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Total synthesis of (–)-agelastatin A: an $S_{\text{H}}2'$ radical azidation strategy



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A reagent generated from $\text{TMSN}_3/\text{KMnO}_4/\text{BnEt}_3\text{NCl}$ was found to promote an $\text{S}_{\text{H}}2'$ radical azidation of a bromo silyl enol ether to furnish an azido silyl enol ether via olefin transposition. With the present azidation protocol, a new synthetic approach to agelastatin A, a potent antitumor marine alkaloid, has been established.

(-)-Agelastatin A (**1**), along with its congener agelastatin B (**2**), was first isolated as a cytotoxic constituent from the Coral Sea sponge *Agelas dendromorpha* by Pietra and co-workers in 1993 (Fig. 1).¹ Thereafter, Molinski and co-workers identified the Indian Ocean sponge *Cymbastela* sp. as another source that produces **1** along with agelastatins C (**3**) and D (**4**), two additional agelastatin members.² In 2010, Al-Mourabit and co-workers reported the isolation of agelastatins E (**5**) and F (**6**) from the New Caledonian sponge *A. dendromorpha*.³ Early biological assessments of agelastatins conducted by the aforementioned laboratories have revealed that compound **1** exhibits remarkable properties, including antitumor activity,^{1,3} brine shrimp toxicity,² and insecticidal activity.² In addition, Meijer and Pettit have found that agelastatin A (**1**) is a potent inhibitor of GSK-3 β , a pivotal serine/threonine kinase.⁴ Hale and El-Tanani have reported that agelastatin A (**1**) dramatically decreases β -catenin levels in cancer cells and inhibits cancer cell proliferation by arresting cell cycle at G2 phase.⁵

The biological significance of agelastatin A (**1**) has made it an attractive target for medicinal studies.^{6,7} For instance, Movassaghi's comparative cytotoxicity assay of all agelastatin members, *i.e.*, A (**1**) to F (**6**), has successfully validated the relevance of agelastatin A (**1**)

Total synthesis of (-)-agelastatin A: an $\text{S}_{\text{H}}2'$ radical azidation strategy†

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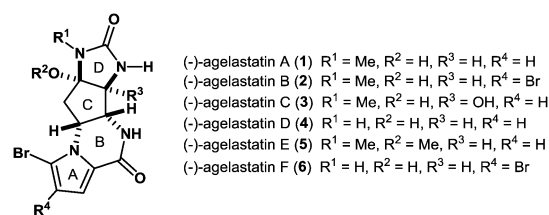


Fig. 1 Agelastatin alkaloids.

as a promising anticancer agent.^{7a} In addition, structure–activity relationship (SAR) studies on agelastatin analogues have recently been disclosed by the groups of Molinski,⁸ Romo/Liu,⁹ and Movassaghi,¹⁰ boosting the applications of agelastatin particularly to blood cancer chemotherapy.

Our group has also been engaged in synthetic and medicinal studies on **1** and has demonstrated that agelastatin analogues potentially attenuate brain cancer.¹¹ Furthermore, our SAR study has revealed that structural modifications of the N1-substituent of the D-ring of **1** could retain the *in vitro* and *in vivo* therapeutic efficacies of agelastatin analogues.^{12,13} Movassaghi's group has further clarified that D-ring modifications expand the scope of derivatization of agelastatins to access potent analogues.¹⁰

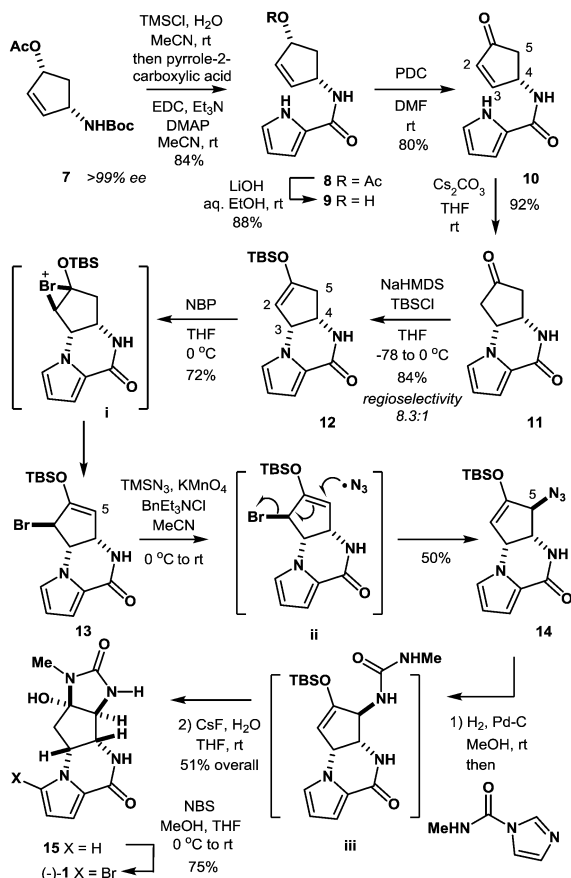
In the present study, we have established a new route to agelastatin A (**1**) through an $\text{S}_{\text{H}}2'$ radical azidation protocol using $\text{TMSN}_3/\text{KMnO}_4/\text{BnEt}_3\text{NCl}$ that enables the allylic transposition of a bromo silyl enol ether into an azido silyl enol ether, which serves as a useful D-ring precursor of the target natural product (Scheme 1).

The synthesis was commenced with Boc-protected amino-alcohol derivative **7** (>99% ee).¹⁴ The Boc group of **7** was removed with hydrochloric acid (HCl) generated *in situ* from TMSCl in aq. MeCN to provide an ammonium salt (structure not shown). After evaporation of the solvents under reduced pressure, the resultant crude product was coupled with pyrrole-2-carboxylic acid using EDC, Et_3N , and DMAP in MeCN to furnish compound **8** in 84% yield. Then, compound **8** was hydrolyzed with LiOH in aq. EtOH to provide alcohol **9** in 88% yield. PDC oxidation of alcohol **9** in DMF delivered enone **10** in

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization of new compounds including NMR spectra. CCDC 1852628. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc05697h



Scheme 1 Total synthesis of (-)-agelastatin A (1).

80% yield, which, upon treatment with Cs_2CO_3 in THF, gave tricyclic ketone **11** via a conjugate addition of the pyrrole nitrogen to the enone double bond. No racemization at C4 position took place in this transformation (**9** \rightarrow **10** \rightarrow **11**), retaining the optical purity of **11** (>99% ee).¹⁵ Then, ketone **11** was subjected to enolization with NaHMDS followed by *O*-silylation with *tert*-butyldimethylsilyl chloride to produce silyl enol ether **12** along with its minor regioisomer **16** (**12**:**16** = 8.3:1) (Fig. 2). Obviously, major product **12** was not ideal for further functionalization as it lacked a reactive alkene functionality at C5 position. However, we found that **12** and **16** underwent olefin isomerization with a trace acid probably due to their strained nature.¹⁶ Therefore, we envisioned that the brominative olefin transposition of **12** would take place via a bromonium formation followed by deprotonation to allow net olefin transposition that affords an enol ether suitable for C5 functionalization. To our delight, the treatment of silyl enol ether **12** with

Fig. 2 TBS enol ethers **12** and **16** generated from **11**.

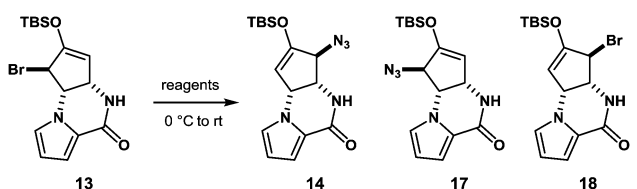
N-bromophthalimide (NBP) was found to deliver allylic bromide **13** in stereoselective and regioselective manners as we had expected.

With compound **13** in possession, the nitrogen functionalization at C5 position was examined to access key intermediate **14** (Table 1). An attempted ionic $\text{S}_{\text{N}}2'$ azidation of **13** with NaN_3 in DMF was unsuccessful (entry 5), giving rise to a desilylated product. To this end, we expected that the electrophilic nitrogen radical species would preferentially undergo an addition reaction with the electron-rich enol double bond to facilitate $\text{S}_{\text{H}}2'$ radical azidation to deliver compound **14**.

An azide radical is known to be generated from an anionic azide by oxidation processes. The Magnus protocol represents such an example, which utilizes trimethylsilylazide (TMSN_3) in combination with iodosylbenzene (PhIO) in CH_2Cl_2 at low temperature (-78°C). The Magnus method was proved to afford desired product **14** albeit in moderate yield (entry 8).¹⁷ Therefore, we sought a new reagent system to deliver an azido radical and found that the treatment of **13** with TMSN_3 (10 equiv.)/ KMnO_4 (0.3 equiv.)/ BnEt_3NCl (0.3 equiv.) successfully produced azide **14** in 50% yield along with regioisomeric azide **17** (21%) and bromide **18** (3%)¹⁸ (entry 1). In the absence of KMnO_4 , no reaction took place and unreacted **13** was recovered (entries 6 and 7). When catalytic KMnO_4 (0.1 equiv.) was used in combination with TMSN_3 (10 equiv.) and BnEt_3NCl (0.1 equiv.) in either the presence or absence of molecular oxygen (O_2), the chemical yield was low, suggesting that catalysis by O_2 in the present radical azidation was not operative (entries 2 and 3). Increasing the amount of $\text{Mn}(\text{VII})$ reagent was found to have no impact on the improvement of the chemical yields (entry 4).

It should be mentioned that the addition of TMSN_3 to the mixture of KMnO_4 and BnEt_3NCl at 0°C caused the evolution of molecular nitrogen (N_2) accompanied by a color change of the solution from purple to dark brown, suggesting the production of low-valent manganese species from the $\text{Mn}(\text{VII})$ reagent. Although the reactive species responsible for the present radical azidation remains unclear, we assume that permanganate(VII) (MnO_4^-) reacts with TMSN_3 to generate a low-valent manganese azide complex that serves as a metastable azide radical source. To clarify this hypothesis, we measured the amount of nitrogen gas (N_2) that was generated from the reagent system. When KMnO_4 (0.33 mmol) was treated with BnEt_3NCl (0.33 mmol) and a large excess of TMSN_3 (11.1 mmol), 20–24 mL (ca. 0.9–1.1 mmol) of molecular nitrogen, which corresponds to ca. 3.0 equiv. relative to 1.0 equiv. of permanganate ion (MnO_4^-), was generated. Assuming that 1.0 equiv. of permanganate reacts with 5.0 equiv. of TMSN_3 to produce 3.0 equiv. of molecular nitrogen, we propose that a pentavalent $\text{Mn}(\text{V})$ species is produced from the $\text{Mn}(\text{VII})$ species (Scheme 2).

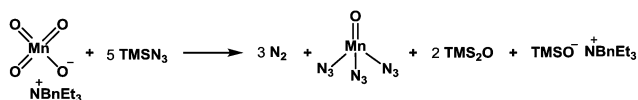
Jiao and co-workers have reported that $\text{Mn}(\text{III})$ generated from MnBr_2 in the presence of molecular oxygen serves as an effective catalyst to generate an azide radical from TMSN_3 .^{19a} We have examined $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ in combination with TMSN_3 (6 equiv.) as a possible source of azido radical and found that desired material **14** could be similarly produced in 42% yield along with **17** (8%) (entry 9).^{19b} This result suggests that $\text{Mn}(\text{III})$ azide complex is likely responsible for the present radical azidation. Based on these observations, we currently assume that metastable $\text{Mn}(\text{V})$

Table 1 Azidation of bromide **13** with various reagents


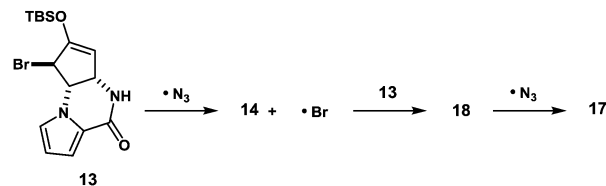
Entry	Reagents (equiv.)	Time	Yield ^a (%)			
			14	17	18	13 ^b
1	KMnO ₄ (0.3), BnEt ₃ NCl (0.3), TMSN ₃ (10), MeCN	40 min	50	21	3	Trace
2	KMnO ₄ (0.1), BnEt ₃ NCl (0.1), TMSN ₃ (10), MeCN	40 min	30	4	12	30
3	KMnO ₄ (0.1), BnEt ₃ NCl (0.1), TMSN ₃ (10), MeCN, O ₂	40 min	31	5	11	21
4	KMnO ₄ (0.6), BnEt ₃ NCl (0.6), TMSN ₃ (10), MeCN	40 min	43	11	4	9
5	NaN ₃ (1.1), DMF ^c	15 min	—	—	—	— ^d
6	BnEt ₃ NCl (0.3), TMSN ₃ (10), MeCN	75 min	—	—	—	90
7	TMSN ₃ (10), MeCN	70 min	—	—	—	89
8	PhIO (1.2), TMSN ₃ (2.4), CH ₂ Cl ₂ ^e	40 min	24	17	14	6
9	Mn(OAc) ₃ ·2H ₂ O (3), TMSN ₃ (6), MeCN ^c	11 h	42	8	—	—

^a Isolated yields after purification by column chromatography. ^b Recovered unreacted starting material. ^c The reaction was conducted at r.t.

^d Bromoketone (60%) was produced. ^e The reaction was conducted at -78 °C.



Scheme 2 Plausible generation of Mn(v) azide species.

Scheme 3 Plausible mechanisms of the production of regioisomeric byproducts **17** and **18**.

species is generated from Mn(VII) with excess TMSN₃ and that Mn(V) provides 3 equiv. of azido radical to finally become Mn(II), which no longer serves as a radical source. To elucidate the formation of the meta-stable Mn species, we carried out a comparison experiment: after stirring the reagents for 60 min, excess remaining TMSN₃ was completely removed under reduced pressure. Then, the residual solid that likely contains the Mn species was diluted with MeCN and mixed with substrate **13**. As a result, almost identical yields of products **14** (48%), **17** (22%), and **18** (6%) were obtained as in the case of entry 1, indicating that the Mn(V) azide complex is generated as a reactive meta-stable reagent.

The formation of compounds **17** and **18**, which provides an insight into the mechanism of the present azidation, also requires elaboration (Scheme 3). When azide **14** and isomeric azide **17** were separately subjected to the same reaction conditions for 1 h, only a trace amount of corresponding azide **17** and **14** was produced along with the unreacted starting azides, respectively. This indicates that both azides **14** and **17**, once produced, were hardly susceptible to the S_H2' azidation. In contrast, when isomeric bromide **18** was treated with the reagent, compounds **14** (34%), **17** (27%), and **18** (12%) were obtained similar to the case of **13**. Based on these results, we propose that the addition of an azide radical to bromide **13** generates a Br radical that undergoes rapid addition to substrate **13** to generate regioisomeric bromide **18**. Then, **18** is further converted into compound **17** *via* a radical azidation.

With azide **14** in possession, we further endeavored to accomplish the total synthesis. Thus, azide **14** was subjected to catalytic hydrogenation followed by one-pot urea formation with Batey's reagent²⁰

and subsequent desilylative cyclization with CsF to afford tetracyclic compound **15** in 51% yield over three steps. It should be mentioned that no purification was required in the three-step sequence, allowing ease of experimental operations. Finally, the known bromination protocol was applied to compound **15** to furnish (–)-agelastatin A (**1**).

In conclusion, we have established a new approach to (–)-agelastatin A (**1**) by the strategic implementation of brominative olefin transposition and subsequent S_H2' radical azidation. The present approach features a late-stage construction of D-ring that would allow facile production of D-ring analogues. We believe that the present synthesis would facilitate further development of new agelastatin analogues.

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Conflicts of interest

The authors declare no conflicts of interest.

Notes and references

- (a) M. D'Ambrosio, A. Guerriero, C. Debitus, O. Ribes, J. Puset, S. Leroy and F. J. Pietra, *J. Chem. Soc., Chem. Commun.*, 1993, 1305; (b) M. D'Ambrosio, A. Guerriero, G. Chiasera and F. Pietra,

- Helv. Chim. Acta*, 1994, **77**, 1895; (c) M. D'Ambrosio, A. Guerriero, M. Ripamonti, C. Debitus, J. Waikedre and F. Pietra, *Helv. Chim. Acta*, 1996, **79**, 727.
- 2 T. W. Hong, D. R. Jimenez and T. F. Molinski, *J. Nat. Prod.*, 1998, **61**, 158.
- 3 S. Tilvi, C. Moriou, M. Martin, J. Gallard, J. Sorres, K. Patel, S. Petek, C. Debitus, L. Ermolenko and A. Al-Mourabit, *J. Nat. Prod.*, 2010, **73**, 720.
- 4 (a) L. Meijer, A. M. Thunnissen, A. W. White, M. Garnier, M. Nikolic, L. H. Tsai, J. Walter, K. E. Cleverley, P. C. Salinas, Y. Z. Wu, J. Biernat, E. M. Mandelkov, S. H. Kim and G. R. Pettit, *Chem. Biol.*, 2000, **7**, 51; (b) G. R. Pettit, S. Ducki, D. L. Herald, D. L. Doubek, J. M. Schmidt and J.-C. Chapuis, *J. Oncol. Res.*, 2005, **15**, 11.
- 5 (a) C. K. Mason, S. McFarlane, P. G. Johnston, P. Crowe, P. J. Erwin, M. M. Domostoj, F. C. Campbell, S. Manaviazar, K. J. Hale and M. El-Tanani, *Mol. Cancer Ther.*, 2008, **7**, 548; (b) M. Harmata, *Strategies and Tactics in Organic Synthesis*, Elsevier Academic Press, London, 2005, ch. 11, vol. 6, pp. 352–394.
- 6 For selected reviews on total synthesis of agelastatins, see: (a) G. Dong, *Pure Appl. Chem.*, 2010, **82**, 2231; (b) T. Yamaoka, Y. Ichikawa and H. Kotsuki, *J. Synth. Org. Chem., Jpn.*, 2012, **70**, 615.
- 7 (a) D. Stien, G. T. Anderson, C. E. Chase, Y. Koh and S. M. Weinreb, *J. Am. Chem. Soc.*, 1999, **121**, 9574; (b) K. S. Feldman and J. C. Saunders, *J. Am. Chem. Soc.*, 2002, **124**, 9060; (c) K. S. Feldman, J. C. Saunders and M. L. Wroblewski, *J. Org. Chem.*, 2002, **67**, 7096; (d) K. J. Hale, M. M. Domostoj, D. A. Tocher, E. Irving and F. Scheinmann, *Org. Lett.*, 2003, **5**, 2927; (e) M. M. Domostoj, E. Irving, F. Scheinmann and K. J. Hale, *Org. Lett.*, 2004, **6**, 2615; (f) F. A. Davis and J. Deng, *Org. Lett.*, 2005, **7**, 621; (g) B. M. Trost and G. Dong, *J. Am. Chem. Soc.*, 2006, **128**, 6054; (h) Y. Ichikawa, T. Yamaoka, K. Nakano and H. Kotsuki, *Org. Lett.*, 2007, **9**, 2989; (i) D. P. Dickson and D. J. Wardrop, *Org. Lett.*, 2009, **11**, 13414; (j) N. Hama, T. Matsuda, T. Sato and N. Chida, *Org. Lett.*, 2009, **11**, 2687; (k) P. M. Wehn and J. Du Bois, *Angew. Chem., Int. Ed.*, 2009, **48**, 3802; (l) F. A. Davis, J. Zhang, Y. Zhang and H. Qiu, *Synth. Commun.*, 2009, **39**, 1914; (m) B. M. Trost and G. Dong, *Chem. – Eur. J.*, 2009, **15**, 6910; (n) M. Movassaghi, D. S. Siegel and S. Han, *Chem. Sci.*, 2010, **1**, 561; (o) Y. Menjo, A. Hamajima, N. Sasaki and Y. Hamada, *Org. Lett.*, 2011, **13**, 5744; (p) T. Kano, R. Sakamoto, M. Akakura and K. Maruoka, *J. Am. Chem. Soc.*, 2012, **134**, 7516; (q) J. C. P. Reyes and D. Romo, *Angew. Chem., Int. Ed.*, 2012, **51**, 6870; (r) P. A. Duspara and R. A. Batey, *Angew. Chem., Int. Ed.*, 2013, **52**, 10862; (s) A. H. Antropow, K. Xu, R. J. Buchsbaum and M. Movassaghi, *J. Org. Chem.*, 2017, **82**, 7720; (t) Y. Yao, X. Wang and G. Liang, *Tetrahedron*, 2017, **73**, 4538.
- 8 E. P. Stout, M. Y. Choi, J. E. Castro and T. F. J. Molinski, *J. Med. Chem.*, 2014, **57**, 5085.
- 9 (a) M. Jouanneau, B. McClary, J. C. P. Reyes, R. Chen, Y. Chen, W. Plunkett, X. Cheng, A. Z. Milinichik, E. F. Albone, J. O. Liu and D. Romo, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 20927; (b) B. McClary, B. Zinshteyn, M. Meyer, M. Jouanneau, S. Pellegrino, G. Yusupova, A. Schuller, J. C. P. Reyes, J. Lu, Z. Gou, S. Ayinde, C. Luo, Y. Dang, D. Romo, M. Yusupov, R. Green and J. O. Liu, *Cell Chem. Biol.*, 2017, **24**, 605.
- 10 A. H. Antropow, K. Xu, R. J. Buchsbaum and M. Movassaghi, *J. Org. Chem.*, 2017, **82**, 7720.
- 11 (a) T. Yoshimitsu, T. Ino and T. Tanaka, *Org. Lett.*, 2008, **10**, 5457; (b) T. Yoshimitsu, T. Ino, N. Futamura, T. Kamon and T. Tanaka, *Org. Lett.*, 2009, **11**, 34025; (c) D. Shigeoka, T. Kamon and T. Yoshimitsu, *Beilstein J. Org. Chem.*, 2013, **9**, 860.
- 12 (a) Z. Li, T. Kamon, D. A. Personett, T. Caulfield, J. A. Copland, T. Yoshimitsu and H. W. Tun, *Med. Chem. Commun.*, 2012, **3**, 233; (b) Z. Li, D. Shigeoka, T. R. Caulfield, T. Kawachi, Y. Qiu, T. Kamon, M. Arai, H. W. Tun and T. Yoshimitsu, *Med. Chem. Commun.*, 2013, **4**, 1093.
- 13 H. W. Tun, T. Yoshimitsu, D. Shigeoka, T. Kamon, Z. Li, Y. Qiu and T. R. Caulfield, *US Pat.*, US9464093B2, 2016.
- 14 (a) M. J. Mulvihill, J. I. Gage and M. J. J. Miller, *J. Org. Chem.*, 1998, **63**, 3357; (b) C. Cesario, L. P. Tardibono and M. J. J. Miller, *J. Org. Chem.*, 2009, **74**, 448.
- 15 The optical purity was unambiguously confirmed by ^1H NMR analysis of Mosher esters derived from an alcohol that was prepared by reduction of ketone **11** with NaBH_4 (for the details, see the ESI †).
- 16 (a) A. Deyine, G. Dujardin, M. Mammeri and J.-M. Poirier, *Synth. Commun.*, 1998, **28**, 1817; (b) K. Inanaga, Y. Ogawa, Y. Nagamoto, A. Daigaku, H. Tokuyama, Y. Takemoto and K. Takasu, *Beilstein J. Org. Chem.*, 2012, **8**, 658.
- 17 P. Magnus, M. B. Roe and C. J. Hulme, *J. Chem. Soc., Chem. Commun.*, 1995, 263.
- 18 The structure of regioisomeric bromide **18** was unambiguously confirmed by X-ray crystallographic analysis (CCDC 1852628) † .
- 19 (a) X. Sun, X. Li, S. Song, Y. Zhu, Y.-F. Liang and N. Jiao, *J. Am. Chem. Soc.*, 2015, **137**, 6059; (b) Y. Zhao, Y. Hu, H. Wang, X. Li and B. Wan, *J. Org. Chem.*, 2016, **81**, 4412.
- 20 P. A. Duspara, Md. S. Islam, A. J. Lough and R. A. Batey, *J. Org. Chem.*, 2012, **77**, 10362.