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# The dual role of thiourea in the thiotrifluoromethylation of alkenes†

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Alkenes substituted with a thiourea undergo C–CF<sub>3</sub> followed by intramolecular C–S bond formation with the Togni reagent and trifluoroacetic acid (TFA) at room temperature; thiols and thioamides are not suitable S-sources for this reaction. This anti-addition process involves a CF<sub>3</sub> radical, and affords CF<sub>3</sub>-substituted thiazolines and thiazines for medicinal applications. A metal or photoredox catalyst is not required as the thiourea acts as a reductant, as well as serving as an S-source capable of adding to a C-centered radical. Mechanistic work comparing the reactivity of thiourea, urea, thioamide and thiol in the context of alkene trifluoromethylation demonstrates that in this series, the thiourea is unique for its ability to release CF<sub>3</sub> radical from the Togni reagent, and to orchestrate trifluoromethylation followed by S-cyclization with both activated and unactivated alkenes.

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## Introduction

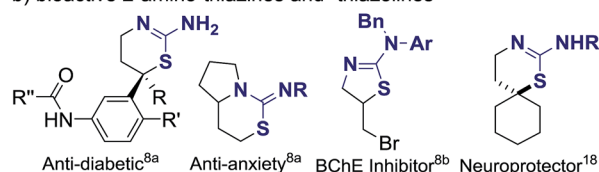
A large number of pharmaceuticals contain a trifluoromethyl group because this structural motif affects the properties of organic molecules.<sup>1</sup> The installation of trifluoromethyl groups onto sp<sup>3</sup> hybridized carbon has progressed significantly with numerous addition reactions of CF<sub>3</sub> across alkenes. Alkene vicinal functionalizations featuring C–CF<sub>3</sub> combined with C–H, C–C or C–heteroatom bond formation have been disclosed, most requiring a transition metal or photoredox catalyst to activate the CF<sub>3</sub> reagent (Scheme 1a).<sup>2</sup> Vicinal difunctionalizations involving sulfur heteroatom are notoriously rare; this process is much more challenging as, in contrast to amines and alcohols, thiols undergo facile S-trifluoromethylation with the Togni or Umemoto reagents in the absence of catalyst.<sup>3</sup> A case of alkene thiotrifluoromethylation was reported by Langlois in 2000.<sup>4</sup> In this process, photolysis of CF<sub>3</sub>SO<sub>2</sub>SPh generates a CF<sub>3</sub> radical (CF<sub>3</sub>•) that adds to the alkene; this step affords a weakly nucleophilic radical that reacts with CF<sub>3</sub>SO<sub>2</sub>SPh to provide the thioether product and the chain propagating trifluoromethylsulfonyl radical. The reagent in this reaction serves

both as CF<sub>3</sub> and S-source, thereby minimizing S–CF<sub>3</sub> bond formation. In a related approach, Zard reported the net addition of S-trifluoromethyl xanthates reagents onto alkenes, a process initiated with lauroyl peroxide.<sup>5</sup> The abundance of sulfur containing heterocycles in medicinal chemistry<sup>6</sup> prompted us to study alkene difunctionalization *via* C–CF<sub>3</sub> and C–S bond formation where the CF<sub>3</sub> and SR groups would not stem from a single reagent. In 2015, Liu and co-workers reported a case of intermolecular difunctionalization with the copper-catalyzed

### a) trifluoromethylation/heterocyclization of alkenes



### b) bioactive 2-amino-thiazines and -thiazolines



### c) trifluoromethylation/thiocyclization of alkenes (this work)



Scheme 1 Trifluoromethylation/thiocyclization of alkenes (M = metal, Pc = photoredox catalyst).

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trifluoromethylthiocyanation of alkenes; this process requires trimethylsilylisocyanate, a silicon-based S-source that acts as Lewis acid to activate the Togni reagent.<sup>7</sup>

In our design plan, we opted to examine the reactivity of olefins with pending thioureas, a decision driven by synthetic and mechanistic considerations. Trifluoromethylation followed by C–S bond formation would afford novel trifluoromethylated 2-amino-thiazolines and 2-amino-thiazines for applications in medicinal chemistry.<sup>8</sup> Selected 2-amino-thiazines and -thiazolines are important scaffolds in the development of aspartate beta-secretase enzyme (BACE-1) inhibitors, a therapeutic target for Alzheimer's disease,<sup>9</sup> and are common motifs in several bioactive compounds (Scheme 1b). Mechanistically, the ability of thioureas to act as reducing agent<sup>10</sup> and radical scavenger<sup>11</sup> suggests that this group may induce the release of CF<sub>3</sub>· from the Togni reagent,<sup>12</sup> and serve as an S-source capable of adding on a C-centered radical. Here we report that thiourea-substituted alkenes undergo C–CF<sub>3</sub> followed by C–S bond formation with the Togni reagent and TFA. This operationally simple reaction does not require a metal catalyst, and affords diverse CF<sub>3</sub>-substituted 2-amino-thiazolines and thiazines resulting from overall anti-addition across the C=C π bond (Scheme 1c).

## Results and discussion

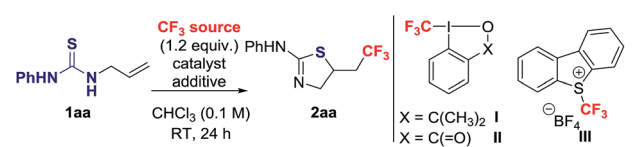
To identify suitable reaction conditions, we selected the unactivated alkene **1aa**, and the Togni **I**, **II**<sup>13</sup> and Umemoto **III**<sup>14</sup> reagents as CF<sub>3</sub> source (Table 1).<sup>15</sup> The desired 2-amino-thiazoline **2aa** resulting from trifluoromethylation followed by S-

cyclization was formed in low yield when the reaction was carried out at room temperature in CHCl<sub>3</sub> with **I**, **II** or **III** in the absence of catalyst or additive (Table 1, entries 1–3). No side-products resulting from oxidative dimerization or S–CF<sub>3</sub> bond formation were detected. The conversion of **1aa** into **2aa** decreased at 60 °C (Table 1, entries 2 and 3).

Activation of the Togni reagents by protonation with Brønsted acid is well documented,<sup>16</sup> but not typically considered for CF<sub>3</sub> addition onto alkenes. We envisioned that upon protonation of **II** with trifluoroacetic acid (TFA), the resulting highly electrophilic iodine centre could undergo S–I(III) coordination with the thiourea functionality followed by single electron transfer (SET) with more effective release of CF<sub>3</sub> radical. Gratifyingly, 62% of **2aa** was observed after 1 h when the reaction was conducted in the presence of 2 equiv. of TFA, and the yield reached 76% after 24 h (Table 1, entry 4). The reaction was less effective using 1 equiv. of TFA (Table 1, entry 5). The presence of the acid did not induce protocyclization, and its benefit was not significant with Umemoto **III** (Table 1, entry 6).

With the conditions described in entry 4 of Table 1, the scope of the thiotrifluoromethylation was investigated (Scheme 2). Allyl and metallyl thioureas afforded 2-amino-thiazolines **2aa** and **2ba** in 80% and 96%, respectively. A range of *para*-substituted styrenes underwent thiotrifluoromethylation with yields up to 92%. The reaction was extended to 1,2-dihydronaphthalenes, 2*H*-chromene, 2*H*-thiochromene and indene; in this series, all thiazolines were formed as a single stereoisomer resulting from anti-addition (d.r. > 20 : 1).<sup>17</sup> The 1,2-dihydronaphthalene scaffold was selected to investigate the tolerance of the reaction to variation of the thiourea *N*-substituent. The resulting products anti-**2ga–2gl** were isolated in yields ranging from 53% to 83%. No reaction occurred with **1gm**, a substrate possessing the free NH<sub>2</sub> sub-motif. The corresponding 2-amino-thiazoline **2gm** was obtained by a detour pathway involving *in situ* deprotection of the *N*-*t*Bu group of **2gi** under acidic conditions. The thiotrifluoromethylation of the chiral substrate 1-(1-(3,4-dihydronaphthalen-1-yl)propyl)-3-phenylthiourea provided adduct **2gn** in moderate yield as a mixture of diastereomers (ratio = 3.5 : 1).<sup>15</sup> Thiazines are also within reach applying this methodology. The spirocyclic product **2ka** was obtained in 53% yield and an eroded d.r. = 6 : 1 favoring the anti-isomer. Styrenes, with different points of attachment for the thiourea, delivered additional trifluoromethylated scaffolds. The 2,2,2-trifluoroethyl-substituted 4*H*-benzo[*d*][1,3]-thiazin-2-amines **2la** and **2ma** were obtained in moderate yields. Products possessing the CF<sub>3</sub> group on the thiazine ring itself were accessible from 3-substituted 1-cinnamyl-thioureas; for example, **2na** was isolated in 40% yield with a d.r. > 20 : 1. In this series, substituents on the aryl rings are well tolerated. The reaction with the internal alkyl-substituted alkene, (*E*)-1-(hex-2-en-1-yl)-3-phenylthiourea delivered a mixture of 5-*exo*- and 6-*endo*-regioisomers in a ~1 : 1 ratio (isolated yields were 22% and 20%, respectively).<sup>15</sup> The spirocyclic thiazine anti-**2ra**, a CF<sub>3</sub>-substituted analogue of a neuroprotector,<sup>18</sup> was prepared in 60% yield (d.r. > 20 : 1, after purification). A larger scale reaction on 2.3 mmol provided consistent yield of **2ra** (61%), an indicator of the robustness of the process. Thiazine **2rc** is a trifluoromethylated analogue of

Table 1 Optimization of reaction parameters



Entry	CF <sub>3</sub> source	Catalyst	Additive	Yield <sup>a</sup> (%)
1	<b>I</b>	—	—	7
2	<b>II</b>	—	—	33, 21 <sup>b</sup>
3	<b>III</b>	—	—	12, 7 <sup>b</sup>
4	<b>II</b>	—	TFA (2 equiv.)	76, 62 <sup>c</sup>
5	<b>II</b>	—	TFA (1 equiv.)	69
6	<b>III</b>	—	TFA (2 equiv.)	13
7 <sup>d</sup>	<b>II</b>	—	TFA (2 equiv.)	59
8	<b>II</b>	<b>A</b> (5 mol%)	—	21
9	<b>II</b>	<b>A</b> (100 mol%)	<b>B</b> (1 equiv.)	33
10 <sup>e</sup>	<b>II</b>	<b>C</b> (5 mol%)	—	20
11 <sup>e</sup>	<b>II</b>	<b>D</b> (2 mol%)	—	31
12 <sup>e</sup>	<b>III</b>	<b>C</b> (5 mol%)	—	40
13 <sup>e</sup>	<b>III</b>	<b>D</b> (2 mol%)	—	38

<sup>a</sup> Determined by <sup>19</sup>F NMR integration relative to an internal standard (C<sub>6</sub>H<sub>5</sub>CF<sub>3</sub>). <sup>b</sup> Reaction at 60 °C. <sup>c</sup> Reaction time is 1 h. <sup>d</sup> Reaction in CH<sub>3</sub>CN. <sup>e</sup> 14 W bulb as light source (λ<sub>max</sub> = 452 nm). **A** = Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub>. **B** = 1,10-phenanthroline. **C** = Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub>. **D** = methylene blue. TFA = trifluoroacetic acid.





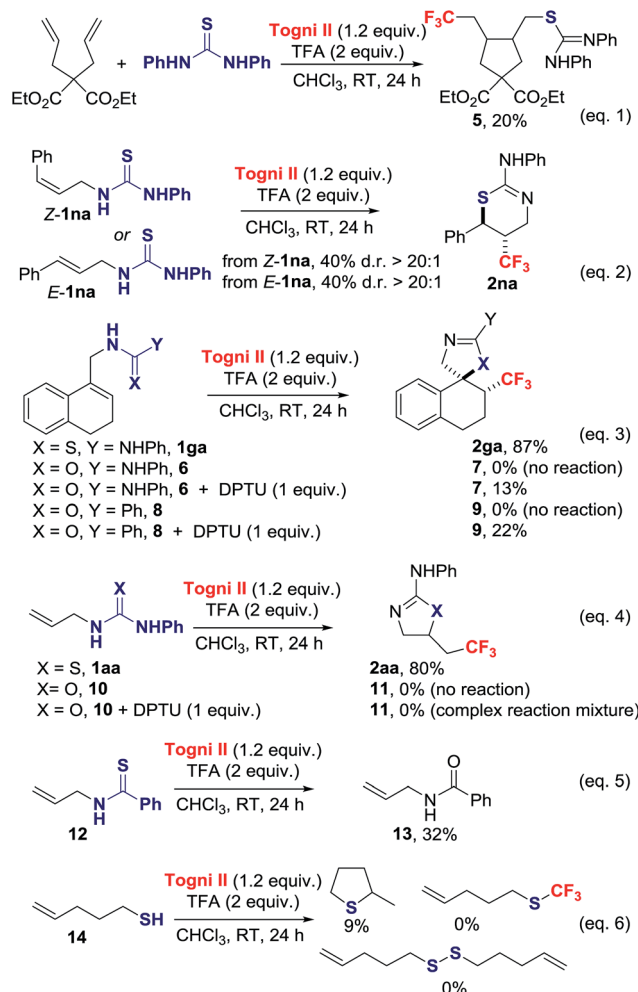
**Scheme 2** Substrate scope of the reaction. <sup>a</sup>The reaction was performed on a 0.3 mmol scale; yield of isolated product; d.r. > 20 : 1 by <sup>19</sup>F NMR of crude reaction. <sup>b</sup>Relative configuration established by single crystal X-ray diffraction analysis; for **2ga** and **2ka**, analysis was performed on the derivatives **3** and **4**, respectively. <sup>c</sup>**2gm** and **2rc** were obtained by *in situ* deprotection of **2gi** and **2rb**, respectively; yields from the alkene. <sup>d</sup>d.r. = 3.5 : 1. <sup>e</sup>d.r. = 6 : 1. <sup>f</sup>61% yield when the reaction was scaled up to 2.3 mmol. <sup>g</sup>d.r. = 5 : 1. PMB = *para*-methoxybenzyl.

a scaffold found in BACE-1 inhibitors for treating Alzheimer's disease;<sup>19</sup> this thiazine was obtained by deprotection with CAN of the *N*-PMB group of **2rb**. Finally, the method also gave access to the CF<sub>3</sub>-containing thiazepine **2sa**.

## Mechanistic experiments

We probed the mechanism of this reaction with a series of experiments (Scheme 3). The presence of 1 equiv. of TEMPO significantly inhibited the thiotrifluoromethylation of **1aa**, yielding 23% of TEMPO-CF<sub>3</sub> and 6% of **2aa**.<sup>15</sup> Complete inhibition for the formation of **2aa** was observed in the presence of benzoquinone. The cyclopentane **5** was isolated in 20% yield when diethyl 2,2-diallylmalonate was submitted to the reaction conditions in the presence of 1 equiv. of *N,N*-diphenylthiourea (DPTU);<sup>20</sup> in the absence of thiourea, no reaction occurred (eqn (1)). Both *E*-**1na** and *Z*-**1na** gave anti-**2na** with d.r. > 20 : 1 (eqn (2)). Collectively, these data indicate that a CF<sub>3</sub> radical is involved in the reaction.

Next, we investigated the uniqueness of the thiourea functionality for its ability to induce CF<sub>3</sub>• formation. We compared the reactivity of the thiourea **1ga** with the corresponding urea **6**



**Scheme 3** Mechanistic experiments.



Mechanistically, we discarded the possibility of *S*-cyclization prior to trifluoromethylation because this sequence would convert alkenes such as **1na** into a thiazoline *via* 5-*exo*-trig cyclization, and the thiazine anti-**2na** is the only product observed in the crude reaction mixture (eqn (2)).<sup>23</sup> We propose

## Conclusions

In summary, we developed the first trifluoromethylation followed by *S*-cyclization across C=C  $\pi$  bonds using thiourea as the S-source. The substrate itself, through its thiourea functionality, acts as an initiator, thereby avoiding metal species or light/photoredox catalysts to induce facile formation of the CF<sub>3</sub> radical that adds to the alkene. Thiourea can react with C-centered radical, so a range of alkenes including unactivated systems underwent facile thio-trifluoromethylation. This reaction is an attractive method for medicinal and other applications, because of its broad substrate scope, anti-selectivity and operational simplicity. The discovery that *N,N*-diphenylthiourea is an effective additive to induce the trifluoromethylation-cyclization of ureas and benzamides opens the possibility to investigate the value of this category of activators for the development of novel metal-free trifluoromethylation across double bonds.

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## Notes and references

- 1 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.
- 2 For a recent review, see: E. Merino and C. Nevado, *Chem. Soc. Rev.*, 2014, **43**, 6598. For metal-catalysed and photochemical trifluoromethylation across alkenes, see: (a) A. T. Parsons and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2011, **50**, 9120; *Angew. Chem.*, 2011, **123**, 9286; (b) J. Xu, Y. Fu, Y. D. Luo, Y. Jiang, B. Xiao, Z. Liu, T. Gong and L. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 15300; (c) X. Wang, Y. Ye, S. Zhang, J. Feng,





- Y. Xu, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2011, **133**, 16410; (d) R. Shimizu, H. Egami, Y. Hamashima and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2012, **51**, 4577; *Angew. Chem.*, 2012, **124**, 4655; (e) S. Mizuta, O. Galicia-López, K. M. Engle, S. Verhoog, K. Wheelhouse, G. Rassias and V. Gouverneur, *Chem.-Eur. J.*, 2012, **18**, 8583; (f) P. G. Janson, I. Ghoneim, N. O. Ichenko and K. J. Szabó, *Org. Lett.*, 2012, **14**, 2882; (g) Y. Yasu, T. Koike and M. Akita, *Angew. Chem., Int. Ed.*, 2012, **51**, 9567; *Angew. Chem.*, 2012, **124**, 9705; (h) R. Zhu and S. L. Buchwald, *J. Am. Chem. Soc.*, 2012, **134**, 12462; (i) R. Zhu and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 12655; *Angew. Chem.*, 2013, **125**, 12887; (j) C. Feng and T.-P. Loh, *Chem. Sci.*, 2012, **3**, 3458; (k) X. Wu, L. Chu and F. Qing, *Angew. Chem., Int. Ed.*, 2013, **52**, 2198; *Angew. Chem.*, 2013, **125**, 2254; (l) H. Egami, S. Kawamura, A. Miyazaki and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2013, **52**, 7841; *Angew. Chem.*, 2013, **125**, 7995; (m) C. Feng and T.-P. Loh, *Angew. Chem., Int. Ed.*, 2013, **52**, 12414; *Angew. Chem.*, 2013, **125**, 12640; (n) N. O. Ilchenko, P. G. Janson and K. J. Szabó, *Chem. Commun.*, 2013, **49**, 6614; (o) S. Mizuta, S. Verhoog, K. M. Engle, T. Khotavivattana, M. O'Duill, K. Wheelhouse, G. Rassias, M. Médebielle and V. Gouverneur, *J. Am. Chem. Soc.*, 2013, **135**, 2505; (p) X. Wu, L. Chu and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2013, **52**, 2198; *Angew. Chem.*, 2013, **125**, 2254. For metal-free trifluoromethylation across alkenes, see: (q) Y. Li and A. Studer, *Angew. Chem., Int. Ed.*, 2012, **51**, 8221; *Angew. Chem.*, 2012, **124**, 8345; (r) B. Zhang, C. Muck-Lichtenfeld, C. G. Daniliuc and A. Studer, *Angew. Chem., Int. Ed.*, 2013, **52**, 10792; *Angew. Chem.*, 2013, **125**, 10992; (s) D. J. Wilger, N. J. Gesmundo and D. A. Nicewicz, *Chem. Sci.*, 2013, **4**, 3160; (t) W. Kong, M. Casimiro, N. Fuentes, E. Merino and C. Nevado, *Angew. Chem., Int. Ed.*, 2013, **52**, 13086; *Angew. Chem.*, 2013, **125**, 13324; (u) H. Egami, Y. Usui, S. Kawamura, S. Nagashima and M. Sodeoka, *Chem.-Asian J.*, 2015, **10**, 2190; (v) N.-Y. Yang, Z.-L. Li, L. Ye, B. Tan and X.-Y. Liu, *Chem. Commun.*, 2016, **52**, 9052.
- 3 X.-H. Xu, K. Matsuzaki and N. Shibata, *Chem. Rev.*, 2015, **115**, 731.
- 4 T. Billard, R. Roques and B. R. Langlois, *Tetrahedron Lett.*, 2000, **41**, 3069. For a trifluoromethylchlorosulfonylation, see: D. B. Bagal, G. Kachkovskiy, M. Knorn, T. Rawner, B. N. Bhanage and O. Reiser, *Angew. Chem., Int. Ed.*, 2015, **54**, 6999; *Angew. Chem.*, 2015, **127**, 7105.
- 5 F. Bertrand, V. Peveré, B. Quiclet-Sire and S. Zard, *Org. Lett.*, 2001, **3**, 1069.
- 6 For a review, see: M. Feng, B. Tang, S. H. Tang and X. Jiang, *Curr. Top. Med. Chem.*, 2016, **16**, 1200.
- 7 Z. Liang, F. Wang, P. Cheng and G. Liu, *Org. Lett.*, 2015, **17**, 2438.
- 8 (a) M. Asif, *Journal of Pharmaceutical and Applied Chemistry*, 2015, **1**, 49; (b) G. Makhaeva, N. Boltneva, S. V. Lushchekina, O. G. Serebryakova, T. S. Stupina, A. A. Terentiev, I. V. Serkov, A. N. Proshin, O. G. Bachurin and R. J. Richardson, *Bioorg. Med. Chem.*, 2016, **24**, 1050.
- 9 (a) A. K. Ghosh and H. L. Osswald, *Chem. Soc. Rev.*, 2014, **43**, 6765; (b) R. Vassar, *Alzheimer's Res. Ther.*, 2014, **6**, 89; (c) L. L. Winneroski, M. A. Schiffler, J. A. Erickson, P. C. May, S. A. Monk, D. E. Timm, J. E. Audia, J. P. Beck, L. N. Boggs, A. R. Borders, R. D. Boyer, R. A. Brier, K. J. Hudziak, V. J. Klimkowski, G. P. Losada, B. M. Mathes, S. L. Stout, B. M. Watson and D. J. Mergott, *Bioorg. Med. Chem.*, 2015, **23**, 3260.
- 10 The ionization potential of urea and thiourea is 10.27 eV and 8.5 eV respectively. M. Baldwin, A. Kirkien-Konasiewicz, A. G. Loudon, A. Maccoll and D. Smith, *Chem. Commun.*, 1966, 574.
- 11 (a) M. Wasil, B. Halliwell, M. Grootveld, C. P. Moorhouse, D. C. Hutchison and H. Baum, *Biochem. J.*, 1987, **243**, 867; (b) M. Whiteman and B. Halliwell, *Free Radical Biol. Med.*, 1997, **22**, 1309; (c) M. C. Araujo, L. M. Antunes and C. S. Takahashi, *Teratog. Carcinog. Mutagen.*, 2001, **21**, 175.
- 12 J. Charpentier, N. Früh and A. Togni, *Chem. Rev.*, 2015, **115**, 650.
- 13 P. Eisenberger, S. Gishig and A. Togni, *Chem.-Eur. J.*, 2006, **12**, 2579.
- 14 (a) T. Umemoto and S. Ishihara, *Tetrahedron Lett.*, 1990, **31**, 3579; (b) T. Umemoto and S. Ishihara, *J. Am. Chem. Soc.*, 1993, **115**, 2156; (c) T. Umemoto, *Chem. Rev.*, 1996, **96**, 1757.
- 15 For details, see the ESI.†
- 16 (a) R. Koller, Q. Huchet, P. Battaglia, J. M. Welch and A. Togni, *Chem. Commun.*, 2009, 5993; (b) J. N. Brantley, A. V. Samant and F. D. Toste, *ACS Cent. Sci.*, 2016, **2**, 341.
- 17 N. Noto, K. Miyazawa, T. Koike and M. Akita, *Org. Lett.*, 2015, **17**, 3710.
- 18 S. V. Blokhina, T. V. Volkova, M. V. Ol'khovich, A. V. Sharapova, A. N. Proshin, S. O. Bachurin and G. L. Perlovich, *Eur. J. Med. Chem.*, 2014, **77**, 8.
- 19 A. E. Minatti, J. D. Low, J. R. Allen, J. Chen, Y. Cheng, T. Judd, Q. Liu, P. Lopez, W. Quia, R. Rumfelt, N. Rzaa, Q. X. Tamayo, B. Yang and W. Zhong, WO2013142613A1, 2014.
- 20 A. Studer, *Angew. Chem., Int. Ed.*, 2012, **51**, 8950; *Angew. Chem.*, 2012, **124**, 9082.
- 21 In the absence of TFA, thioamide **10** undergoes oxidative dimerization. I(III)-Mediated conversion of thioamide into amide is known N. K. Downer-Riley and Y. A. Jackson, *Tetrahedron*, 2008, **64**, 7741.
- 22 C. E. Hoyle and C. N. Bowman, *Angew. Chem., Int. Ed.*, 2010, **49**, 1540; *Angew. Chem.*, 2010, **122**, 1584.
- 23 P. D. Morse and D. A. Nicewicz, *Chem. Sci.*, 2015, **6**, 270.
- 24 O. Sala, N. Santschi, S. Jungen, H. P. Lüthi, M. Iannuzzi, N. Hauser and A. Togni, *Chem.-Eur. J.*, 2016, **22**, 1704.
- 25 The oxidation of **D** with **B** regenerates **1aa**.

