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Photocatalytic ATRA Reaction Promoted by Iodo-Bodipy and Sodium Ascorbate

G. Magagnano,^{a,b} A. Gualandi,^{*a} M. Marchini,^{a,c} L. Mengozzi,^a P. Ceroni,^{*a,c} and P. G. Cozzi^{*a}

Using ascorbate as sacrificial reductant, Iodo-Bodipy dye 1b is able to promote the ATRA reaction between bromoderivatives and alkenes. This finding expands the possibility to use Bodipy dyes to promote photocatalytic reactions in efficient ways.

Organic photocatalysts have recently found a renewed interest in the chemical community.¹ The use of photocatalyst (PC) able to absorb visible light allowed the exploitation of unprecedented reactivity in synthetic chemistry thanks to the different chemical properties of the excited state (*PC).² In particular, *PC is at the same time a stronger reductant and a stronger oxidant compared to the electronic ground state and it is able to promote electron transfer processes (ET) that are thermodynamically endoergonic in the dark. Indeed, metal complexes,³ semiconductors,⁴ or dyes⁵ can be used to efficiently generate radicals from suitable precursors.⁶ The use of metal free PCs is particularly intriguing to develop green photocatalytic methodologies in which simple organic molecules are combined through otherwise elusive reaction pathways.⁷ A plethora of commercially available organic photocatalysts have been reported, but most of them suffered from several drawbacks, such as low photo and/or thermal stabilities,⁸ poor efficiencies,⁹ and slow reaction rates.¹⁰ In the quest for organic photocatalysts with improved properties, boron-dipyrromethene (Bodipy) compounds (Figure 1) have been recognized as suitable candidates due to their photophysical properties: large molar absorption coefficients in the visible spectral region, excellent thermal and photochemical stabilities and high fluorescence quantum yields (an useful tool to investigate the reactivity of the lowest singlet excited state). The Ramaiah research group¹¹ and

Jing/Zhang group¹² recently reported interesting photocatalytic transformations promoted by Bodipy dyes. These findings were based on the generation of singlet oxygen¹³ by the Bodipy-based photocatalysts. Based on these reports, it seems that the employment of Bodipy dyes in photocatalytic reactions, may be limited to oxidations in which singlet oxygen is a key intermediate, or other photocatalytic reactions that are initiated by energy transfer. In this communication, we showed that the easily accessible Iodo-Bodipy compound **1f** is an effective photocatalyst for ATRA (Atom-Transfer Radical Addition) reactions. This chemistry, pioneered by Kharasch almost 70 years ago,¹⁴ has evolved to become an atom economical and effective methodology for the direct functionalization of alkene substrates. Through a new and quite interesting mechanistic picture, the herein presented method affords good results in terms of efficiency and reaction scope.

It is well accepted that ATRA proceeds through a radical chain propagation mechanism. Stephenson,¹⁵ and Melchiorre¹⁶ have proposed photoredox methodologies for generating radical intermediates under mild reaction conditions.

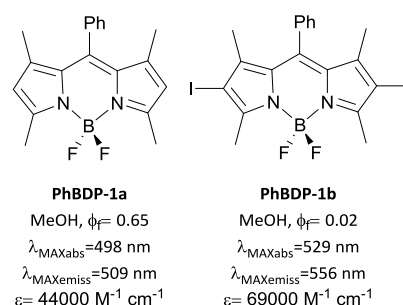
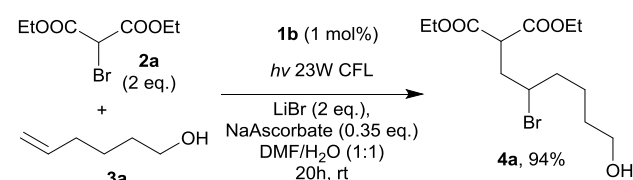


Figure 1. Relevant Bodipy molecules and their photophysical properties. Data from ref 12a.

With the idea to use Bodipy molecules as photocatalysts to induce an energy transfer process for ATRA reactions,¹⁶ we started our initial explorations by selecting the reaction of diethyl 2-bromo-malonate (**2a**) and 5-hexenol (**3a**; Scheme 1). Unfortunately, by exploring various solvents and reaction

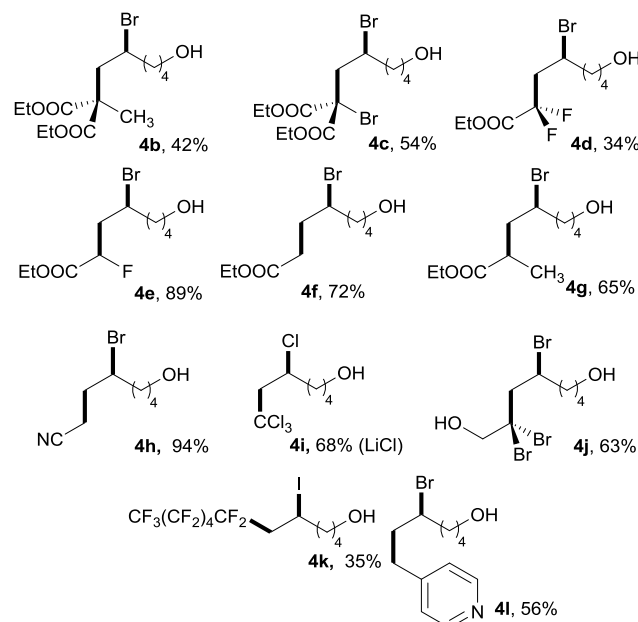
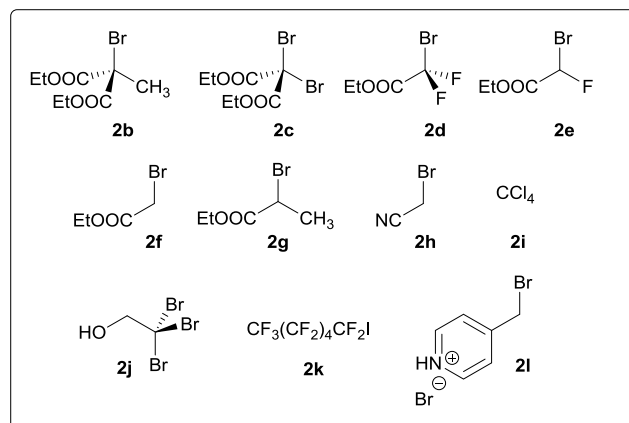
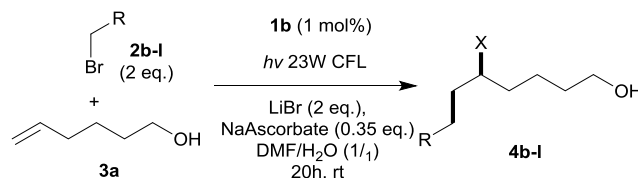
conditions under 23W CFL irradiation at room temperature, all experiments were unsuccessful (see ESI). However, we noted the drastic color change when the reaction was performed in the presence of Et_3N . By reasoning that electron transfer between the Bodipy and the sacrificial electron donor had occurred, the reaction was settled up in the presence of different reducing agents (see ESI). Pleasantly, we achieved complete conversion when the model reaction was performed in the presence of 0.35 equiv of sodium ascorbate in DMF:H₂O as reaction solvent (Scheme 1). As noted by Stephenson,¹⁵ the presence of LiBr was producing better isolated yields.



Scheme 1. Optimized reaction conditions.

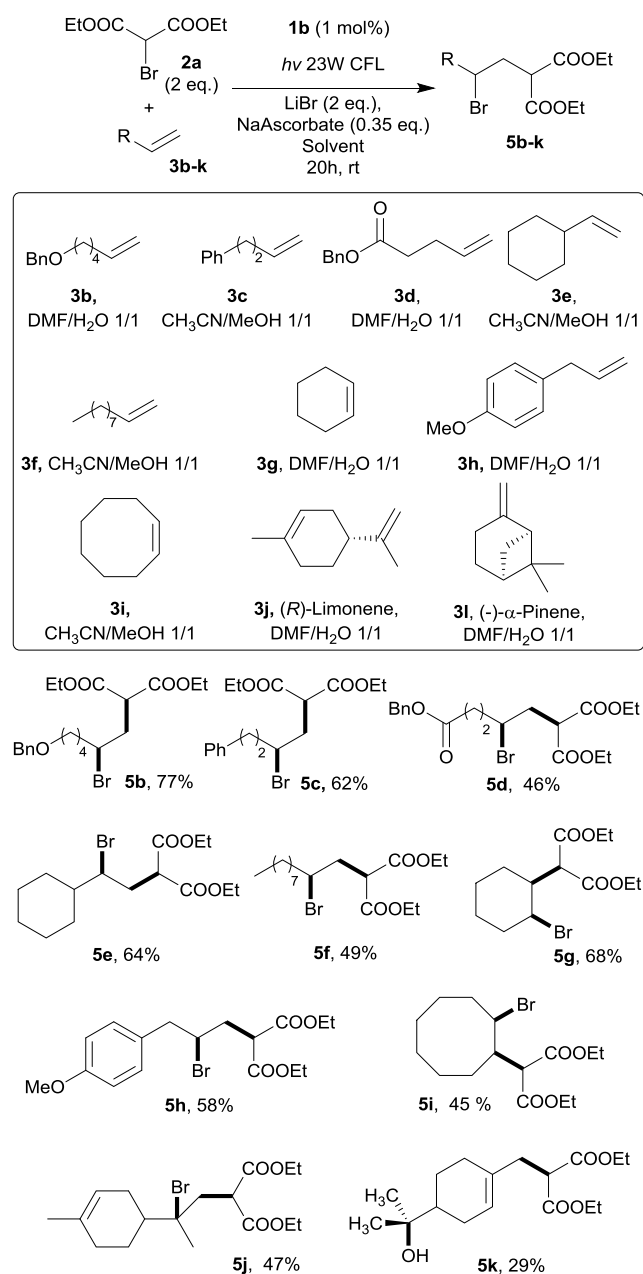
While the iodo Bodipy **1b** was an effective catalyst, the employment of the catalyst **1a** gave no reaction. The photochemical ATRA reaction showed a good synthetic potential. As illustrated in Scheme 2, differently substituted organic halides (**2a–m**) underwent the desired reaction with **3a** to provide adducts **4a–m** from moderate to good isolated yields. The method allowed the direct introduction of functional groups other than an ester: indeed bromoacetonitrile, carbon tetrachloride and perfluorohexyl iodide are compelling substrates. It is worth mentioning that in the case of **2g** a shorter reaction time compared to the methodologies reported in literature is observed.¹⁷

The novelty, compared to the previously reported methodologies,^{15,16} is the successful use of bromoacetate and haloalkyl pyridine salt to generate the corresponding radical and add them to the alkene in good yield (**4l**). Next, we have studied the reactivity of different olefins with **2a** (Scheme 3). Both terminal olefins and the inherently less reactive internal cyclic alkenes, including cyclohexene, and cyclooctene, were reactive substrates. The lower yields compared to other protocols^{15,16} are only caused by the limited substrate solubility in the solvent mixture, whose choice is dictated by the need to dissolve sodium ascorbate and Bodipy. Our protocol is clearly more competitive with alkenes showing a better solubility in aqueous media. Despite these problems, the protocol gave moderate yields with all substrates tested, thus enabling the construction of complex frameworks **5a–k** from simple precursors. The naturally occurring (*R*)-limonene and (-)- β -pinene can be successfully employed in the ATRA process, furnishing respectively adducts **5j** and **5k**. It is quite interesting to note the presence of the product **5k** derived from a rearrangement.¹⁷ The determination of the ascorbate mode of action is of great interest because it would open new ways and possibilities for the design and application of Bodipys in photochemical processes. In order to determine the reaction mechanism we performed several experiments on the model reaction depicted in Scheme 1. Control experiments highlighted that both visible light irradiation and the presence of **1b** are necessary to promote the reaction (see ESI).



Scheme 2. Scope of the photochemical ATRA reaction promoted by iodo-Bodipy **1b** with different halides and substrate **3a**.

To remove the eventual contribution of the UV component of the CFL lamp, we performed the reaction using white LEDs with $\lambda \geq 400$ nm, obtaining the desired product in comparable yield to the standard conditions (see ESI). Since none of the components of the reaction mixture is absorbing visible light except **1b** (Figure S2), during the photoreaction **1b** is selectively excited and promotes the ATRA reaction. The presence of organic bases such as lutidine are not relevant,¹⁶ allowing the use of substrate such as hydrobromide salt (Scheme 2, **2l**). To get better insights into the reaction mechanism from the photochemical point of view, we studied the photophysical properties of **1b** and the quenching of its lowest excited states. **1b** shows a fluorescence band with maximum at 529 nm^{18,19} and a weak phosphorescence band at



Scheme 3. Scope of the photochemical ATRA reaction promoted by iodo-Bodipy **1b** with different alkenes and substrate **2a**.

760 nm (Figure S1) with a lifetime of 0.22 ms. As expected, the presence of iodo substituents promotes inter system crossing to populate the phosphorescent T₁ excited state, as previously observed for different iodo derivatives of Bodipy dyes.²⁰ Upon addition of the reagents (up to the concentration used in the photoreaction) to a solution of **1b** in DMF:H₂O 1:1 (v/v), no significant quenching of the fluorescence of **1b** is observed. On the other hand, sodium ascorbate and diethyl 2-bromomalonate **2a** bring about a decrease of the phosphorescence quantum yield and the corresponding lifetime. By the classic Stern-Volmer plot,²¹ we estimated the corresponding quenching constants (see e.g., Figure 2). Under the experimental conditions used in the photoreaction, the lifetime of the phosphorescent excited state of **1b** is quenched 2.5 times by addition of diethyl 2-bromo-malonate 0.5 M with lithium bromide 0.5 M (without lithium salt, no quenching is

observed), and 10⁴ times in the presence of sodium ascorbate 0.088 M (buffered at pH 5).

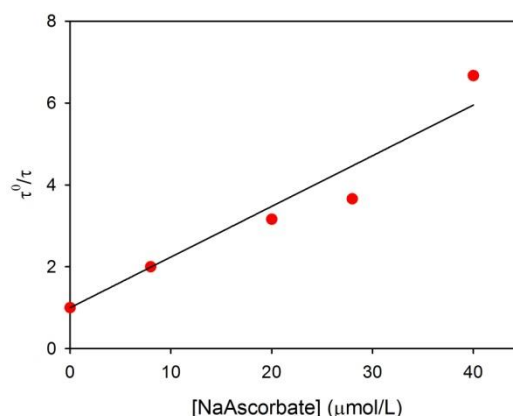


Figure 2 Lifetime of **1b** phosphorescent excited state in DMF:H₂O 1:1 (v/v) in the absence (τ^0) and in the presence (τ) of increasing amount of NaAscorbate. The slope represents the Stern-Volmer constant, i.e. the product of the quenching constant and τ^0 .

We can thus conclude that, under the experimental conditions used, sodium ascorbate is the main quencher of the lowest triplet excited state of **1b** and we propose the catalytic mechanism depicted in Figure 3. The Bodipy photocatalyst is reduced to [Bodipy]^{•-} using sodium ascorbate as the electron donor. [Bodipy]^{•-} has a sufficiently strong reduction potential (-1 to -1.54 V vs SCE)²² to effectively convert the alkyl halides (-0.5 to -1.5 V vs SCE)^{15b} to electrophilic free radicals, that undergo addition to alkenes. The ATRA product, as suggested by Stephenson,¹⁵ can subsequently be formed via two different routes: either by propagation (path A) or by oxidation to the cation followed by nucleophilic trapping (path B). For ATRA using classical radical initiators, propagation has been shown to be an operative mechanism.⁶

The possible presence of carbenium ion as intermediates was studied by adding different nucleophiles to the reaction, such as azides or LiCl. However, in both cases no mixed products were revealed. The propagation pathway A was furthermore supported by the absence of mixed Cl/Br products obtained conducting the reaction between CCl₄ and **3a** in the presence of excess LiBr (2.5 equiv) (Scheme 4). We observed exclusively the product **4i** deriving from the chlorine addition, while Stephenson reported a mixture of Cl/Br products **4i/4i'** under his reaction conditions.¹⁵ To exclude a radical-polar crossover mechanism, an intermolecular trapping experiment in which carbon tetrachloride (2.0 equiv) and 5-hexen-1-ol were subjected to the standard reaction conditions, in the presence of excess LiBr (2.5 equiv). After 24h of irradiation no product **4i'** derived from nucleophilic trapping of a carbocation intermediate was observed supporting the propagation pathway

Consistent with the formation of a quite reactive and unstable radical anion of the Bodipy (mechanism depicted in Figure 3), the model photo-organocatalytic ATRA reaction was completely inhibited by the presence of oxygen. Even the opening of the reaction vessel under flow of inert gas to take samples for GC or HPLC analysis caused the immediate quenching of the reaction. Therefore, the experiment performed alternating 1h periods of light irradiation and

complete darkness in order to verify the presence of a radical chain mechanism did not yield any reliable information as

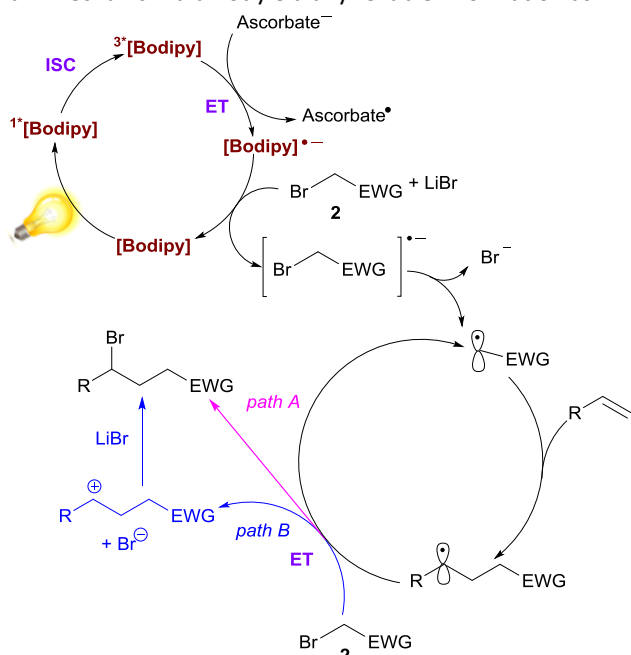
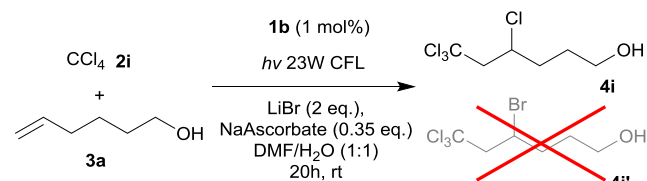


Figure 3. Proposed mechanistic pathway for the Bodipy promoted ATRA reaction.



Scheme 4. Control experiment to discriminate between the propagation reaction pathway A and the radical polar crossover pathway B.

opening of the reaction flask to quantify the consumption of alkene stopped the reaction. In addition, if the reaction is performed in the presence of catalytic or stoichiometric amount of TEMPO or bis(1,1-dimethylethyl)-4-methylphenol (BHT), no products or other adducts were detected by GC-MS analysis confirming the presence of catalytic radical intermediates.

In conclusion, we reported the successful use of Iodo-Bodipy dyes for ATRA reaction, through an oxidative quenching with a cheap and abundant sacrificial reductant. These findings are enhancing the applicability of stable and tailored Bodipy dyes in photocatalysis, opening new possibilities for their employment in other reactions. In addition, we showed that bromoalkyl pyridine salts can be used for ATRA reactions, for a direct and simple synthesis of pyridine derivatives.

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Notes and references

- a) D. A. Nicewicz and D. W. C. MacMillan, *Science* 2008, **322**, 77–80; b) A. Bauer, F. Westkämper, S. Grimme and T. Bach, *Nature*, 2005, **436**, 1139–1140; c) M. A. Ischay, Z. Lu and T. P. Yoon, *J. Am. Chem. Soc.* 2010, **132**, 8572–8574; d) J. M. R. Narayanam, J. W. Tucker and C. R. J. Stephenson, *J. Am. Chem. Soc.* 2009, **131**, 8756–8757.
- a) M. D. Karkas, B. S. Matsuura and C. R. J. Stephenson, *Science* 2015, **349**, 1285–1286; b) R. Brimiouille, D. Lenhart, M. M. Maturi and T. Bach, *Angew. Chem. Int. Ed.* 2015, **54**, 3872–3890; c) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.* 2013, **113**, 5322–5363; d) V. Balzani, G. Bergamini and P. Ceroni, *Angew. Chem. Int. Ed.* 2015, **54**, 11320–11337
- H. Huo, X. Shen, C. Wang, L. Zhang, P. Röse, L.-A. Chen, K. Harms, M. Marsch, G. Hilt and E. Meggers, *Nature* 2014, **515**, 100–103.
- P. Riente, A. Matas Adams, J. Albero, E. Palomares and M. A. Pericás, *Angew. Chem., Int. Ed.* 2014, **53**, 9613–9616.
- a) M. Cherevatskaya, M. Neumann, S. Fuldner, C. Harlander, S.; Kümmel, S. Dankesreiter, A. Pfitzner, K. Zeitler and B. König, *Angew. Chem., Int. Ed.* 2012, **51**, 4062–4066, b) S. P. Pitre, C. D. McTiernan, and J. C. Scaiano, *ACS Omega* 2016, **1**, 66–76; c) D. A. Nicewicz and T. M. Nguyen *ACS Catal.* 2014, **4**, 355–360.
- A. Studer and D. P. Curran, *Angew. Chem. Int. Ed.* 2016, **55**, 58–102.
- M. L. Marin, L. S. Juanes, A. Arques, A. M. Amat and M. A. Miranda, *Chem. Rev.* 2012, **112**, 1710–1750.
- M. A. Miranda, A. M. Amat and A. Arques, *Catal. Today* 2002, **76**, 113–117.
- S. Lin, M. A. Ischay, C. G. Fry and T. P. Yoon, *J. Am. Chem. Soc.*, 2011, **133**, 19350–19353.
- Y. Miyake, K. Nakajima and Y. Nishibayashi, *J. Am. Chem. Soc.*, 2012, **134**, 3338–3341.
- N. Adarsh, M. Shanmugasundaram, R. R. Avirah and D. Ramaiah, *Chem.–Eur. J.* 2012, **18**, 12655–12662.
- a) W. Li, L. Li, H. Xiao, R. Qi, Y. Huang, Z. Xie, X. Jing and H. Zhang, *RSC Advances* 2013, **3**, 13417–13421; b) W. Li, Z. Xie and X. Jing, *Catal. Commun.* 2011, **16**, 94–97; c) W. Li, W. Zhang, X. Dong, L. Yan, R. Qi, W. Wang, Z. Xie and X. Jing, *J. Mater. Chem.* 2012, **22**, 17445–17448.
- a) D. P. Curran, *Synthesis* 1988, 489–513 ; c) b) M. Kamigaito, T. Ando, M. Sawamoto, *Chem. Rev.* 2001, **101**, 3689–3746.
- a) M. S. Kharasch, E. V. Jensen, W. H. Urry, *Science* 1945, **102**, 128.
- a) J. D. Nguyen, J.W. Tucker, M. D. Konieczynska and C. R. J. Stephenson, *J. Am. Chem. Soc.* 2011, **133**, 4160–4163; b) C.-J. Wallentin, J. D. Nguyen, P. Finkbeiner and C. R. J. Stephenson, *J. Am. Chem. Soc.* 2012, **134**, 8875–8884.
- E. Arceo, E. Montroni and P. Melchiorre, *Angew. Chem. Int. Ed.* 2015, **52**, 12064–12068.
- The low yield in the substrate **5k** (29 %) are due the concomitant elimination. The alkene product was isolated in 18 % yields (see SI for its structure). The addition of water after the rearrangement is determined by the probable generation of a carbenium ion in the aqueous condition. See SI for full characterization and NMR data for structural assignments for **5k**.
- L. Huang, J. Zhao, S. Guo, C. Zhang, and J. Ma, *J. Org. Chem.* 2013, **78**, 5627–5637.
- X.-F. Zhang, X. Yang, K. Niu and H. Geng, *J. Photochem. Photobiol. A: Chemistry* 2014, **285**, 16–20.
- J. Zhao, K. Xu, W. Yang, Z. Wang and F. Zhong, *Chem. Soc. Rev.* 2015, **44**, 8904–8939.
- Photochemistry and Photophysics: Concepts, Research, Applications*, V. Balzani, P. Ceroni, A. Juris, Wiley-VCH, 2014
- L. Huang, W. Yang, and J. Zhao. *J. Org. Chem.* 2014, **79**, 10240–10255.