and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 3066–3072.
- 60 The combination of CuBr and 1,10-phenanthroline also promotes conversion of **5** to **6** (Fig. S8†).

