



CrossMark
click for updates

Cite this: *Chem. Sci.*, 2017, 8, 1195

The dual role of thiourea in the thiotrifluoromethylation of alkenes†

Paolo Ricci,‡^a Tanatorn Khotavivattana,‡^a Lukas Pfeifer,^a Maurice Médebielle,^b John Richard Morphy^c and Véronique Gouverneur*^a

Alkenes substituted with a thiourea undergo C–CF₃ 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 CF₃ radical, and affords CF₃-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 CF₃ radical from the Togni reagent, and to orchestrate trifluoromethylation followed by S-cyclization with both activated and unactivated alkenes.

Received 23rd June 2016
Accepted 30th September 2016

DOI: 10.1039/c6sc02790c

www.rsc.org/chemicalscience

Introduction

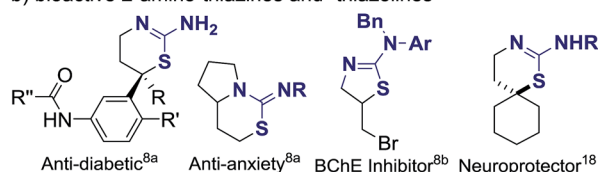
A large number of pharmaceuticals contain a trifluoromethyl group because this structural motif affects the properties of organic molecules.¹ The installation of trifluoromethyl groups onto sp³ hybridized carbon has progressed significantly with numerous addition reactions of CF₃ across alkenes. Alkene vicinal functionalizations featuring C–CF₃ 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 CF₃ reagent (Scheme 1a).² 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.³ A case of alkene thiotrifluoromethylation was reported by Langlois in 2000.⁴ In this process, photolysis of CF₃SO₂SPh generates a CF₃ radical (CF₃•) that adds to the alkene; this step affords a weakly nucleophilic radical that reacts with CF₃SO₂SPh to provide the thioether product and the chain propagating trifluoromethylsulfonyl radical. The reagent in this reaction serves

both as CF₃ and S-source, thereby minimizing S–CF₃ bond formation. In a related approach, Zard reported the net addition of S-trifluoromethyl xanthates reagents onto alkenes, a process initiated with lauroyl peroxide.⁵ The abundance of sulfur containing heterocycles in medicinal chemistry⁶ prompted us to study alkene difunctionalization *via* C–CF₃ and C–S bond formation where the CF₃ 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

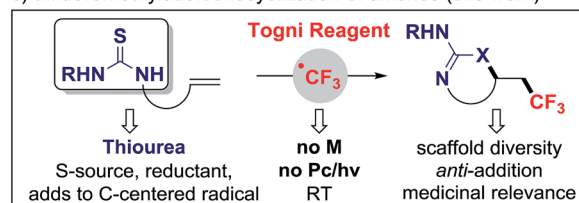
a) trifluoromethylation/heterocyclization of alkenes



b) bioactive 2-amino-thiazines and -thiazolines



c) trifluoromethylation/thiocyclization of alkenes (this work)



^aChemistry Research Laboratory, Department of Chemistry, Oxford University, OX1 3TA, UK. E-mail: veronique.gouverneur@chem.ox.ac.uk; Fax: +44 (0)1865 285002

^bUniversité de Lyon, Université Claude Bernard Lyon I, ICBMS UMR CNRS – UCBL – CPE – INSA 5246, Equipe Synthèse de Molécules d'Intérêt Thérapeutique (SMITh), 43 bd du 11 Novembre 1918, Villeurbanne 69622, France

^cMedicinal Chemistry, Eli Lilly and Company Limited, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey, GU20 6PH, UK

† Electronic supplementary information (ESI) available. CCDC 1474239–1474241. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6sc02790c

‡ These authors contributed equally to this work.

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



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

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.⁸ 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,⁹ and are common motifs in several bioactive compounds (Scheme 1b). Mechanistically, the ability of thioureas to act as reducing agent¹⁰ and radical scavenger¹¹ suggests that this group may induce the release of CF₃· from the Togni reagent,¹² and serve as an S-source capable of adding on a C-centered radical. Here we report that thiourea-substituted alkenes undergo C–CF₃ 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 CF₃-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**¹³ and Umemoto **III**¹⁴ reagents as CF₃ source (Table 1).¹⁵ 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 CHCl₃ 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–CF₃ 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,¹⁶ but not typically considered for CF₃ 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 CF₃ 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).

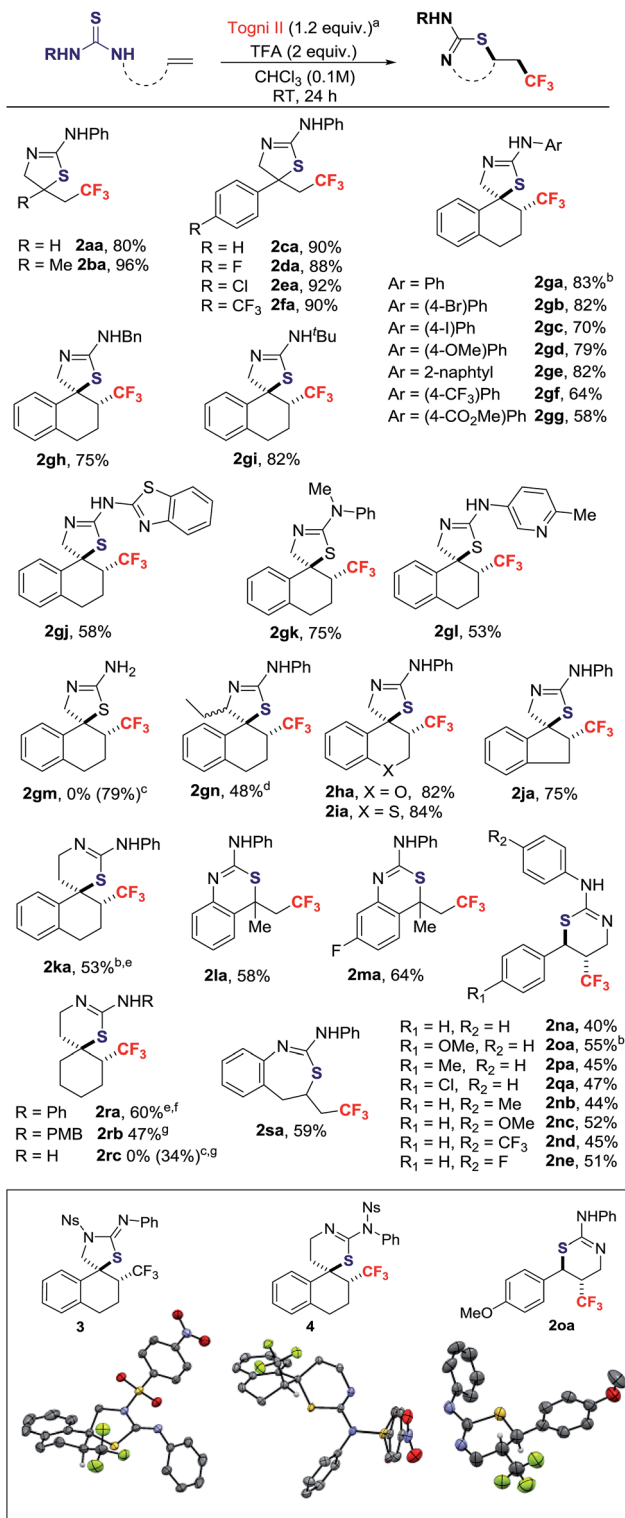
With the conditions described in entry 4 of Table 1, the scope of the thiotrifluoromethylation was investigated (Scheme 2). Allyl and metallyl thioureas afforded 2-amino-thiazolines **2aa** and **2ba** in 80% and 96%, respectively. A range of *para*-substituted styrenes underwent thiotrifluoromethylation 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).¹⁷ 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 NH₂ 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).¹⁵ 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 CF₃ 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).¹⁵ The spirocyclic thiazine anti-**2ra**, a CF₃-substituted analogue of a neuroprotector,¹⁸ 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 ₃ source | Catalyst | Additive | Yield ^a (%) |
|-----------------|------------------------|---------------------|-----------------------|------------------------|
| 1 | I | — | — | 7 |
| 2 | II | — | — | 33, 21 ^b |
| 3 | III | — | — | 12, 7 ^b |
| 4 | II | — | TFA (2 equiv.) | 76, 62 ^c |
| 5 | II | — | TFA (1 equiv.) | 69 |
| 6 | III | — | TFA (2 equiv.) | 13 |
| 7 ^d | II | — | TFA (2 equiv.) | 59 |
| 8 | II | A (5 mol%) | — | 21 |
| 9 | II | A (100 mol%) | B (1 equiv.) | 33 |
| 10 ^e | II | C (5 mol%) | — | 20 |
| 11 ^e | II | D (2 mol%) | — | 31 |
| 12 ^e | III | C (5 mol%) | — | 40 |
| 13 ^e | III | D (2 mol%) | — | 38 |

^a Determined by ¹⁹F NMR integration relative to an internal standard (C₆H₅CF₃). ^b Reaction at 60 °C. ^c Reaction time is 1 h. ^d Reaction in CH₃CN. ^e 14 W bulb as light source (λ_{max} = 452 nm). A = Cu(CH₃CN)₄PF₆, B = 1,10-phenanthroline. C = Ru(bpy)₃(PF₆)₂. D = methylene blue. TFA = trifluoroacetic acid.





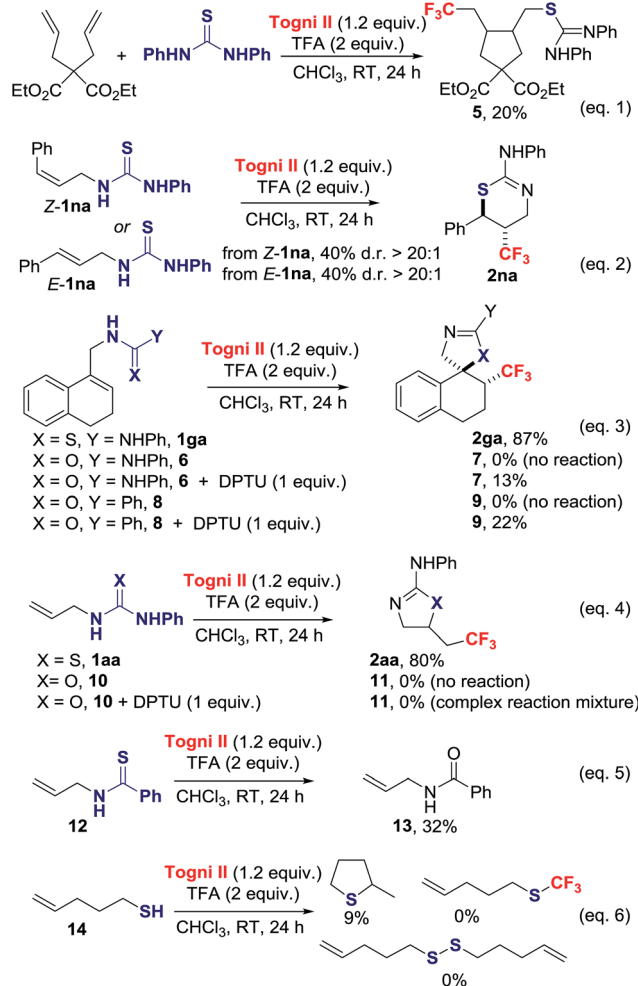
Scheme 2 Substrate scope of the reaction. ^aThe reaction was performed on a 0.3 mmol scale; yield of isolated product; d.r. > 20 : 1 by ¹⁹F NMR of crude reaction. ^bRelative configuration established by single crystal X-ray diffraction analysis; for **2ga** and **2ka**, analysis was performed on the derivatives **3** and **4**, respectively. ^c**2gm** and **2rc** were obtained by *in situ* deprotection of **2gi** and **2rb**, respectively; yields from the alkene. ^dd.r. = 3.5 : 1. ^ed.r. = 6 : 1. ^f61% yield when the reaction was scaled up to 2.3 mmol. ^gd.r. = 5 : 1. PMB = *para*-methoxybenzyl.

a scaffold found in BACE-1 inhibitors for treating Alzheimer's disease;¹⁹ this thiazine was obtained by deprotection with CAN of the *N*-PMB group of **2rb**. Finally, the method also gave access to the CF₃-containing thiazepine **2sa**.

Mechanistic experiments

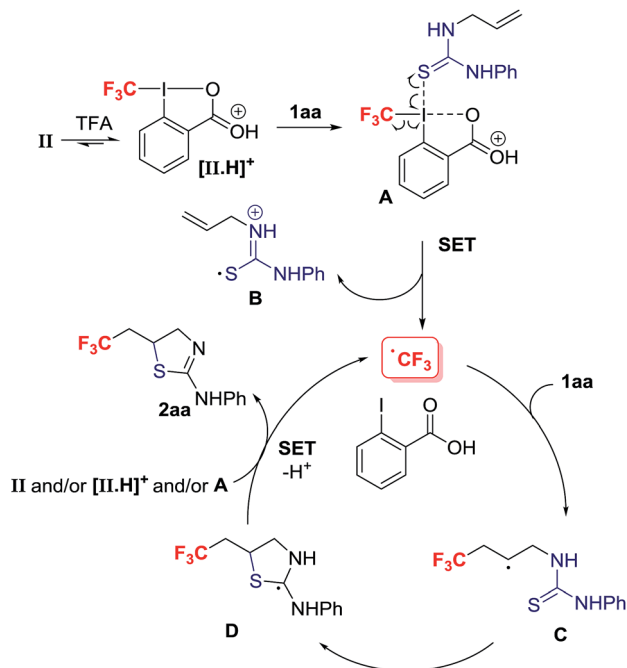
We probed the mechanism of this reaction with a series of experiments (Scheme 3). The presence of 1 equiv. of TEMPO significantly inhibited the thiothiuronium trifluoromethylation of **1aa**, yielding 23% of TEMPO-CF₃ and 6% of **2aa**.¹⁵ Complete inhibition for the formation of **2aa** was observed 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);²⁰ 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 CF₃ radical is involved in the reaction.

Next, we investigated the uniqueness of the thiourea functionality for its ability to induce CF₃· formation. We compared the reactivity of the thiourea **1ga** with the corresponding urea **6**



Scheme 3 Mechanistic experiments.





Scheme 4 Proposed mechanism.

and amide **8** (eqn (3)). We found that **6** and **8** did not react under the standard reaction conditions. Notably, the cyclized products **7** and **9** were isolated in 13% and 22% yield respectively, when the trifluoromethylation was performed in the presence of 1 equiv. of DPTU. In a similar vein, 1-allyl-3-phenylurea **10** did not react under the standard reaction conditions, but was consumed in the presence of DPTU with evidence that CF_3 radical addition to the alkene took place, but cyclization to **11** did not occur (eqn (4)).¹⁵ The thiourea therefore acts as an activator leading to CF_3^\cdot formation, and subsequent addition of this radical on the $\text{C}=\text{C}$ π bond. The contrasting reactivity of thiourea and urea is consistent with their oxidation potentials (+1.19 V vs. SCE in CH_3CN for thiourea **1aa** and +1.56 V vs. SCE in CH_3CN for urea **10**); similar values were found for cyclic voltammetry measurements performed in CH_3CN in the presence of TFA.¹⁵ Moreover, thioureas are superior to ureas for their ability to react with radical acceptor, an additional factor that accounts for the observed difference of reactivity. We considered next thioamides and thiols as alternative S-sources. Under our standard reaction conditions, the thioamide **12** failed to provide the product of thiotrifluoromethylation, but led instead to the corresponding amide **13** (eqn (5)).^{15,21} Pent-4-ene-1-thiol **14** underwent intramolecular thiol-ene ring closure and side reactions other than $\text{S}-\text{CF}_3$ bond formation or oxidative $\text{S}-\text{S}$ dimerization (eqn (6)).^{15,22} The thiourea is therefore unique to enable orchestrated alkene trifluoromethylation followed by *S*-cyclization.

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)).²³ We propose

that activation of the Togni reagent **II** with TFA affords the highly electrophilic iodine(III) species $[\text{II.H}]^+$ that can associate with **1aa** via iodine-sulphur coordination leading to **A**. Coordination of thiourea to the highly electrophilic $\text{I}(\text{III})$ in $[\text{II.H}]^+$ is unprecedented, but $\text{S}-\text{I}(\text{III})$ coordination has been evoked in the $\text{S}-\text{CF}_3$ bond formation for thiols reacting with the Togni reagent.²⁴ Homolytic dissociation releases **B**, iodobenzoic acid and the electrophilic radical CF_3^\cdot , which is suited to add regioselectively to the alkene substrate **1aa**. The alternative dissociative electron transfer pathway towards CF_3 radical formation is also plausible. The resultant carbon radical **C** undergoes ring closure with $\text{C}-\text{S}$ bond formation to provide adduct **D**, which should be easier to oxidize than **C**; SET to the Togni reagent **II**, $[\text{II.H}]^+$ and/or **A** affords after proton transfer **2aa**, and CF_3^\cdot that starts a new reaction cycle.²⁵ For radicals arising from CF_3^\cdot addition to aryl-substituted alkenes, oxidation prior to *S*-cyclization is viable (Scheme 4).

Conclusions

In summary, we developed the first trifluoromethylation followed by *S*-cyclization across $\text{C}=\text{C}$ π 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_3 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.

Acknowledgements

The authors thank Eli Lilly (P. R.), the Royal Thai Government and SCI (T. K.), and the EU (FP7-PEOPLE-2012-ITN-RADIOMI-316882 to L. P.) for generous funding. V. G. thanks the Royal Society for a Wolfson Research Merit Award, and Prof. S. Zard (Ecole Polytechnique, France) and Prof. J. Burton (University of Oxford, UK) for very helpful discussions.

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. Iichenko 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. Pevere, 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. Rzas, 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**.

