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Exploration of a KI-catalyzed oxidation system for direct construction of bispyrrolidino[2,3-*b*]indolines and the total synthesis of (+)-WIN 64821†

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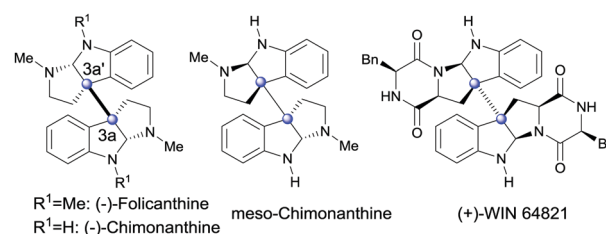
A facile and environmentally benign KI(cat.)/NaBO₃·4H₂O oxidation system has been developed for the tandem oxidative aminocyclization/coupling of tryptamines, affording a series of 3*a*,3*a'*-bispyrrolidino[2,3-*b*]indolines with high efficiency (up to 94% yield). This reaction features an electrophilic “I⁺” mechanism, which is importantly quite different from and milder than the typical radical-involving process, and can be readily amplified for the total synthesis of (+)-WIN 64821.

Oxidation is one of the most important transformations for organisms to produce functional molecules. *In vivo*, the oxidation of tryptophan or tryptamine can result in a big family of structurally complex and biologically important 3*a*,3*a'*-bispyrrolidino[2,3-*b*]indoline alkaloids (Fig. 1), which show antifungal, antiviral and cytostatic activities.¹ Despite its significance for biological and medicinal chemistry, realizing this biotransformation by means of organic chemistry, especially with a catalytic amount of assistant oxidation reagent, is still rare and synthetically challenging.² To date, several groups have devoted much pioneering effort to this aspect.^{3,4} However, most of the current solutions require either equivalent amounts of transition metals or excess of strong acid or base. Furthermore, these methodologies generally give insufficient yields. Therefore, the development of a catalytic and transition-metal-free oxidative system for the efficient synthesis of 3*a*,3*a'*-bispyrrolidino[2,3-*b*]indolines under mild condition is in demand.

During the past fifteen years, the iodide-catalyzed oxidative reaction has received widespread attention because of its versatile reactivity and environmentally benign property.^{5,6} In general, however, these systems are mostly limited to the application of

synthesis of relatively simple organic compounds, and only a few can give access to sterically complex frameworks, such as those with the vicinal all-carbon quaternary centers.⁷ As indicated in Scheme 1, the oxidation systems mediated by a catalytic amount of iodide have not been expanded to effect the tandem coupling/cyclizations of tryptamine or tryptophan to construct the more complex 3*a*,3*a'*-bispyrrolidino[2,3-*b*]indoline **6**, **8** and **11** with vicinal all-carbon quaternary centers. Instead, they are only applicable to mediate the simple cyclization to produce the monomer products **1–4** (Scheme 1(a)).⁸ Due to our continuing interest in the synthesis of 3*a*,3*a'*-bispyrrolidino[2,3-*b*]indoline alkaloids,⁹ we thus try to develop an alternative effective iodide-catalyzed oxidative system, which we expect will enable the coupling/cyclizations as shown in Scheme 1(b). Herein, we describe our research results.

To achieve the hypothesis above, our initial optimization started toward the oxidation of tryptamine **5a** with screening the oxidants and solvents using KI as a catalyst (Table 1). Fortunately, after testing H₂O₂ in several solvents, only TFE (trifluoroethanol) could generate the desired dimeric products (**6a** and **6a'**) with a moderate 44% yield (entry 5), while the other solvents gave inferior results (entries 1–4). Subsequently, both organic (entries 6 and 7) and inorganic oxidants were screened (entries 8 and 9), among which, NaBO₃·4H₂O gave the best yield (64%, entry 9). In addition, other conditions which involved varying the iodide catalysts, additives, concentrations and component equivalents were widely investigated,¹⁰ with the conditions in entry 10 giving the best result (68% yield).

Fig. 1 Representative bispyrrolidino[2,3-*b*]indoline alkaloids.

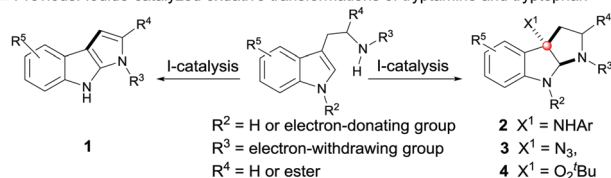
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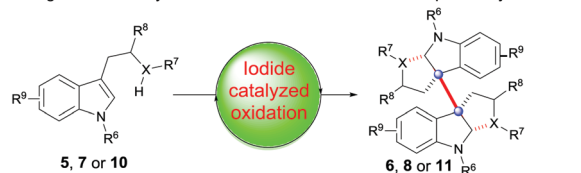
† Electronic supplementary information (ESI) available. CCDC 1940250. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc08646c

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a. Previous: Iodide-catalyzed oxidative transformations of tryptamine and tryptophan



b. Our design: Iodide-catalyzed construction of vicinal all-carbon quaternary architecture



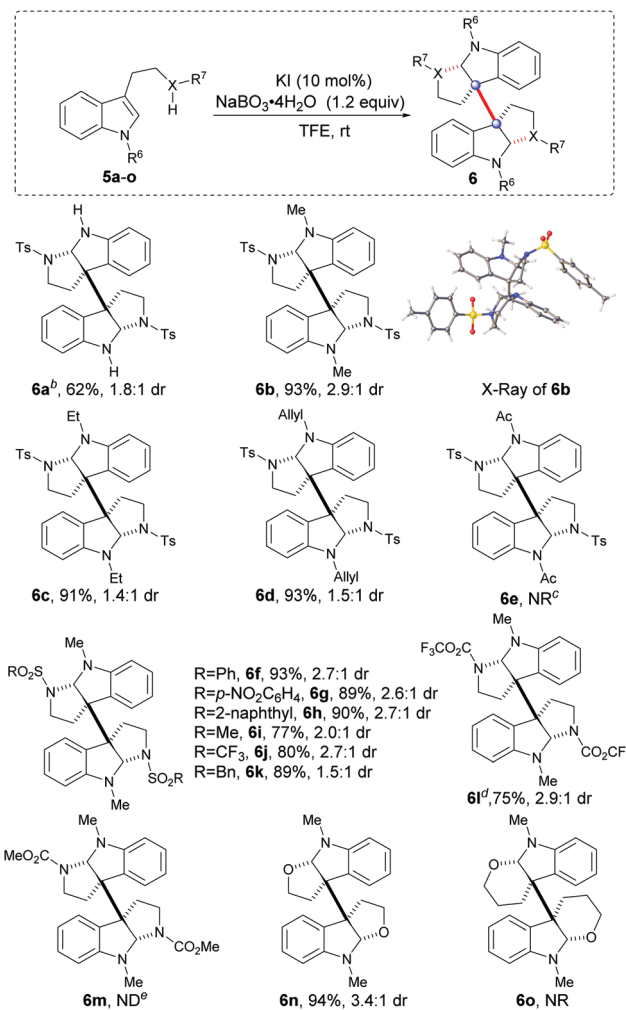
Scheme 1 (a) Previous I-catalyzed oxidation of tryptamine or tryptophan; (b) our design.

Table 1 Optimization of the conditions for the iodide-catalyzed oxidative dimerization of tryptamine^a

Entry	Solvent	Oxidant	Time	Yield ^b (%)
1	CH ₃ CN	H ₂ O ₂ ^c	24 h	NR ^d
2	Toluene	H ₂ O ₂	24 h	NR
3	THF	H ₂ O ₂	24 h	NR
4	CH ₂ Cl ₂	H ₂ O ₂	24 h	NR
5	TFE	H ₂ O ₂	4 h	44
6	TFE	^t BuO ₂ H ^e	10 h	53
7	TFE	<i>m</i> -CPBA	10 min	ND ^f
8	TFE	O ₂ ^g	24 h	NR
9	TFE	NaBO ₃ ·4H ₂ O	1.5 h	64
10 ^h	TFE	NaBO ₃ ·4H ₂ O	2 h	68

^a Unless otherwise noted, reactions were carried out with **5a** (0.2 mmol), KI (20 mol%) and oxidant (2.0 equiv.) in 2 mL solvent. The dr was 1.8:1 determined by ¹H NMR. ^b Determined by ¹H NMR. ^c 50 wt% in water. ^d No reaction was observed. ^e 5.5 M in decane. ^f Not detected. ^g 1 atm. ^h Reaction was carried out with **5a** (0.2 mmol), KI (10 mol%) and NaBO₃·4H₂O (1.2 equiv.) in 2 mL TFE.

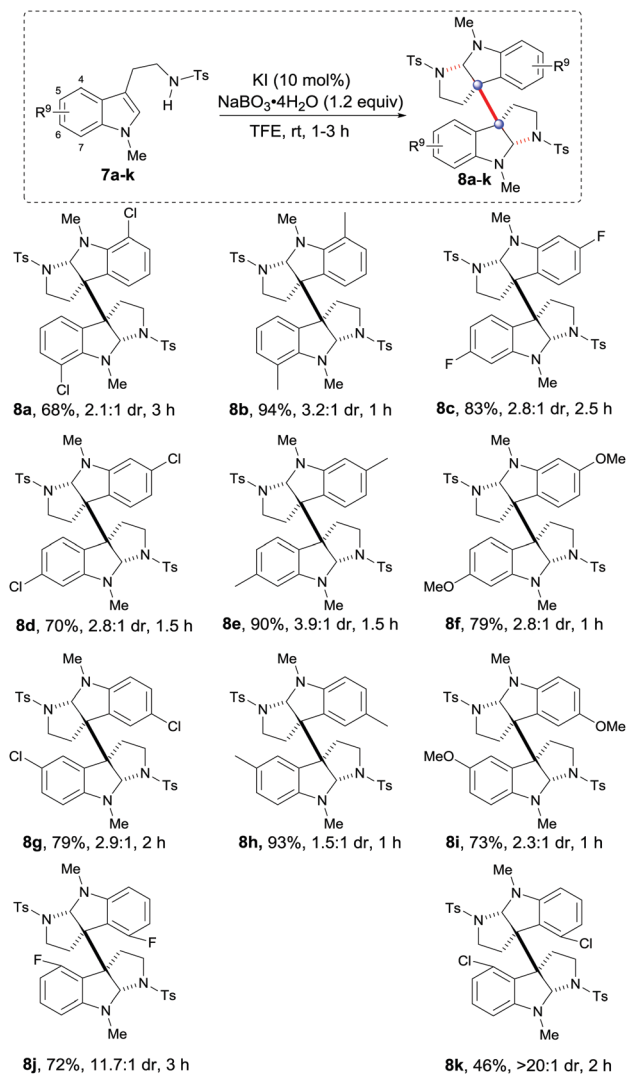
With the optimal catalytic oxidative system in hand, we then expanded the tryptamine substrate scope by varying the substituents R⁶ and X-R⁷ (Table 2, **5a–m**). Initially, when X-R⁷ was selected as *N*-tosyl, varying the substituents R⁶ (**5b–d**) with the EDGs (electron-donating groups, e.g., methyl, ethyl and allyl) generally led to excellent reaction results (**6b–d**, 91–93% yields, 1.4:1 to 2.9:1 dr), while the EWG (electron-withdrawing group, e.g., Ac) substituted substrate (**5e**) remained inactive to give product **6e**. Subsequently, when the optimal methyl was selected as R⁶ (as indicated in **6f–l**), varying substitution of R⁷ (X = N) with the strong EWG sulfonyl (**5f–k**) and trifluoroacetyl (**5l**) could drive the reactions with satisfactory results (**6f–l**, 75–93% yields, 1.5:1 to 2.9:1 dr). Exceptionally, when a carbamate was introduced to tryptamine (**5m**, X-R⁷ = *N*-CO₂Me), the reaction could not give the desired product **6m**, but gave a complex mixture

Table 2 Investigation of R⁶ and X-R⁷ of tryptamines for oxidative dimerization^a

^a Unless otherwise noted, all reactions were carried out with **5** (0.2 mmol), KI (10 mol%) and NaBO₃·4H₂O (1.2 equiv.) in 2 mL TFE and reacted for 1 h. Isolated yields and dr were determined by ¹H NMR. ^b Reacted for 2 h. ^c No reaction was observed after 24 h. ^d Reacted for 3 h. ^e Not detected.

accompanied by a partial starting material. It was also important that when tryptophol **5n** and 3-indolepropanol **5o** were separately subjected to the catalytic oxidative systems, interestingly, the former could react efficiently to give the tetrahydrofuran **6n** with an excellent yield of 94%, while the latter gave a mixture without hexahydropyran **6o** detected.

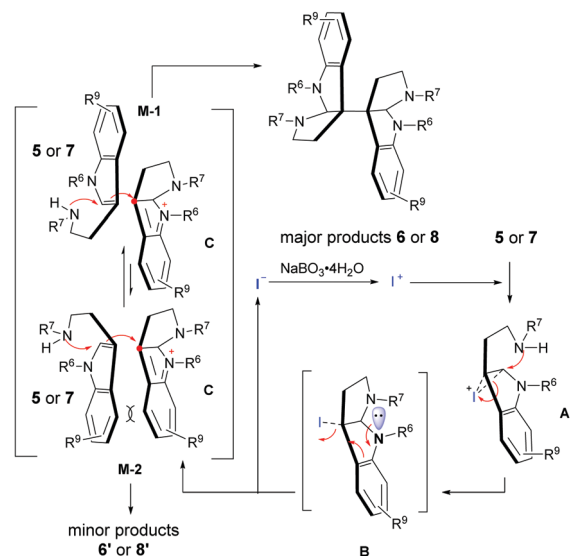
Next, a wide range of tryptamines with different substituents on the benzene rings were tested. As shown in Table 3, both EWG and EDG substituents at C₇, C₆ and C₅ of the benzene rings were effective for the expected oxidative dimerization reactions and generally gave satisfactory results (**8a–i**, 68–94% yield, 1.5:1 to 3.9:1 dr). The differences of these examples in the reaction time revealed that the EDG substituents were more favorable for reaction rates than the EWGs (**8f**, **8i** vs. **8a**, **8c**, **8j**, and **8k**). Notably, the C₄-F and C₄-Cl substituted tryptamines **7j** and **7k** could give **8j** and **8k** with excellent diastereoselectivities (11.7:1 and >20:1 dr)

Table 3 Investigation of benzene ring substituted tryptamines for oxidative dimerization^a

^a Unless otherwise noted, all reactions were carried out with **5** (0.2 mmol), KI (10 mol%) and NaBO₃·4H₂O (1.2 equiv.) in 2 mL TFE and reacted for 1 h. Isolated yields and dr were determined by ¹H NMR.

and acceptable yields (72% and 46%), probably due to the steric interaction between F or Cl and C_{3a} or C_{3a'}.

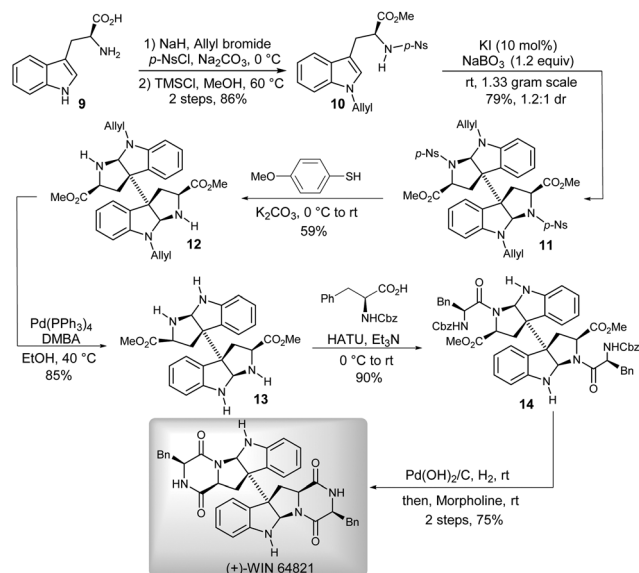
In order to elucidate the mechanism of this catalytic oxidative coupling/cyclization reaction, we also conducted some additional control experiments (Scheme S1, ESI[†]).¹⁰ According to the experimental results, addition of the radical scavengers such as TEMPO (2,2,6,6-tetramethylpiperidinoxy) or DMPO (5,5-dimethyl-1-pyrroline *N*-oxide) was found to have little influence on the reaction, while use of the electrophilic iodide reagent NIS (*N*-iodosuccinimide) could efficiently promote the desired reaction with similar results (77% yield, 2.8:1 dr) compared to the standard reaction (Table 2, **6b**). Therefore, an electrophilic "I⁺" mechanism (Scheme 2) rather than the classical radical process was proposed.^{6f} As shown in Scheme 2, the reaction would begin with the oxidation of "I[−]"; thereafter, the resulting electrophilic "I⁺" species could readily interact with the nucleophilic tryptamine (**5** or **7**) to form a cyclic iodonium

**Scheme 2** The plausible mechanism.

ion intermediate **A**.^{3g,8b,11} Subsequently, the active intermediate **A** underwent an intramolecular cyclization to generate the 3-iodohexahydropyrroloindole compound **B**, which was then transferred to indolium **C** and released iodide for further catalytic cycles. Finally, the indolium **C** could couple with another tryptamine (**5** or **7**) through an electrophilic addition/cyclization process *via* either favorable model **M-1** or a sterically hindered model **M-2** to give the major product **6** or **8** and the minor one **6'** or **8'**, respectively. It is worth noting that this stereo-control model was also consistent with the diastereoselectivities obtained from our reactions.¹⁰

To verify the utility of this methodology, the pharmacologically promising agent (+)-WIN 64821 was chosen as a synthetic target (Scheme 3).¹² The efficient construction of the 3*a*,3*a'*-bispyrrolidino[2,3-*b*]indoline motif was the key to approach a concise total synthesis of (+)-WIN 64821. That could be conveniently realized by using our newly developed catalytic oxidative methodology. Initially, we synthesized the precursor **10** for the key reaction from commercially available (*L*)-tryptophan **9**. Then, compound **10** was successfully applied, at the gram-scale, to the KI-catalyzed oxidative coupling/cyclization reaction to give the 3*a*,3*a'*-bispyrrolidino[2,3-*b*]indoline **11** with satisfactory results (79% yield, 1.2:1 dr). Subsequent deprotections of *p*-nitrobenzene sulfonyl and allyl of **11** successively afforded the dimeric diamine **13**, which could be easily condensed with *N*-Cbz-*L*-phenylalanine over three steps^{4d,13} to finally give (+)-WIN 64821.

In conclusion, we have successfully established an iodide-catalyzed oxidative coupling/cyclization approach for the dimerization of tryptamine, tryptophol and tryptophan analogues. This protocol features a plausible catalytic cycle comprising iodide and hypoiodite catalyst states, the use of inexpensive and readily available as well as an environmentally benign system (KI and NaBO₃·4H₂O) and mild reaction conditions. Particularly, it provides a practical solution for the construction of synthetically challenging vicinal all-carbon quaternary motifs. Although it gives moderate diastereoselectivities in some cases, we have optimized it up to



Scheme 3 Asymmetric total synthesis of (+)-WIN 64821.

>20:1 dr by adjusting the substituent at C₄ of the substrate. Furthermore, the synthetic utility of this methodology has been verified by the asymmetric total synthesis of bioactive natural product (+)-WIN 64821.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- P. Ruiz-Sanchis, S. A. Savina, F. Albericio and M. Álvarez, *Chem. – Eur. J.*, 2011, **17**, 1388–1408.
- For reviews of synthesis, see: (a) A. Steven and L. E. Overman, *Angew. Chem., Int. Ed.*, 2007, **46**, 5488–5508; (b) M. A. Schmidt and M. Movassaghi, *Synlett*, 2008, 313–324; (c) J. Kim and M. Movassaghi, *Chem. Soc. Rev.*, 2009, **38**, 3035–3050; (d) L. M. Repka and S. E. Reisman, *J. Org. Chem.*, 2013, **78**, 12314–12320; (e) J. Kim and M. Movassaghi, *Acc. Chem. Res.*, 2015, **48**, 1159–1171; (f) J. Song, D.-F. Chen and L.-Z. Gong, *Natl. Sci. Rev.*, 2017, **4**, 381–396.
- For representative pioneer examples, see: (a) A. I. Scott, F. McCapra and E. S. Hall, *J. Am. Chem. Soc.*, 1964, **86**, 302–303; (b) T. Hino, S. Kodato, K. Takahashi, H. Yamaguchi and M. Nakagawa, *Tetrahedron Lett.*, 1978, **19**, 4913–4916; (c) H. Ishikawa, H. Takayama and N. Aimi, *Tetrahedron Lett.*, 2002, **43**, 5637–5639; (d) T. Newhouse and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 10886–10887; (e) M. Movassaghi and M. A. Schmidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 3725–3728; (f) J. Kim and M. Movassaghi, *J. Am. Chem. Soc.*, 2010, **132**, 14376–14378; (g) Y.-X. Li, H.-X. Wang, S. Ali, X.-F. Xia and Y.-M. Liang, *Chem. Commun.*, 2012, **48**, 2343–2345; (h) S. Tadano, Y. Mukaeda and H. Ishikawa, *Angew. Chem., Int. Ed.*, 2013, **52**, 7990–7994.
- For recent progress, see: (a) M. Tayu, K. Higuchi, T. Ishizaki and T. Kawasaki, *Org. Lett.*, 2014, **16**, 3613–3615; (b) D. Sun, C. Xing, X. Wang, Z. Su and C. Li, *Org. Chem. Front.*, 2014, **1**, 956–960; (c) M. Ding, K. Liang, R. Pan, H. Zhang and C. Xia, *J. Org. Chem.*, 2015, **80**, 10309–10316; (d) K. Liang, X. Deng, X. Tong, D. Li, M. Ding, A. Zhou and C. Xia, *Org. Lett.*, 2015, **17**, 206–209; (e) M. Tayu, Y. Suzuki, K. Higuchi and T. Kawasaki, *Synlett*, 2016, 941–945; (f) S. Tadano, Y. Sugimachi, M. Sumimoto, S. Tsukamoto and H. Ishikawa, *Chem. – Eur. J.*, 2016, **22**, 1277–1291.
- For representative pioneer examples, see: (a) T. Dohi, A. Maruyama, M. Yoshimura, K. Morimoto, H. Tohma and Y. Kita, *Angew. Chem., Int. Ed.*, 2005, **44**, 6193–6196; (b) M. Ochiai, Y. Takeuchi, T. Katayama, T. Sueda and K. Miyamoto, *J. Am. Chem. Soc.*, 2005, **127**, 12244–12245; (c) R. D. Richardson, T. K. Page, S. Altermann, S. M. Paradine, A. N. French and T. Wirth, *Synlett*, 2007, 538–542; (d) T. Dohi, A. Maruyama, N. Takenaga, K. Senami, Y. Minamitsuji, H. Fujioka, S. B. Caemmerer and Y. Kita, *Angew. Chem., Int. Ed.*, 2008, **47**, 3787–3790; (e) M. Uyanik, M. Akakura and K. Ishihara, *J. Am. Chem. Soc.*, 2009, **131**, 251–262; (f) K. Miyamoto, Y. Sei, K. Yamaguchi and M. Ochiai, *J. Am. Chem. Soc.*, 2009, **131**, 1382–1383; (g) M. Uyanik, H. Okamoto, T. Yasui and K. Ishihara, *Science*, 2010, **328**, 1376–1379; (h) M. Uyanik, T. Yasui and K. Ishihara, *Angew. Chem., Int. Ed.*, 2010, **49**, 2175–2177; (i) J. Zhang, D. Zhu, C. Yu, C. Wan and Z. Wang, *Org. Lett.*, 2010, **12**, 2841–2843.
- For selected reviews, see: (a) M. Uyanik and K. Ishihara, *ChemCatChem*, 2012, **4**, 177–185; (b) P. Finkbeiner and B. J. Nachtsheim, *Synthesis*, 2013, 979–999; (c) F. V. Singh and T. Wirth, *Chem. – Asian. J.*, 2014, **9**, 950–971; (d) X.-F. Wu, J.-L. Gong and X. Qi, *Org. Biomol. Chem.*, 2014, **12**, 5807–5817; (e) F. Berthiol, *Synthesis*, 2015, 587–603; (f) D. Liu and A. Lei, *Chem. – Asian. J.*, 2015, **10**, 806–823; (g) M. S. Yusubov and V. V. Zhdankin, *Resour.-Effic. Technol.*, 2015, **1**, 49–67; (h) A. Yoshimura and V. V. Zhdankin, *Chem. Rev.*, 2016, **116**, 3328–3435; (i) R. Chen, J. Chen, J. Zhang and X. Wan, *Chem. Rec.*, 2018, **18**, 1292–1305; (j) A. Claraz and G. Masson, *Org. Biomol. Chem.*, 2018, **16**, 5386–5402; (k) A. Flores, E. Cots, J. Bergès and K. Muñoz, *Adv. Synth. Catal.*, 2019, **361**, 2–25.
- For selected examples, see: (a) M. Uyanik, T. Yasui and K. Ishihara, *Angew. Chem., Int. Ed.*, 2013, **52**, 9215–9218; (b) M. Ngatimin, R. Frey, A. Levens, Y. Nakano, M. Kowalczyk, K. Konstas, O. E. Hutt and D. W. Lupton, *Org. Lett.*, 2013, **15**, 5858–5861; (c) H. Wu, Y.-P. He, L. Xu, D.-Y. Zhang and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2014, **53**, 3466–3469; (d) B. Liu, J. Cheng, Y. Li and J.-H. Li, *Chem. Commun.*, 2019, **55**, 667–670.
- (a) Z.-J. Cai, S.-Y. Wang and S.-J. Ji, *Org. Lett.*, 2013, **15**, 5226–5229; (b) Z.-Y. Yang, T. Tian, Y.-F. Du, S.-Y. Li, C.-C. Chu, L.-Y. Chen, D. Li, J.-Y. Liu and B. Wang, *Chem. Commun.*, 2017, **53**, 8050–8053; (c) J. Guo, S. Chen, J. Liu, J. Guo, W. Chen, Q. Cai, P. Liu and P. Sun, *Eur. J. Org. Chem.*, 2017, 4773–4777; (d) X. Lu, Y. Bai, Y. Li, Y. Shi, L. Li, Y. Wu and F. Zhong, *Org. Lett.*, 2018, **20**, 7937–7941; (e) Y. Li, L. Li, X. Lu, Y. Bai, Y. Wang, Y. Wu and F. Zhong, *Chem. Commun.*, 2019, **55**, 63–66.
- S.-K. Chen, W.-Q. Ma, Z.-B. Yan, F.-M. Zhang, S.-H. Wang, Y.-Q. Tu, X.-M. Zhang and J.-M. Tian, *J. Am. Chem. Soc.*, 2018, **140**, 10099–10103.
- For details, see ESI†.
- (a) D. Beukeaw, K. Udomsasporn and S. Yotphan, *J. Org. Chem.*, 2015, **80**, 3447–3454; (b) J. Dhineshkumar, K. Gadde and K. R. Prabhu, *J. Org. Chem.*, 2018, **83**, 228–235.
- (a) C. J. Barrow, P. Cai, J. K. Snyder, D. M. Sedlock, H. H. Sun and R. Cooper, *J. Org. Chem.*, 1993, **58**, 6016–6021; (b) M. Wada, H. Suzuki, M. Kato, H. Oikawa, A. Tsubouchi and H. Oguri, *ChemBioChem*, 2019, **20**, 1273–1281.
- C. Pérez-Balado and Á. R. de Lera, *Org. Lett.*, 2008, **10**, 3701–3704.