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Hypervalent iodine-promoted twofold oxidative coupling of amines with amides and thioamides: Chemoselective entryway to oxazoles and thiazoles†

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Direct functionalization of the C(O)–N amide bond is one of the most high-profile research directions in the last decades, however oxidative couplings involving amide bonds and functionalization of thioamide C(S)–N analogues remain an unsolved challenge. Herein, a novel hypervalent iodine-induced twofold oxidative coupling of amines with amides and thioamides has been established. The protocol accomplishes divergent C(O)–N and C(S)–N disconnection by the previously unknown Ar–O and Ar–S oxidative coupling and highly chemoselectively assembles the versatile yet synthetically challenging oxazoles and thiazoles. Employing amides instead of thioamides affords an alternative bond cleavage pattern, which is a result of the higher $n_N{\rightarrow}\pi^*_{C=S}$ conjugation in thioamides. Mechanistic investigations indicate ureas and thioureas generated in the first oxidation as pivotal intermediates to realize the oxidative coupling. These findings open up new vistas for exploring oxidative amide and thioamide bond chemistry in various synthetic contexts.

Introduction

The amide bond undoubtedly belongs to one of the most inert chemical bonds owing to the intramolecular $n_N{\rightarrow}\pi^*_{C=O}$ conjugation and high resonance stabilization (Scheme 1a, left).[1] Notwithstanding that the amide bond is well-recognized as the most stable carboxylic acid derivative, the highly selective C(O)–N activation of amides that enables to sequentially perform chemical operations has invoked a great attention in organic synthesis over the past decades (Scheme 1a, right).[2] This is mostly due to the ubiquitous presence of amide bond in biochemistry, pharmaceuticals, diverse bulk and fine chemicals as well as its versatility in synthetic settings.[3] Indeed, amide bond activation has been experiencing a major progress by means of carefully controlled steric repulsion, conformational restriction and electronic effects to successfully activate N–C(O) bond by ground-state-destabilization of amidic resonance (Scheme 1b, left).[4-7] This mode of activation broadly relies upon disrupting $n_N{\rightarrow}\pi^*_{C=O}$ conjugation to increase negative charge at the nitrogen atom, while this mode should be contrasted with the tremendously important field of electrophilic activation of amides.[4] The current well-developed reaction types are predominantly restricted to sterically twisted amides[8] or electronically activated amides[9] featuring electron-withdrawing groups (EWGs) that facilitate acyl addition or oxidative addition of the C(O)–N bond to a low-valent metal. Comparatively, formamides are much more broadly available than such activated amides, however, there are few examples of the site-specific C(O)–N activation of non-activated formamides (Scheme 1b, right).[10]

Formamides characterized by planarity and featuring electron-donating groups (EDGs) are not amenable to the ground-state-destabilization pathway. The present amide bond activation has been most successful using metal-catalyzed coupling and only implemented to generate architecturally linear molecules by single bond formation thus far.[11]

Thioamides, the closest O to S isosteres of amides in the strictest sense, have served as highly valuable motifs to accomplish synthetic processes.[12] With respect to the structural and electronic characteristics, thioamides feature a shorter C=S bond than the analogous C=O bond in amides. The weaker electronegativity of sulfur and the higher $n_N{\rightarrow}\pi^*_{C=S}$ conjugation render the higher contribution of the polar resonance form. This results in a stronger C(S)–N bond in thioamides, which together with potential side-reactions, such as desulfurization, electrophilic addition, and cyclization, poses a major challenge to chemoselectively cleave the C(S)–N bond (Scheme 1c).[13] Indeed, studies on activation of twisted thioamide bonds are exceedingly scarce, and chemoselective C(S)–N bond activation of non-twisted and non-electronically activated thioamides has not been documented to date.

In continuation of our long-standing interest to discover new modes of activation of amide bonds,[7] herein, we disclose our findings on novel hypervalent iodine-induced twofold oxidative coupling of amines with amides and thioamides (Scheme 1d-e). Of note, the protocol accomplishes divergent C(O)–N and C(S)–N disconnection by the previously unknown Ar–O and Ar–S oxidative coupling. The method represents the first example of combining the inert C(O)–N/C(S)–N coupling with C–H functionalization in a single operation, providing a powerful platform to assemble the versatile yet synthetically challenging oxazoles and thiazoles that are common in pharmaceuticals and agrochemicals[14] but currently lack a practical synthetic route.[15] Employing amides instead of thioamides affords an alternative bond cleavage pattern, which is a result of the higher $n_N{\rightarrow}\pi^*_{C=S}$ conjugation in thioamides, furnishing C2–NR2-substituted benzoxazoles (Scheme 1f).[16] This oxidative pathway outperforms the current dominant

tactic of decorating benzoxazole scaffold (Scheme 1g).[17] Overall, these findings open up new vistas for exploring oxidative amide and thioamide bond chemistry in various synthetic contexts.
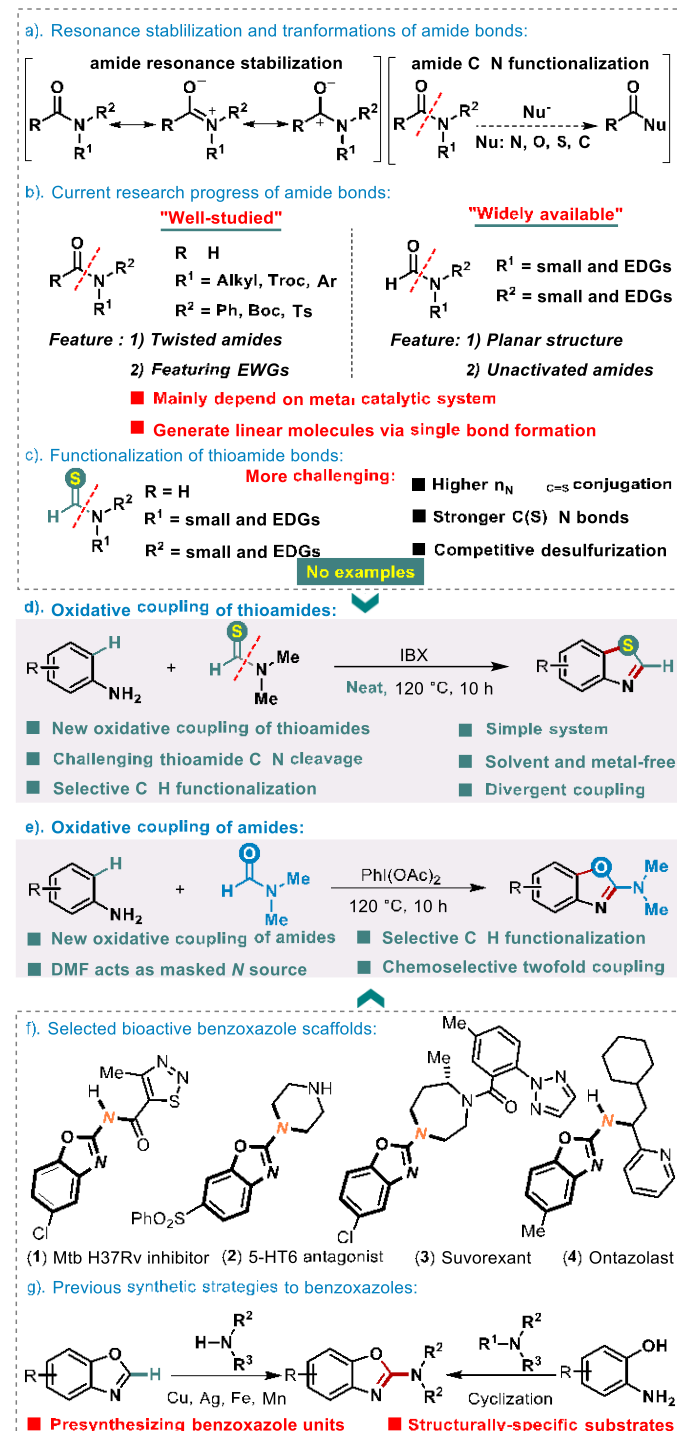
Scheme 1 Amide functionalization and context of this work.

Results and discussion

Initially, we explored the reactivity of commercially available *N*,*N*-dimethylthioamide **2** with β-naphthylamine **1a** (Table 1). After comprehensive screening of reaction

parameters, we were delighted to find that upon treatment with 2-iodoxybenzoic acid (IBX) as an oxidant, these two substrates underwent a formal [3+2] cyclization to produce thiazole derivative **3a** in 70% yield under metal-free and solvent-free conditions (entry 1). The reaction accomplished a series of C(S)–N/C–H cleavages and C–N/C–S bond forming events. Control experiments showed that IBX played an indispensable role in simultaneously realizing this novel C(S)–N thioamide conversion with thiazole ring formation in a single operation (entry 2). Other broadly utilized high-valent I^{3+} oxidants, such as PIDA, PIFA or PhIO, were all feasible but afforded lower yields (entries 3-5). Changes in the reaction temperature (110 °C) or reaction atmosphere were detrimental (entries 6-7). Decreasing the amount of IBX or **2** afforded inferior results (entries 8-9). Interestingly, employing solvents adversely affected the reaction (entries 10-12). It is noteworthy that solvent-free reactions have recently attracted increasing attention due to low-cost and green chemistry considerations.[18] Most notably, during the screening of all reaction parameters, the side-product **3a'** was not observed, indicating a highly efficient oxidative C(S)–N bond cleavage through breaking $n_N \rightarrow \pi^*_{C=S}$ resonance.

Table 1. Optimization of reaction conditions.[a]

Entry	Variations from the standard conditions	Yield of 3a[b] (%)
1	None	70
2	Without IBX	0
3	PIDA instead of IBX	23
4	PIFA instead of IBX	12
5	PhIO instead of IBX	10
6	At 110 °C	34
7	O$_2$ atmosphere	40
8	Reducing loading of IBX to 1.0 equiv	52
9	Reducing loading of 2 to 2.0 equiv	45
10	In DCE (0.25 M)	17
11	In 1,4-Dioxane (0.25 M)	nd
12	In DMSO (0.25 M)	26

[a]Performed on 0.20 mmol scale. [b]Isolated yields. PIDA = phenyliodine(III) diacetate, PIFA = phenyliodine(III) bis(trifluoroacetate), PhIO = iodosylbenzene
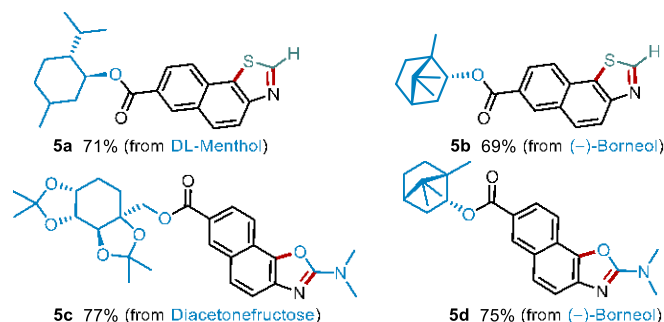
Having identified optimal reaction parameters, we next sought to evaluate the substrate scope of this novel transformation by coupling various naphthylamines with *N*,*N*-dimethylthioformamide **2** (Table 2A). As depicted in Table 2A, a range of 2-naphthylamines reacted smoothly with full regioselectivity at the *α*-site of amine substrates, delivering thiazoles **3a-s** in good yields. The electronically-distinct substituents at 6- and 7-positions, such as methyl (**3b**), methoxy (**3c**, **3h**), methoxycarbonyl (**3d**), cyclopropyl (**3e**), bromo (**3f**, **3g**), furyl (**3i**), thienyl (**3j**), thianthrenyl (**3k**), and a series of diverse-substituted arene systems (**3l-3p**) moieties, all proved to be competent substrates. The structure of **3b** was unambiguously assigned by x-ray single crystallography. Notably, the high-value but usually challenging in oxidative

Table 2. Substrate scope of synthesizing thiazoles and oxazoles.
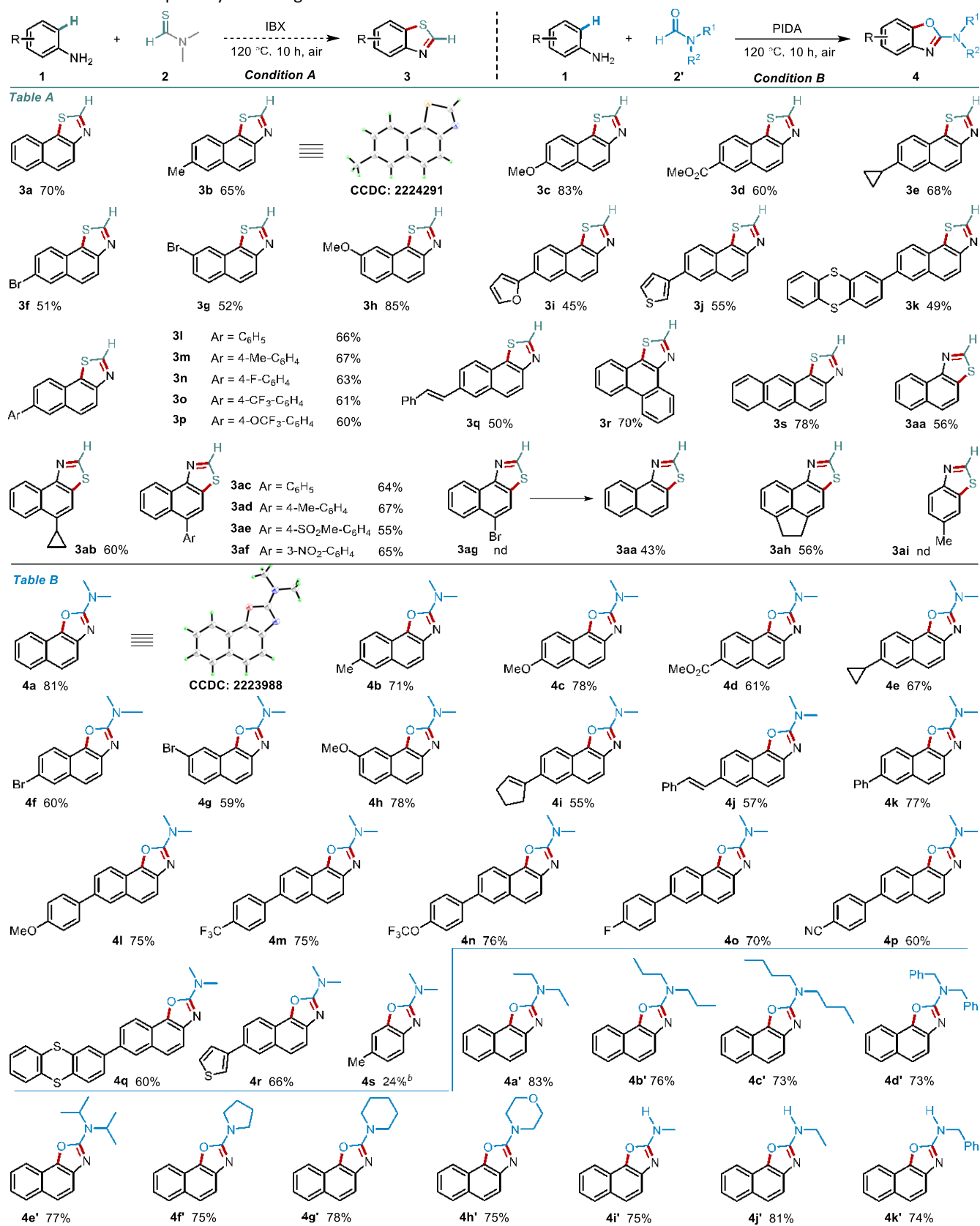
Condition A: Amine **1** (0.2 mmol), thioamide **2** (1.0 mmol), IBX (0.3 mmol), 120 °C, 10 h, air.

Condition B: Amine **1** (0.2 mmol), amide **2'** (5.0 mmol), PIDA (0.4 mmol), 120 °C, 10 h, air; [b]PIFA instead of PIDA.

coupling alkenyl (**3q**) group was retained intact under these conditions, thus providing a versatile handle for downstream modification. Likewise, π-electron-rich phenanthryl- and anthryl-derived thiazoles (**3r-3s**) were equally compatible and prepared in 70% and 78% yields, respectively. Furthermore, the use of 1-naphthylamine to engage in this protocol also furnished the target molecule **3aa** in 56% yield. The naphthyl ring could be diversely decorated with cyclopropyl (**3ab**) or aromatics substituted with alkyl (**3ad**), sulfuryl (**3ae**), or nitro (**3af**) groups. It should be noted that 4-bromo-1-naphthylamine was not tolerated, but delivered the debrominated product **3aa**. However, the readily oxidized dihydro-acenaphthylene unit was well-compatible and generated product **3ah** in 56% yield. At present stage, the reaction is not compatible with simple anilines (**3ai**) probably because of the more stable aromaticity of that than naphthylamines.

We next employed *N,N*-dimethylformamide (DMF) as the structurally closest analog of *N,N*-dimethylthioformamide to participate in this novel methodology (Table 2B). To our surprise, reacting 2-naphthylamine **1a** with DMF resulted in the formation of NMe$_2$-substituted naphthyl-fused oxazole **4a**, wherein the alternative bond cleavage pattern occurred chemoselectively. Considering the unique selectivity with DMF to accomplish the synthesis of 2-amino-substituted benzoxazoles by oxidative coupling, we optimized the reaction conditions (details in ESI). By slightly tuning the conditions by replacing IBX with PIDA, the target **4a** was isolated in 81% yield, and its structure was unambiguously confirmed by x-ray crystallography.

With the optimized conditions in hand, the scope of this benzoxazole formation was investigated (Table 2B). As shown, various naphthylamine counterparts were amenable to this divergent reaction. Specifically, a collection of functionalized naphthylamines, encompassing methyl, methoxy, ester, cyclopropyl, and bromo groups, were subjected to this oxidative process to afford the expected products **4b-4h** in 59-81% yields. Importantly, in this variant by-products resulting from C–N dissociation were not observed, indicating the key difference between n$_N$→π*$_{C=O}$ and n$_N$→π*$_{C=S}$ conjugation resonance under oxidative conditions (vide infra). Strikingly, the sensitive vinyl fragment (**4i-4j**) was well-compatible. An array of electronically-distinct aryl systems (**4k-4p**) and even heterocycles (**4q-4r**) were also feasible while the simple amine behaved unsatisfactory (**4s**). In addition, the substrate scope of amides was subsequently assessed. The results showed that linear (**4a'-4d'**), sterically-bulky (**4e'**), and cyclic (**4f'-4h'**) tertiary amides all underwent smooth cyclization. Notably, this reaction could also be extended to secondary amides, thus resulting in the corresponding NH-secondary amine-tethered heterocycles (**4i'-4k'**) with high value in organic synthesis.

Next, we evaluated further functionalization of several pharmaceutical synthons by these two protocols (Scheme 2). Thus, DL-Menthol and (−)-Borneol derivatives could be easily converted into the corresponding thiazoles **5a** and **5b** in high yields. Likewise, the industrially-important diacetone-β-fructose (DAF) and (−)-Borneol synthons also performed well in this transformation to synthesize value-added oxazoles **5c** and **5d** in 77% and 75% yields.
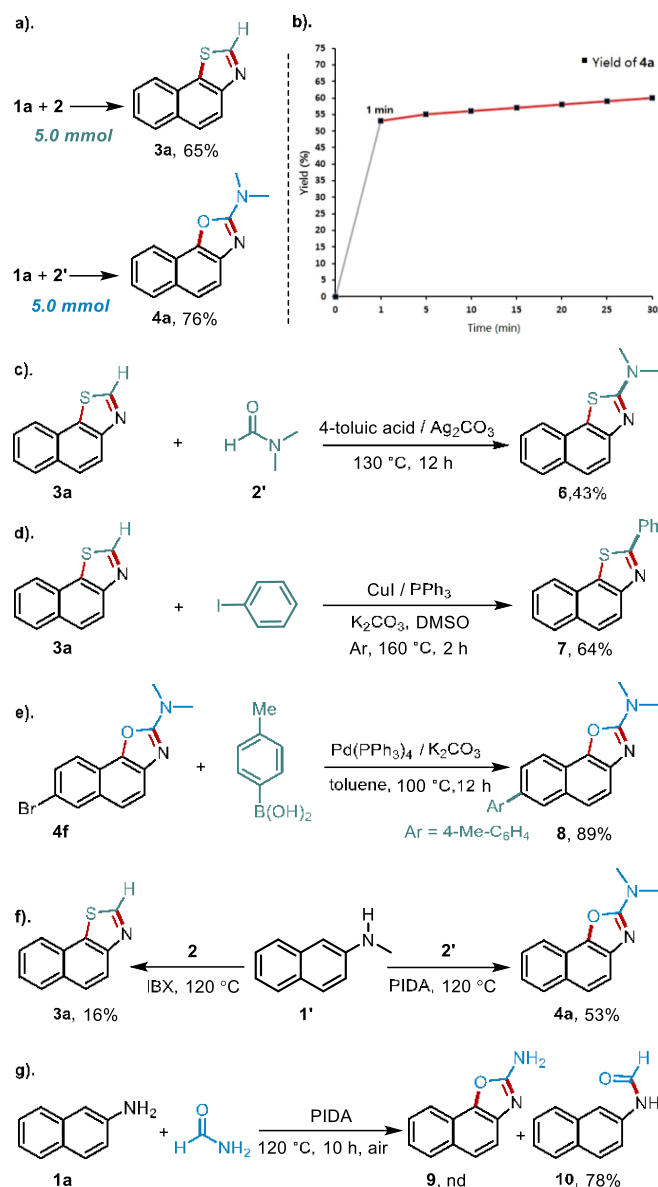
Scheme 3. Applicability of the oxidative methodology.

To showcase the versatility and synthetical value of this new methodology, additional experiments were next conducted. First, scaling-up these two reactions to 5.0 mmol proved to be readily feasible, and both thiazole **3a** and oxazole **4a** were obtained in high yields, attesting to scalability of the protocols (Scheme 3a). Second, shortening the reaction time was feasible to deliver oxazole **4a** in 53% yield after one minute reaction time, which demonstrated exceedingly fast oxidative coupling (Scheme 3b). Next, although the direct synthesis of C2-NR$_2$ substituted thiazoles was not feasible by this method,

**Scheme 2.** Further modification of bioactive synthons.

the product could be readily obtained through functionalizing C–H bond of **1a** with DMF as aminating reagent (Scheme 3c).[19a] Further, using copper-catalysis,[19b] C–H arylation of **1a** with iodobenzene was feasible to generate C2-arylated **7** in 64% yield (Scheme 3d). Likewise, despite of the presence of several coordinating heteroatoms, Suzuki-Miyaura cross-coupling of **4f** proceeded smoothly to deliver **8** in 89% yield (Scheme 3e). Next, the secondary naphthylamine **1'** could be cyclized to generate oxazole product **4a** in 53% yield via C–N bond cleavage, ascribed to the in situ formed free naphthylamine (Scheme 3f). Finally, when formamide was used, the oxazole **9** was not formed, but the reaction produced 78% yield of formylation product **10** (Scheme 3g). This outcome proved the stability of **10** in the presence of hypervalent iodine and provided insights into the reaction mechanism.
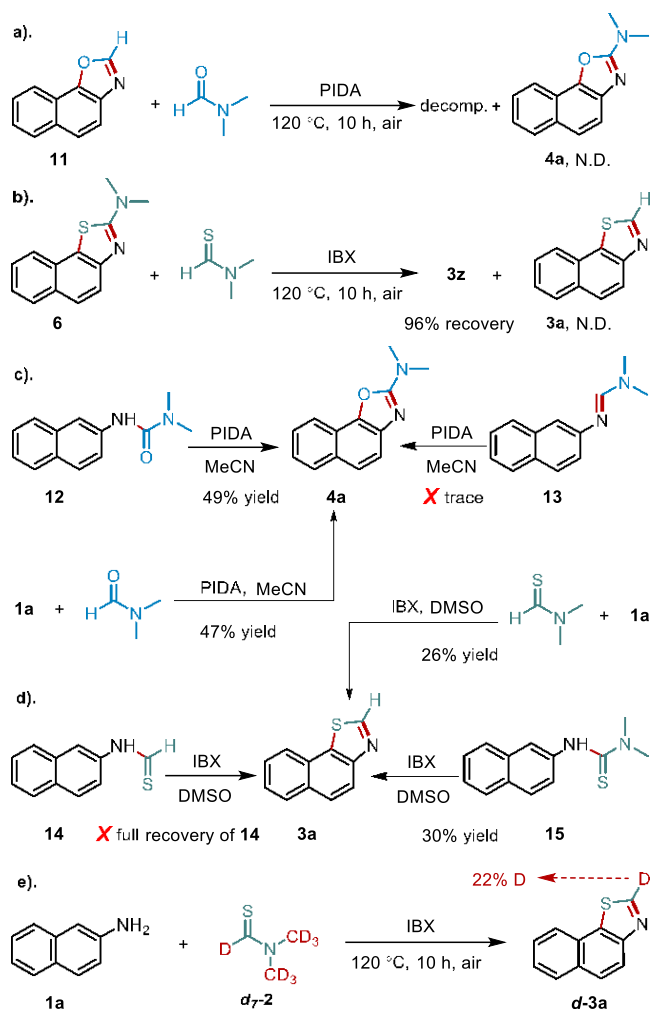
Scheme 4. Studies of the reaction mechanism.

To shed light on this highly chemoselective reaction pathway, several sets of control experiments as well as studies with key intermediates were performed (Scheme 4). As depicted in Schemes 4a-b, C2-free oxazole **11** failed to deliver product **4a**, and conversely, C2-NMe₂ thiazole **6** did not undergo the C–N bond cleavage to afford product **12**. These two results clearly illustrate the divergence of oxidative mechanisms to build oxazole and thiazole rings. To further probe the key reaction intermediates, several possible derivatives were prepared and subjected to the reaction conditions. As such, amidine **13** with high-activity[20] did not

afford the cyclization product, while urea **12** was transformed into the target molecule **4a** in a comparatively high efficiency cf. the reaction between **1a** and DMF (Scheme 4c). On the other hand, employing amine-derived thioformamide **14**, resulted in full recovery, which ruled out the possible intermediacy of thioformamide. However, the use of thiourea **15** resulted in the formation of the target product **3a** with efficiency comparable to the reaction of **1a** and *N,N*-dimethylthioamide (Scheme 4d). Finally, deuterium labelling study with *d₇-N,N*-dimethylthioamide resulted in 22% D incorporation in the C2 position (Scheme 4e).
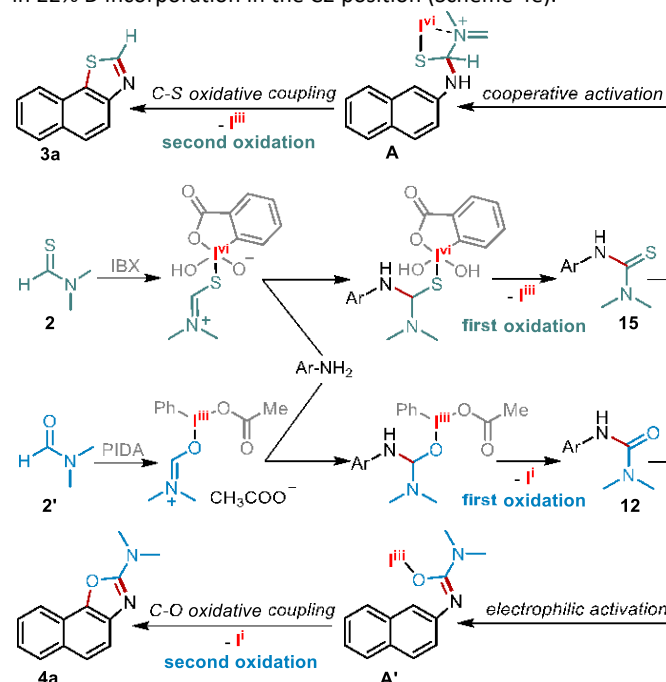
Scheme 5. Possible mechanism.

Overall, these mechanistic studies indicate that urea and thiourea species act as pivotal intermediates to enable the oxidative assembly of oxazoles and thiazoles. The key mechanistic difference results from the divergent $n_N \rightarrow \pi^*_{C=O}$ and $n_N \rightarrow \pi^*_{C=S}$ conjugation, where the stronger conjugation of the thioamide bond induces N–C cleavage under oxidative conditions. A tentative mechanism is proposed in Scheme 5. The reaction commences with electrophilic activation of the C=S and C=O bond by the hypervalent iodine reagent,[21] which is followed by the nucleophilic addition of amine. Subsequently, the first oxidation takes place to give thiourea **15** or urea **12**. At this point, with respect to the generation of thiazoles, the electron-rich intermediate **15** reacts with the hypervalent iodine(VI) to induce a hydride shift to afford **A**, which undergoes the second oxidative coupling by C–H/C–S cyclization. For the generation of oxazoles, the product is obtained by electrophilic activation, the second oxidative coupling by C–H/C–O cyclization and isomerization in the presence of hypervalent iodine(III). In case of thioamides, hypervalent iodine promotes amine dehydrogenation to form iminium.[22a] The key difference in reactivity between amides and thioamides stems from higher reactivity of thioamides to electrophiles[22b-d] and high affinity of sulfur towards hypervalent iodine reagents[23a] with a weaker thiocarbonyl bond that is more susceptible towards reduction.[23b]

Conclusions

In summary, we have developed an unprecedented hypervalent iodine-induced twofold oxidative coupling of amines with amides. This coupling proceeds via a series of C–N/C–O and C–N/C–S forming events enabled by hypervalent iodine oxidants. The previously unknown Ar–O and Ar–S oxidative coupling assembles a collection of versatile yet synthetically challenging oxazoles and thiazoles with highly chemoselectivity. Mechanistic studies demonstrated the importance of thiourea and urea species as the key reaction intermediates. This methodology represents the first example of chemoselective divergent oxidative bond functionalization in amides and thioamides to construct valuable heteroarenes. These findings open up new vistas for exploring oxidative amide and thioamide bond chemistry in various synthetic contexts.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

1   (a) M. Szostak, Amide bond activation: concepts and reactions, *Wiley-VCH.*, New York, 2022; (b) S. Davey, *Nature Chem.*, 2015, **7**, 682; (c) D. Kaiser, A. Bauer, M. Lemmerer and N. Maulide, *Chem. Soc. Rev.*, 2018, **47**, 7899; (d) G. C. Li and M. Szostak, *Chem. Rec.*, 2019, **20**, 649; (e) G. C. Li, S. Y. Ma and M. Szostak, *Trends Chem.*, 2020, **2**, 914; (f) T. B. Boit, A. S. Bulger, J. E. Dander and N. K. Garg, *ACS Catal.*, 2020, **10**, 12109; (g) G. R. Meng, J. Zhang and M. Szostak, *Chem. Rev.*, 2021, **121**, 12746; (h) M. H. Feng, H. Q. Zhang and N. Maulide, *Angew. Chem., Int. Ed.*, 2022, **61**, e202212213.

2   (a) G. Pelletier, W. S. Bechara and A. B. Charette, *J. Am. Chem. Soc.*, 2010, **132**, 12817; (b) J. F. Hu, Y. Zhao, J. J. Liu, Y. M. Zhang and Z. Z. Shi, *Angew. Chem. Int. Ed.*, 2016, **55**, 8718; (c) N. A. Weires, E. L. Baker and N. K. Garg, *Nature Chem.*, 2016, **8**, 75; (d) J. A. Walker Jr., K. L. Vickerman, J. N. Humke and L. M. Stanley, *J. Am. Chem. Soc.*, 2017, **139**, 10228; (e) C.-L. Ji and X. Hong, *J. Am. Chem. Soc.*, 2017, **139**, 15522; (f) A. A. Kadam, T. L. Metz, Y. Q. Qian and L. M. Stanley, *ACS Catal.*, 2019, **9**, 5651; (g) G. J. Wang, Q. Q. Shi, W. Y. Hu, T. Chen, Y. Y. Guo, Z. L. Hu, M. H. Gong, J. C. Guo, D. H. Wei, Z. Q. Fu and W. Huang, *Nat. Commun.*, 2020, **11**, 946.

3   (a) A. Greenberg, C. M. Breneman and J. F. Liebman, The amide linkage: Structural significance in chemistry, biochemistry and materials science, *Wiley-VCH.*, New York, 2000; (b) A. B. Hughes, Amino acids, peptides and proteins in organic chemistry, *Wiley.*, Weinheim, 2011; (c) K. Brix and W. Stocker, Proteases: structure and function, *Springer-Verlag.*, Wien, 2013; (d) B. J. Burkhart, C. J. Schwalen, G. Mann, J. H. Naismith and D. A. Mitchell, *Chem. Rev.*, 2017, **117**, 5389; (e)

A. Karmakar and A. J. L. Pombeiro, *Coord. Chem. Rev.*, 2019, **39**, 86; f) V. Pattabiraman and J. Bode, *Nature*, 2011, **480**, 471.

4   (a) S. A. Ruider and N. Maulide, *Angew. Chem., Int. Ed.*, 2015, **54**, 13856; (b) D. Kaiser, C. J. Teskey, P. Adler and N. Maulide, *J. Am. Chem. Soc.*, 2017, **139**, 16040; (d) H. Takezawa, K. Shitozawa and M. Fujita, *Nat. Chem.*, 2020, **12**, 574.

5   (a) C. P. Chen, P. Liu, M. M. Luo and X. M. Zeng, *ACS Catal.*, 2018, **8**, 5864; (b) C. C. D. Wybon, C. Mensch, C. Hollanders, C. Gadais, W. A. Herrebout, S. Ballet and B. U. W. Maes, *ACS Catal.*, 2018, **8**, 203; (c) C. Hollanders, E. Renders, C. Gadais, D. Masullo, L. V. Raemdonck, C. C. D. Wybon, C. Martin, W. A. Herrebout, B. U. W. Maes and S. Ballet, *ACS Catal.*, 2020, **10**, 4280; (d) Y. Long, Y. L. Zheng, Y. Xia, L. Qu, Y. H. Yang, H. F Xiang and X. G. Zhou, *ACS Catal.*, 2022, **12**, 4688.

6   (a) K. Tani and B. M. Stoltz, *Nature*, 2006, **441**, 731; (b) B. Sliter, J. Morgan and A. Greenberg, *J. Org. Chem.*, 2011, **76**, 2770; (c) S. A. Glover and A. A. Rosser, *J. Org. Chem.*, 2012, **77**, 5492; (d) T. Shiba, T. Kurahashi and S. Matsubara, *J. Am. Chem. Soc.*, 2013, **135**, 13636; (e) H. Nagae, T. Hirai, D. Kato, S. Soma, S. Akebi and K. Mashima, *Chem. Sci.*, 2019, **10**, 2860.

7   (a) S. C. Shi, G. R. Meng and M. Szostak, *Angew. Chem., Int. Ed.*, 2016, **55**, 6959; (b) F. Hu, R. Lalancette and M. Szostak, *Angew. Chem., Int. Ed.*, 2016, **55**, 5062; (c) C. W. Liu and M. Szostak, *Angew. Chem., Int. Ed.*, 2017, **56**, 12718; (d) G. R. Meng, S. C. Shi, R. Lalancette, R. Szostak and M. Szostak, *J. Am. Chem. Soc.*, 2018, **140**, 727; (e) T. L. Zhou, C.-L. Ji, X. Hong and M. Szostak, *Chem. Sci.*, 2019, **10**, 9865; (f) G. C. Li, C.-L. Ji, X. Hong and M. Szostak, *J. Am. Chem. Soc.*, 2019, **141**, 11161; (g) C.-A. Wang, M. M. Rahman, E. Bisz, B. Dziuk, R. Szostak and M. Szostak, *ACS Catal.*, 2022, **12**, 2426; (h) D. X. Zuo, Q. Wang, L. Liu, T. Z. Huang, M. Szostak and T. Q. Chen, *Angew. Chem., Int. Ed.*, 2022, **61**, e202202794.

8   (a) J. Aubé, *Angew. Chem., Int. Ed.*, 2012, **51**, 3063; (b) P. Lei, G. R. Meng and M. Szostak, *ACS Catal.*, 2017, **7**, 1960; (c) L. B. Fu, M. Z. Xu, J. Y. Yu and W. R. Gutekunst, *J. Am. Chem. Soc.*, 2019, **141**, 2906; (d) H. Takezawa, K. Shitozawa and M. Fujita, *Nature Chem.*, 2020, **12**, 574-578.

9   (a) G. R. Meng, P. Lei and M. Szostak, *Org. Lett.*, 2017, **19**, 2158; (b) Y. M. Liu, S. C. Shi, M. Achtenhagen, R. Z. Liu and M. Szostak, *Org. Lett.*, 2017, **19**, 1614; (c) S. Yu, T. Shin, M. S. Zhang, Y. Z. Xia, H. Kim and S. Lee, *Org. Lett.*, 2018, **20**, 7563; (d) J. J. Chen, Y. Z. Xia and S. Lee, *Org. Lett.*, 2020, **22**, 3504; (e) Y. Long, Y. L. Zheng, Y. Xia, L. Qu, Y. H. Yang, H. F. Xiang and X. G. Zhou, *ACS Catal.*, 2022, **12**, 4688.

10 (a) C. Liana Allen, B. N. Atkinson and J. M. J. Williams, *Angew. Chem., Int. Ed.*, 2011, **51**, 1383; (b) T. M. E. Dine, D. Evans, J. Rouden and J. Blanchet, *Chem. Eur. J.*, 2016, **22**, 5894; (c) R. B. Sonawane, N. K. Rasal and S. V. Jagtap, *Org. Lett.*, 2017, **19**, 2078; (d) T. Ghosh, S. Jana and J. Dash, *Org. Lett.*, 2019, **21**, 6690; (e) J. W. Yin, J. Y. Zhang, C. Q. Cai, G.-J. Deng and H. Gong, *Org. Lett.*, 2019, **21**, 387; (f) M.-H. Zhu, Z. R. Cheng, J. L. Wei, H. Tan and N. Jiao, *CCS Chem.*, 2022, 10.31635/ccschem.022.202202585.

11 (a) W. S. Bechara, G. Pelletier and A. B. Charette, *Nature Chem.*, 2012, **4**, 228; (b) H. Yue, L. Guo, S.-C. Lee, X. Liu and M. Rueping, *Angew. Chem., Int. Ed.*, 2017, **56**, 3972; (c) J. Zhuo, Y. Zhang, Z. J. Li and C. Li, *ACS Catal.*, 2020, **10**, 3895; (d) G. S. Lee, J. Won, S. Choi, M.-H. Baik and S. H. Hong, *Angew. Chem., Int. Ed.*, 2020, **59**, 16933.

12 (a) T. Murai, The Chemistry of Thioamides, *Springer.* Singapore, 2019; (b) T. S. Jagodziński, *Chem. Rev.*, 2003, **103**, 197; (c) S. Fukagawa, Y. Kato, R. Tanaka, M. Kojima, T. Yoshino and S. Matsunaga, *Angew. Chem., Int. Ed.*, 2018, **58**, 1153; (d) J. Zhang, Z. L. Liu, Z. Yin, X. F. Yang, Y. M. Ma, R. Szostak and M. Szostak, *Org. Lett.*, 2020, **22**, 9500; (e) M. Saito, S. Murakami, T. Nanjo, Y. Kobayashi and Y. Takemoto, *J. Am. Chem. Soc.*, 2020, **142**, 8130.

13 (a) A. N. Desnoyer and J. A. Love, *Chem. Soc. Rev.*, 2017, **46**, 197; (b) J. Lou, Q. Wang, P. Wu, H. Wang, Y.-G. Zhou and Z. Yu, *Chem. Soc. Rev.*, 2020, **49**, 4307; (c) R. W. Newberry, B. VanVeller, I. A. Guzei and R. T. Raines, *J. Am. Chem. Soc.*, 2013, **135**, 7843; (d) J. Luo, M. Rauch, L. Avram, Y. Ben-David and D. Milstein, *J. Am. Chem. Soc.*, 2020, **142**, 21628.

14 (a) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257; (b) C. A. Grice, K. L. Tays, B. M. Savall, J. M. Wei, C. R. Butler, F. U. Axe, S. D. Bembenek, A. M. Fourie, P. J. Dunford, K. Lundeen, F. Coles, X. H. Xue, J. P. Riley, K. N. Williams, L. Karlsson and J. P. Edwards, *J. Med. Chem.*, 2008, **51**, 4150.

15 (a) D. Ma, X. Lu, L. Shi, H. Zhang, Y. Jiang and X. Liu, *Angew. Chem., Int. Ed.*, 2010, **50**, 1118; (b) Y. Sun, H. Jiang, W. Wu, W. Zeng and X. Wu, *Org. Lett.*, 2013, **15**, 1598; (c) P. Dang, W. L. Zeng and Y. Liang, *Org. Lett.*, 2015, **17**, 34.

16 (a) K. G. Liu, J. R. Lo, T. A. Comery, G. M. Zhang, J. Y. Zhang, D. M. Kowal, D. L. Smith, L. Di, E. H. Kerns, L. E. Schechter and A. J. Robichaud, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1115; (b) G. Pochetti, N. Mitro, A. Lavecchia, F. Gilardi, N. Besker, E. Scotti, M. Aschi, N. Re, G. Fracchiolla, A. Laghezza, P. Tortorella, R. Montanari, E. Novellino, F. Mazza, M. Crestani and F. Loiodice, *J. Med. Chem.*, 2010, **53**, 4354.

17 (a) J. Y. Kim, S. H. Cho, J. Joseph and S. Chang, *Angew. Chem., Int. Ed.*, 2010, **49**, 9899; (b) S. Wertz, S. Kodama and A. Studer, *Angew. Chem., Int. Ed.*, 2011, **50**, 11511; (c) J. Liu and J. M. Hoover, *Org. Lett.*, 2019, **21**, 4510.

18 (a) C. Villa, E. Mariani, A. Loupy, C. Grippo, G. C. Grossia and A. Bargagna, *Green Chem.*, 2003, **5**, 623; (b) V. Polshettiwar and R. S. Varma, *Acc. Chem. Res.*, 2008, **41**, 629; (c) A. Sarkar, S. Santra, S. K. Kundu, A. Hajra, G. V. Zyryanov, O. N. Chupakhin, V. N. Charushinb and A. Majee, *Green Chem.*, 2016, **18**, 4475.

19 (a) Q. Sun, X. G. Bao, *Chem. Commun.*, **2022**, 58, 2216; (b) L. M. Bouchet, A. A. Heredia, J. E. Argüello, L. C. Schmidt, *Org. Lett.* **2020**, 22, 610.

20 (a) P. Debnath, M. Baeten, N. Lefèvre, S. V. Daele and B. U. W. Maes, *Adv. Synth. Catal.,* **2015**, 357, 197; (b) M. Baeten and B. U. W. Maes, *Adv. Synth. Catal.,* **2016**, 358, 826.

21 (a) C. Zhu, Y. Liang, X. Hong, H. Sun, W.-Y. Sun, K. N. Houk and Z. Shi, *J. Am. Chem. Soc.*, 2015, **137**, 7564; (b) T. Otani, A. Tsuyuki, T. Iwachi, S. Someya, K. Tateno, H. Kawai, T. Saito, K. S. Kanyiva and T. Shibata, *Angew. Chem., Int. Ed.*, 2017, **56**, 3906; (c) L. Habert and K. Cariou, *Angew. Chem., Int. Ed.*, 2020, **60**, 171; (d) Y. Wang, M. Yang, Y.-Y. Sun, Z.-G. Wu, H. Dai and S. H. Li, *Org. Lett.*, 2021, **23**, 8750.

22 (a) K. C. Nicolaou, C. J. N. Mathison and T. Montagnon, *J. Am. Chem. Soc.*, 2004, **126**, 5192; (b) N. Mahanta, D. M. Szantai-Kis, E. J. Petersson and D. A. Mitchell, *ACS Chem. Biol.*, 2019, **14**, 142; (c) H. J. Kim, D. W. Graham, A. A. DiSpirito, M. A. Alterman, N. Galeva, C. K. Larive, D. Asunskis, P. M. A. Sherwood, *Science*, 2004, **305**, 1612; (d) A. Okano, R. C. James, J. G. Pierce, J. Xie and D. L. Boger, *J. Am. Chem. Soc.*, 2012, **134**, 8790.

23 (a) D. Kaiser, A. Bauer, M. Lemmerer and N. Maulide, *Chem. Soc. Rev.*, 2018, **47**, 7899; (b) K. B. Wiberg and D. J. Rush, *J. Am. Chem. Soc.*, 2001, **123**, 2038.