Communication

Radical Deuteration with D2O: Catalysis and Mechanistic Insights

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b12105 • Publication Date (Web): 14 Dec 2017

Radical Deuteration with D_2O: Catalysis and Mechanistic Insights

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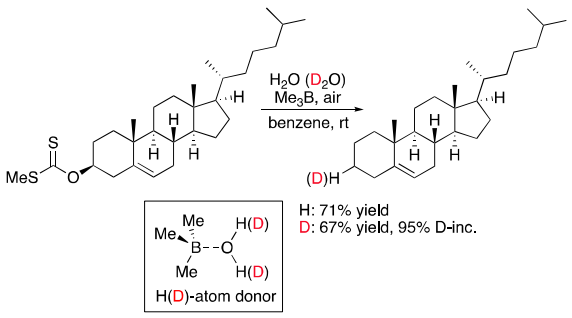
ABSTRACT: Selective incorporation of deuterium atoms into molecules is of high interest for labeling purposes and for optimizing properties of drug candidates. A mild and environmentally benign method for the deuteration of alkyl iodides via radical pathway using D_2O as source of deuterium has been developed. The reaction is initiated and mediated by triethylborane in the presence of dodecanethiol as a catalyst. This method is compatible with a wide range of functional groups and provides the monodeuterated products in good yields and high level of deuterium incorporation. It opens promising opportunities for the development of enantioselective radical reactions. Moreover, a revision of the mechanism of the deoxygenation reaction of xanthates using R_3B and water (Wood deoxygenation) is presented.

Over the last few years, the interest for the incorporation deuterium atoms in drug candidates to improve their metabolism and pharmacokinetic properties has exploded.[1-2] A significant number of deuterated drug candidates (heavy drugs) have been synthesized and submitted to clinical trials.[3-4] Deutetrabenazine (Austedo®) was the first deuterated drug to reach the market in 2017.[5-6] Preparation of organic compounds that are selectively labeled with a deuterium atom remains a challenging synthetic problem.[7] Alkyl halides are often used as starting material to introduce a deuterium atom via protonation of the corresponding organometallic derivative but this method suffers from a low functional group compatibility.[8-11] Alternatively, the radical deuteration using organotin deuterides has been developed.[12] Despite its efficiency and high functional group compatibility, this method relies on toxic[13] and expensive deuterating agents prepared from $LiAlD_4$ that contaminates the products even after careful purification.[13-14] Developing a radical procedure using D_2O as a source of deuterium atoms represents by far the most appealing procedure in term of mildness (functional group tolerance), sustainability and cost.[15] Wood and co-workers reported a very attractive method for Barton-McCombie deoxygenation of alcohols employing H_2O (and D_2O) as the hydrogen (deuterium) atom source (Scheme 1).[16] This method was extended to deiodination,[17] reductive addition[18] and radical cyclization[19] reactions. To explain this unexpected reactivity of water, the O–H bond is too strong to be involved in homolytic reactions, activation of the water molecule by complexation with trialkylborane was proposed.[18, 20-23] We report here, that this mechanism represents in the deuteration process only a minor pathway, and that an *in situ* generated thiol is acting as a highly active catalyst. Taking advantage of the thiol catalysis, we report also an efficient method for the conversion of alkyl iodides to the corresponding deuterated compounds with D_2O as a unique source of deuterium atoms.

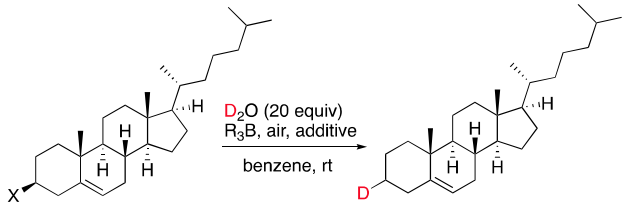


Scheme 1. Wood procedure for the deoxygenation of alcohols with D_2O.

Attempts to use the method of Wood (Et_3B, D_2O, air) for the preparation of deuterated deoxycholesterol **2** starting from the cholesteryl iodide **1a** gave deceiving results.[17] Only 7% of D-incorporation was obtained at best (table 1, entry 1). Running the reaction under the exact same conditions with the xanthate **1b** afforded product **2** with 85% D-incorporation (Table 1, entry 2), in good agreement with the report of Wood (95% and 88% D-incorporation with Me_3B and and Bu_3B, respectively) (Table 1, entries 3 and 4). This striking difference of D-incorporation between the xanthate and the iodide is not compatible with the reported mechanism. Moreover, based on kinetic and mechanistic investigations by Newcomb[24-25] and us,[22] it was anticipated that triethylborane would compete with the $R_3B{\cdot}D_2O$ complex as hydrogen atom donor for alkyl

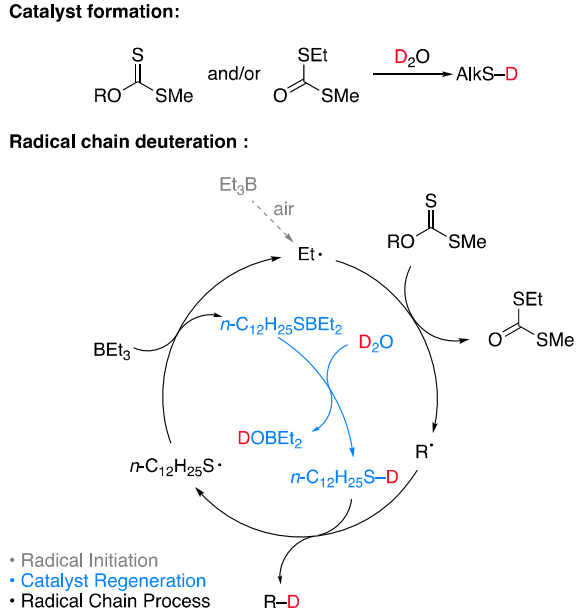
radicals leading to low deuterium incorporation. The high level of deuteration obtained with xanthates such as **1b** remained puzzling.

Table 1. Deuteration of **1a**, **1b** and **1c** using R_3B, D_2O and air.



Entry	Substrate	R_3B	Additive (mol%)	Yield	D-inc.
1	**1a**	Et_3B	–	38%	7%
2	**1b**	Et_3B	–	20%	85%
3[16]	**1b**	Me_3B	–	67%[a]	95%
4[16]	**1b**	Bu_3B	–	19%[a]	88%
5	**1c**	Et_3B	–	29%	87%
6	**1a**	Et_3B	$C_{12}H_{25}SH$ (0.17)	53%	64%
7	**1a**	Et_3B	$C_{12}H_{25}SH$ (1.0)	63%	81%

A plausible hypothesis for the discrepancy between the deuteration of the iodide **1a** and the xanthate **1b** is that, under the reaction conditions (Lewis acidity of Et_3B, presence of water, long reaction time), partial hydrolysis of the xanthate (or of the ethyl methyl dithiocarbonate formed during the reaction) is taking place generating methanethiol (and ethanethiol) that can act as a catalyst in the deuteration process. Since the presence of these volatile thiols is difficult to detect, the dodecyl xanthate **1c** derived from cholesterol was prepared. The radical deuteration of **1c** afforded the deoxygenated product **2** in similar yield and deuterium incorporation as the methyl xanthate **1b**. However, at the end of the reaction, the presence of 0.17 mol% of dodecanethiol in the reaction mixture was detected by gas chromatography. The total amount of thiol in solution is possibly higher since we could not detect the formation of ethanethiol due to its volatility. The deuteration of the iodide **1a** was repeated in the presence of 0.17 mol% of dodecanethiol. A marked increase in yield and deuterium incorporation (64%) was observed (Table 1, entries 6). When 1 mol% of thiol was used, 81% deuterium incorporation was reached, a result similar to the one obtained for the xanthates **1a** and **1b** (Table 1, entry 5). Therefore, it is reasonable to assume that the main pathway for the deoxygenation of the xanthate in presence of D_2O and a trialkylborane is catalyzed by an *in situ* generated thiol. The mechanism involving the $Et_3B{\cdot}D_2O$ complex represents a minor reaction pathway, as demonstrated by the low level of deuteration during the deiodination process (Table 1, entry 1). Since the hydrolysis of the xanthates is a slow process, the thiol catalyzed reaction is favored by the long reaction time (up to 24 h) necessary for the deoxygenation of xanthates (Scheme 2). Slow hydrolysis of either the starting xanthate or the thiocarbonate by-product provides the deuterated alkanethiol catalyst. After hydrogen atom transfer to the alkyl radical, the alkanethiyl radical[26] reacts with triethylborane to afford an ethyl radical that sustain the chain process and a thioborinic ester (R_2BSR'). Facile hydrolysis of the thioborinic ester (Scheme 2, blue part) gives the regenerated catalyst. Such a mechanism is supported by the work of Mikhailov[27] showing that in presence of of oxygen, trialkylborane R_3B react with a thiol R'SH to give the corresponding thioborinic ester and the corresponding alkane RH. Interestingly, in the presence of a stoichiometric amount of an alcohol, only a catalytic amount of the thiol was necessary to consume all the trialkylborane. A few years later, a radical mechanism was proposed for this reaction by Davies and Roberts.[28] The formation of the non-deuterated product results most probably from hydrogen atom abstraction involving the trialkyborane.[24-25]

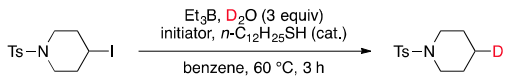


Scheme 2. Revised mechanism for the deoxygenation of xanthate employing D_2O as the deuterium atom source.

Interestingly, our mechanistic study has shown that a deiodination process involving D_2O may also be suitable for the preparation of deuterated compounds (Table 1, entry 7). Optimization of the procedure was performed with 4-iodo-1-tosylpiperidine **3**.[29] As a catalyst, dodecanethiol was used due to its low volatility and neutral odor. As initiator and chain transfer reagent, triethylborane (Et_3B) was selected due to its commercial availability. Me_3B would have been a better choice due to the lack of stabilization of the methyl relative to the ethyl radical (more efficient iodine atom transfer) and the lower hydrogen donor ability of Me_3B relative to Et_3B (higher D-incorporation). Unfortunately, this reagent is not commercially available in Europe. In the initial

experiments, di-*tert*-butylhyponitrite (DTBHN) was chosen as an initiator.

Table 2. Optimization of the radical deiodination of **3** with D_2O as a source of deuterium.



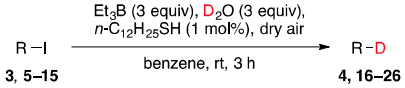
3 **4**

Entry	Initiator	*n*-$C_{12}H_{25}SH$	Yield	D-inc.
1	DTBHN	–	71%	32%
2	DTBHN	1 mol%	96%	82%
3	DTBHN	2 mol%	89%	89%
4	DTBHN	5 mol%	88%	92%
5	DTBHN	10 mol%	77%	93%
6	DTBHN	5 mol%[b]	89%	90%
7	Air[a]	1 mol%	89%	92%

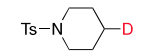
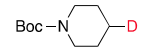
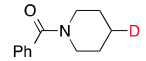
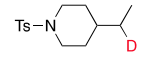
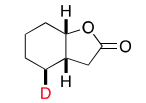
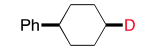
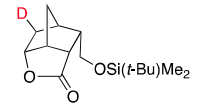
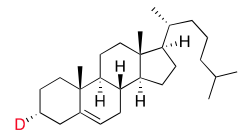
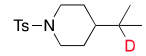
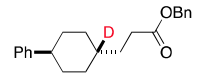
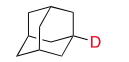
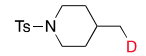
a) Reaction at room temperature. b) $Et_2BS(n\text{-}C_{12}H_{25})$ was used instead of *n*-$C_{12}H_{25}SH$.

In the absence of catalyst, the reaction gave as expected a low level of D-incorporation (32%) and a moderate yield (Table 2, entry 1). The use of 1 mol% of dodecanethiol significantly increases the yield (96%) and the D-incorportation (82%) (entry 2). Increasing the amount of catalyst has a positive effect on the D-incorporation (up to 90%) but the yield decreased (Table 2, entries 3–5). This result can be rationalized by the fact that increasing the concentration of the thiol favor the hydrogen transfer to the ethyl radical before it can abstract an iodine atom. Under these conditions, full consumption of the starting iodide **3** is difficult to reach. It is remarkable to note that the catalyst was used in its non-deuterated form. We assumed that the thiol is immediately converted to the corresponding thioborinic ester, consuming rapidly all the S–H hydrogen atoms.[27] This reaction is presumably initiated by traces of residual oxygen in the solvent. In order to check this, the reaction was run with 5 mol% of preformed *n*-docecyl diethylthioborinate ($n\text{-}C_{12}H_{25}SBEt_2$) (Table 2, entry 6). Under these conditions, the yield and D-incorporation match the ones obtained with 5 mol% of the thiol (Table 2, entry 4). To avoid contamination by H_2O, all initial experiments (Table 2, entries 1–6) were performed with di-*tert*-butylhyponitrite (DTBHN) as an initiator rather than air. However, slow addition of air[30] dried by bubbling through concentrated sulfuric acid, gave excellent results with 1 mol% of catalyst (Table 2, entry 7). The optimized procedure involving initiation with dry air and 1 mol% of dodecanethiol was tested with a broad range of iodides. Results are summarized in Table 3.

Table 3. Scope of the thiol catalyzed deuterative deiodination process.



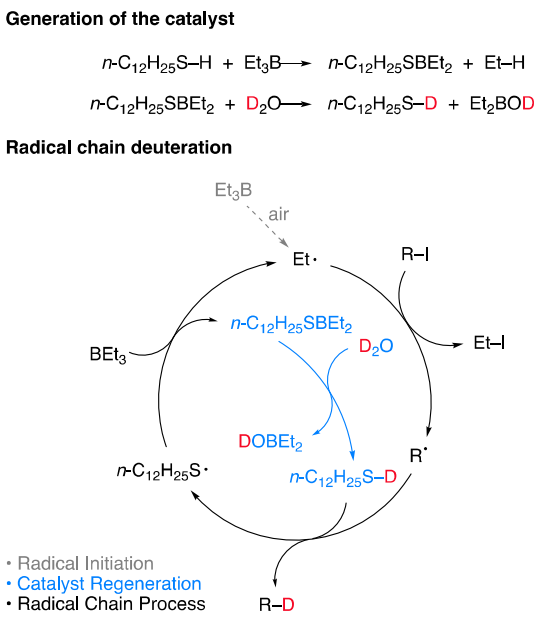
3, 5–15 **4, 16–26**

Entry	R–I	R–D[a]		Yield	D-inc.
1	**3**		**4**	89% 48%	92% 98%[b]
2	**5**		**15**	78%	96%
3	**6**		**16**	91%	94%
4	**7**		**17**	93%	96%
5	**8**		**18**	82%[c]	91%
6	**9**		**19**	87%[d,e]	95%
7	**10**		**20**	85%[f] 84%[f,g]	85% 89%[c]
8	**1a**		**2**	73%[h]	93%
9	**11**		**21**	79%	77%
10	**12**		**22**	84%[i]	96%
11	**13**		**23**	78%[b]	83%
12	**14**		**24**	43%	91%

a) Major isomer shown when applicable. b) Using 5 equivalents of dodecanethiol. c) *exo*/*endo* 5:1 d) Yield determined by GC using nonadecane as an internal standard. e) *cis*/*trans* 3:1. f) *exo*/*endo* 95:5. g) Initiation with DTBHN (1 equiv) at 60 °C and 5 mol% of dodecanethiol. h) α/β 3:1. i) *trans*/*cis* ≥95:5.

A series of secondary alkyl iodides was investigated first (Table 3, entries 1–8). The reaction afforded the deiodinated product in 73–93% yields and high level of deuterium incorporation (80–96%). The presence of functional groups containing C–H bonds that are prone to hydrogen atom abstraction by thiyl radical such as amides (entries 1–4), lactones (entry 5 and 7), silyl ether (entry 7), benzylic and allylic systems (entries 6 and 8) are well tolerated. By using 5 mol% of the thiol catalyst, a very high level of deuterium incorporation can be reached but the yield went down due to incomplete conversion. Similar results were obtained with tertiary iodides (Table 3, entries 9–11) with a more important fluctuation of the

level of deuterium incorporation (77–96%). Finally, a primary alkyl iodide was tested (Table 3, enty 12). As anticipated, the deuterated compound was obtained in lower yield (43%) due to a slower iodine atom transfer between the ethyl radical and the substrate[31] but with a good level of deuterium incorporation. The mechanism of the deiodination process is depicted in Scheme 3. At first, the non-deuterated dodecanethiol is converted to the thioborinic ester by a rapid reaction with triethylborane (the thiol is added to the triethylborane solution before adding the D_2O and the iodide). This is a fast radical process, initiated by traces amount of oxygen.[27-28] Interestingly, very high level of deuteration can be obtained even when a large amount of non-deuterated thiol is used. This may be due to the fast conversion of the thiol to the thioborinic ester before the reaction start or to the fact that the non-deuterated thiol is reacting faster with the ethyl radical than the thiol-d_1 due to a kinetic istotope effect.[24-25] In other word, the non-productive hydrogen atom transfer to the ethyl radical consumed selectively the non-deuterated catalyst. Hydrolysis of the thioborinic ester with D_2O afforded the dodecanethiol-d_1, the real catalyst of the reaction. The chain reaction starts with an ethyl radical generated by the reaction of Et_3B with oxygen (initiation step). This ethyl radical abstracts the iodine atom generating the alkyl radical. Deuteration of the radical by the dodecanethiol-d_1 gave the deuterated product together with a thiyl radical that sustains the chain process by reacting with Et_3B. The lower conversion obtained when a higher catalyst loading was used results from the competitive deuteration of the ethyl radical relative to the the iodine atom transfer process leading to a non-productive chain reaction.[32] The formation of the non-deuterated product can be explained by a competitive reaction involving Et_3B as a source of hydrogen atom. A rate constant $k_H = 0.6 \times 10^4\ M^{-1}\ s^{-1}$ has been reported for the hydrogen atom transfer from Et_3B to a secondary alkyl radical.[24-25]



Scheme 3. Proposed mechanism for the radical deuteration of alkyl iodides catalyzed by a thiol.

In conclusion, our study demonstrates that a thiol generated *in situ* is acting as a catalyst in the triethylborane-water mediated xanthates deoxygenation process reported by Wood and co-workers. Based on this observation, a thiol-catalyzed deuterative deiodination reaction has been developed. The reaction chain process is mediated by Et_3B and uses D_2O as a source of deuterium atom. Beside its obvious synthetic interest, this reaction offers new opportunities to develop catalytic enantioselective reactions.[33-36] Work in this direction is currently in progress.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization of all new products

Copies of ^{1}H- and ^{13}C-NMR spectra

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The Swiss National Science Foundation (Project 200020_152782 and 200020_172621), the State Secretariat for Education, Research and Innovation (SBFI Nr. C14.0096) and the COST Action CM1201 (short-term scientific mission of VS) are gratefully acknowledged for their support. We thank Dr. Julien Furrer and Mr. Ilche Gjuroski for their support in measuring ^{2}H-NMR-spectra.

REFERENCES

1. Zhu, Y.; Zhou, J.; Jiao, B., *ACS Med. Chem. Lett.* **2013,** *4*, 349-352.
2. Zhang, Y.; Tortorella, M. D.; Wang, Y.; Liu, J.; Tu, Z.; Liu, X.; Bai, Y.; Wen, D.; Lu, X.; Lu, Y.; Talley, J. J., *ACS Med. Chem. Lett.* **2014,** *5*, 1162-1166.
3. Katsnelson, A., *Nat. Med.* **2013,** *19*, 656.
4. Mullard, A., *Nat. Rev. Drug Discov.* **2016,** *15*, 219-221.
5. Schmidt, C., *Nat. Biotech.* **2017,** *35*, 493-494.
6. New Drug Application (NDA): 208082. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=208082.

7. Maltais, F.; Jung, Y. C.; Chen, M.; Tanoury, J.; Perni, R. B.; Mani, N.; Laitinen, L.; Huang, H.; Liao, S.; Gao, H.; Tsao, H.; Block, E.; Ma, C.; Shawgo, R. S.; Town, C.; Brummel, C. L.; Howe, D.; Pazhanisamy, S.; Raybuck, S.; Namchuk, M.; Bennani, Y. L., *J. Med. Chem.* **2009,** *52*, 7993-8001.
8. MacWood, G. E.; Urey, H. C., *J. Chem. Phys.* **1936,** *4*, 402-406.
9. Leblanc, M. E.; Morse, A. T.; Leitch, L. C., *Can. J. Chem.* **1956,** *34*, 354-358.
10. Pocker, Y.; Exner, J. H., *J. Am. Chem. Soc.* **1968,** *90*, 6764-6773.
11. Caldwell, R. A., *J. Org. Chem.* **1970,** *35*, 1193-1194.
12. Curran, D. P.; Ramamoorthy, P. S., *Tetrahedron* **1993,** *49*, 4841-4858.
13. Boyer, I. J., *Toxicology* **1989,** *55*, 253-298.
14. Crich, D.; Sun, S., *J. Org. Chem.* **1996,** *61*, 7200-7201.
15. During the writing of this manuscript, the of deuteration and tritiation of pharmaceutical compounds mediated by thiols using isotopically labeled water was reported: Loh, Y. Y.; Nagao, K.; Hoover, A. J.; Hesk, D.; Rivera, N. R.; Colletti, S. L.; Davies, I. W.; MacMillan, D. W. C., *Science* **2017,** *358*, 1182-1187.
16. Spiegel, D. A.; Wiberg, K. B.; Schacherer, L. N.; Medeiros, M. R.; Wood, J. L., *J. Am. Chem. Soc.* **2005,** *127*, 12513-12515.
17. Medeiros, M. R.; Schacherer, L. N.; Spiegel, D. A.; Wood, J. L., *Org. Lett.* **2007,** *9*, 4427-4429.
18. Allais, F.; Boivin, J.; Nguyen, V. T., *Beilstein J. Org. Chem.* **2007,** *3*, 46-47.
19. Davy, J. A.; Mason, J. W.; Moreau, B.; Wulff, J. E., *J. Org. Chem.* **2012,** *77*, 6332-6339.
20. Boivin, J.; Nguyen, V. T., *Beilstein J. Org. Chem.* **2007,** *3*, 45-47.
21. Hioe, J.; Karton, A.; Martin, J. M. L.; Zipse, H., *Chem. Eur. J.* **2010,** *16*, 6861-6865.
22. Povie, G.; Marzorati, M.; Bigler, P.; Renaud, P., *J. Org. Chem.* **2013,** *78*, 1553-1558.
23. Povie, G.; Renaud, P., *Chimia* **2013,** *67*, 250-252.
24. Jin, J.; Newcomb, M., *J. Org. Chem.* **2007,** *72*, 5098-5103.
25. Jin, J.; Newcomb, M., *J. Org. Chem.* **2008,** *73*, 4740-4742.
26. For a review on the chemistry of thiyl radicals, see: Dénès, F.; Pichowicz, M.; Povie, G.; Renaud, P., *Chem. Rev.* **2014,** *114*, 2587-2693.
27. Mikhailov, B. M.; Bubnov, Y. N., *Zh. Obs. Khim.* **1960,** *31*, 160-166.
28. Davies, A. G.; Roberts, B. P., *Acc. Chem. Res.* **1972,** *5*, 387-392.
29. Ollivier, C.; Renaud, P., *J. Am. Chem. Soc.* **2000,** *122*, 6496-6497.
30. Curran, D. P.; McFadden, T. R., *J. Am. Chem. Soc.* **2016,** *138*, 7741-7752.
31. Povie, G.; Ford, L.; Pozzi, D.; Soulard, V.; Villa, G.; Renaud, P., *Angew. Chem.* **2016,** *128*, 11387-11391.
32. Extension of the reaction to debromination is not expected to work since the competitive deuteration of the ethyl radical is expected to be faster than the bromine atom transfer step. Exceptionnally reactive bromides may represent an exception.
33. Haque, M. B.; Roberts, B. P.; Tocher, D. A., *J. Chem. Soc., Perkin Trans. 1* **1998**, 2881-2890.
34. Dang, H.-S.; Elsegood, M. R. J.; Kim, K.-M.; Roberts, B. P., *J. Chem. Soc. Perk. Trans. 1* **1999**, 2061-2068.
35. Cai, Y.; Roberts, B. P., *J. Chem. Soc., Perkin Trans. 2* **2002**, 1858-1868.
36. Brill, Z. G.; Grover, H. K.; Maimone, T. J., *Science* **2016,** *352*, 1078-1082.

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