Organic LETTERS

Letter

pubs.acs.org/OrgLett

Amine Activation: Synthesis of *N*-(Hetero)arylamides from Isothioureas and Carboxylic Acids

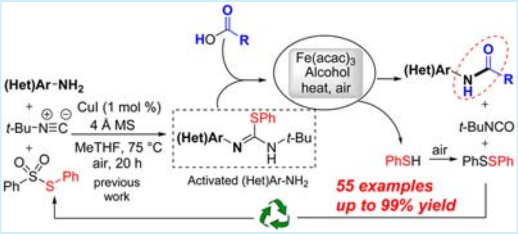
Yan-Ping Zhu,[†] Sergey Sergeyev,[†] Philippe Franck,[†] Romano V. A. Orru,[‡] and Bert U. W. Maes*[,†]

[†]Organic Synthesis, Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, 2020 Antwerp, Belgium

[‡]Department of Chemistry and Pharmaceutical Sciences and Amsterdam Institute for Molecules, Medicines and Systems (AIMMS), VU University Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands

Supporting Information

ABSTRACT: A novel method for *N*-(hetero)arylamide synthesis based on rarely explored amine activation, rather than classical acid activation, is reported. The activated amines are easily prepared using a three-component reaction with commercial reagents. The new method shows a broad scope including challenging amides not (efficiently) accessible via classical protocols.

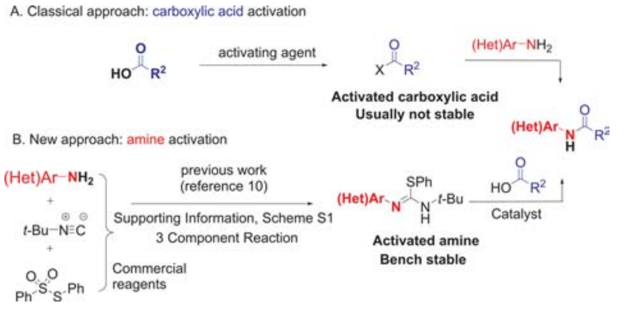


The synthesis of the amide functional group is paramount in organic chemistry. This structural motif is truly ubiquitous and is present in (bio)polymers (e.g., nylon, proteins), peptides, natural products (e.g., paclitaxel, penicillin), ligands for catalysis, synthetic drugs, and agrochemicals.[1] The main classical route for its synthesis is based on the activation of a carboxylic acid through formation of an acyl chloride, acyl imidazole, anhydride, or activated ester, followed by reaction with an amine.[2] The formation of activated esters with phosphonium/uronium/guanidinium salts, based on (azo)-benzotriazole derivatives such as HOBt or HATU, is currently the most successful and popular method. However, due to their explosive nature, transportation and storage issues resulted in the development of (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylaminomorpholinocarbenium hexafluorophosphate (COMU).[3] The prevalence of the amide functionality and the plethora of coupling reagents available for carboxylic acid activation might give the impression that amide synthesis is a mature transformation. However, this is incorrect as practice proves that often even simple amides resist formation. This triggers the development of new and more complex and expensive coupling reagents. More recently, Lewis acids based on boron species or metal salts have been reported as suitable catalysts, allowing direct coupling of amine and carboxylic acid when water is simultaneously removed.[4] The difficulty in driving reactions to completion and limited catalyst stability restrict the take up of this technology in industry. Although all these methods cited are very useful for the synthesis of a variety of amides, there are still limitations with respect to amide scope (electronics and sterics), functional group tolerance, and chemoselectivity toward other nucleophiles, which require upfront protection, thus reducing the efficiency of the process. On the basis of these limitations, many interesting alternative procedures have been developed from precursors other than amines and/or carboxylic acids.[5a−s] However, procedures starting from carboxylic acids and amines are still the most interesting, due to the widespread availability of these building blocks. For challenging amides, derived from sterically hindered carboxylic acids and electron-deficient and/or sterically hindered (hetero)aromatic amines, for instance, the classical approaches give a low yield or often even fail, and no general efficient synthetic method is currently available. This is illustrated by the synthesis of *N*-mesityl-2,4,6-trimethylbenzamide from 2,4,6-trimethylbenzoic acid and 2,4,6-trimethylaniline (Supporting Information, Scheme S2). A variety of classical coupling reagents under different conditions were tested but generally no reaction product was formed; only with PyBOP was a moderate yield obtained.[6a−e] These poor results and the frequent occurrence of the *N*-(hetero)arylamide moiety in active ingredients (AI) stimulated us to develop a new synthetic method. The importance of this amide subclass can be illustrated by the list of FDA-approved drugs of 2015 and the top 100 drugs based on prescription. In the former list 15% and in the latter 9% of the drugs feature the *N*-(hetero)arylamide entity.[7a,b] Top selling agrochemicals, such as the fungicides boscalid and fluxapyroxad, also often contain such a structural moiety.[8]

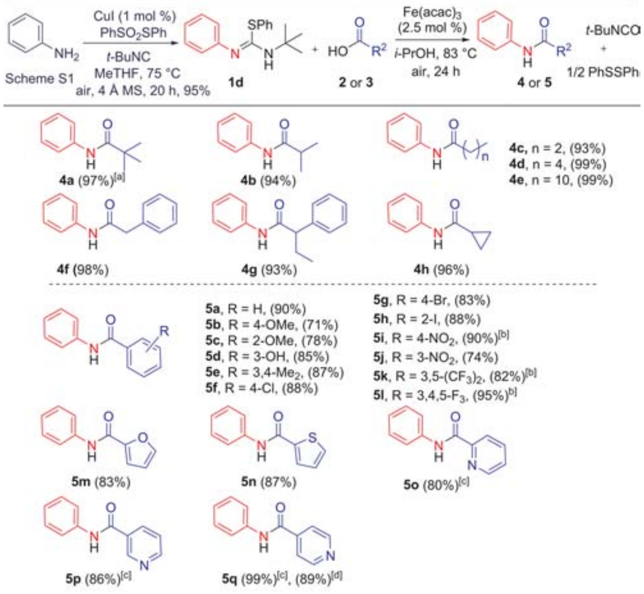
We initially focused our efforts on the development of a new synthetic protocol for *N*-(hetero)arylamide synthesis as an example of challenging amide synthesis. Our new approach involves (hetero)arylamine activation by transformation into the corresponding isothiourea, followed by reaction with carboxylic acid under base metal catalysis (Scheme 1).[9] The activation of (hetero)arylamine can be done in high yield in one step by using our recently developed three-component reaction (Scheme S1).[10] The reagents (*tert*-butyl isocyanide and *S*-phenyl benzenethiosulfonate) required for amine activation are

Received: July 29, 2016
Published: August 29, 2016

Scheme 1. Classical (A) and New Strategy (B) for N-(Hetero)arylamide Synthesis from (Hetero)aromatic Amines and Carboxylic Acids



Scheme 2. Scope of Carboxylic Acids 2 and 3[a]



[a] Reaction conditions: 1 (0.3 mmol), 2, or 3 (0.36 mmol), Fe(acac)$_3$ (2.5 mol %), i-PrOH (2 mL), 83 °C, air, 24 h: (a) 72% of PhSSPh was isolated; (b) o-xylene (2 mL), 130 °C, 24 h; (c) 2-butanol (2 mL), 98 °C, 48 h; (d) Fe(acac)$_3$ (5 mol %), 72 h.

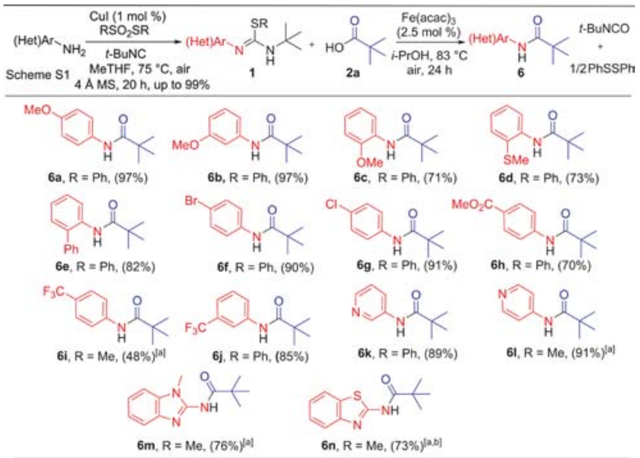
commercially available. While classical synthetic approaches for amide synthesis involve carboxylic acid activation (C → N direction), few procedures are based on amine activation (N → C direction: isocyanide,[11] imidazolylcarbonyl,[12] iminophosphorane[13]) (Scheme 1). Moreover, isothioureas are bench-stable compounds, while activated carboxylic acids are usually unstable and have to be generated in situ.

Optimization of the reaction conditions was performed using *N-tert*-butyl-*S*-methyl-*N*′-phenylisothiourea (**1a**), as activated aniline, and pivalic acid (**2a**) as model reagents. A catalyst screening in DMF revealed that Fe(acac)$_3$ was optimal (Table S1). Further screening showed that the reaction worked well in 2-propanol (93% yield) when 1.2 equiv of **2a** and 15 mol % of Fe(acac)$_3$ were used at 83 °C (Tables S2 and S3). Considering that substituents can have a significant influence on the amide formation, a series of isothioureas (**1a**−**f**) were prepared via our 3CR and tested (Table S4).[10] After all, the substituent on the sulfur and one nitrogen atom can be freely selected by simply altering the thiosulfonate and isocyanide reagents in the activation step. The results indicated that activated aniline equipped with a sterically hindered *N-tert*-butyl and an *S*-phenyl is the most reactive. When *N-tert*-butyl-*S*,*N*′-diphenylisothiourea (**1d**) was used instead of **1a**, full conversion could be achieved with only 2.5 mol % catalyst, and the desired product **4a** was isolated in 97% (Scheme 2). When the scale of the reaction was increased to 5 mmol (17 times), a similar yield was obtained (Table S4, entry 7).

We first investigated the carboxylic acid scope with activated aniline (Scheme 2). Alkanoic acids (**2**) generally performed very well in reaction with activated aniline **1d**. Branched (**2b**,**g**), linear (**2c**−**e**), as well as cyclic (**2h**) systems gave the desired amides **4** in excellent yields. In addition, acids featuring a further activation of the methylene α to the carbonyl by a phenyl group (**2f**,**g**) selectively reacted with **1d**. Next, we turned our attention to arenecarboxylic acids (**3**) (Scheme 2). Benzoic acid (**3a**) gave *N*-phenylbenzamide (**5a**) in 90% yield. Electron-donating groups (4-OMe (**3b**), 2-OMe (**3c**), 3,4-Me$_2$ (**3e**)) and halogens (4-Cl (**3f**), 4-Br (**3g**), 2-I (**3h**)) in different positions of the benzoic acid gave the corresponding products **5b**−**h** in 71−88% yields. Even a free hydroxyl group as in 3-hydroxybenzoic acid (**3d**) performed smoothly to provide the corresponding amide **5d** in 85% yield. Notably, benzoic acids featuring strong electron-withdrawing groups (4-nitro (**3i**), 3-nitro (**3j**), 3,5-bis(trifluoromethyl) (**3k**), 3,4,5-trifluoro (**3l**)) provided the desired products **5i**−**l** in 74−95% yield. For most of these benzoic acids, formation of *N-tert*-butyl-*N*′-phenylurea (**10**) was observed as a side reaction.[14] Substitution of 2-propanol by *o*-xylene restored the selectivity but required a higher reaction temperature. Heteroarenecarboxylic acids such as furan-2-carboxylic acid (**3m**), thiophene-2-carboxylic acid (**3n**), and isomeric pyridinecarboxylic acids (**3o**-**q**) also reacted smoothly to give the corresponding products **5m**−**q** in good yields (80−99%). The azine-type systems (**5o**−**q**) are particularly challenging (acids are zwitterions) and converted more slowly. More catalyst (5 mol %) or a higher boiling alcohol can be used to speed up the reaction in these cases.

The *N-tert*-butyl-*N*′-(hetero)aryl-*S*-phenylisothiourea (**1**) scope was investigated using pivalic acid (**2a**) as a model sterically encumbered carboxylic acid (Scheme 3). Isothiourea derived from anilines bearing electron-donating substituents (4-

Scheme 3. Scope of *N-tert*-Butyl-*N*′-(hetero)aryl-*S*-phenylisothiourea 1[a]



[a] Reaction conditions: 1 (0.3 mmol), 2 or 3 (0.36 mmol), Fe(acac)$_3$ (2.5 mol %), i-PrOH (2 mL), 83 °C, air, 24 h; (a) Fe(acac)$_3$ (15 mol %); (b) o-xylene (2 mL), 130 °C, 24 h.

DOI: 10.1021/acs.orglett.6b02247
Org. Lett. 2016, 18, 4602−4605

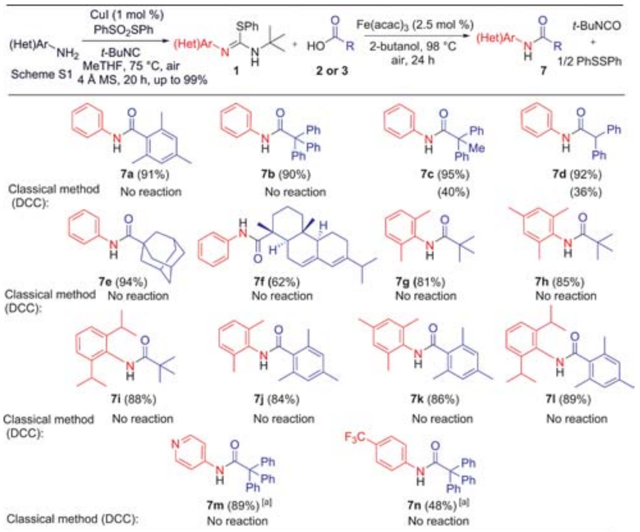
OMe (**1h**), 3-OMe (**1i**), 2-OMe (**1j**), and 2-SMe (**1k**)), an *o*-phenyl (**1l**), and halogen substituents (4-Br (**1m**), 4-Cl (**1n**)) underwent the reaction smoothly to afford the corresponding products (**6a–g**) in good to excellent yields. Electron-withdrawing groups (4-CO_2Me (**1o**), 4-CF_3 (**1p**), 3-CF_3 (**1q**)) were also well tolerated (**6h–j**). Pleasingly, activated heteroareneamines reacted smoothly under standard conditions. Reaction of **2a** with *N*-*tert*-butyl-*S*-phenyl-*N*′-(3-pyridinyl)isothiourea (**1r**) gave *N*-(3-pyridinyl)pivalamide (**6k**) in 89% yield. *N*-*tert*-Butyl-*N*′-(hetero)aryl-*S*-phenylisothiourea (**1**) containing a (vinylogous) amidine could not be obtained in good yield from the corresponding amine using our 3CR due to decomposition. Therefore, the corresponding *S*-methyl analogues were used for these specific heteroareneamines, prepared by using commercial *S*-methylmethanethiosulfonate as reagent.[10] Both azine (4-aminopyridine (**1s**)) and azole (2-amino-1-methyl-1*H*-benzimidazole (**1t**) and 2-aminobenzothiazole (**1u**)) derived *S*-methylisothiourea yielded the desired pivalamides in 73–91% yield (**6l–n**). These are interesting cases as acyl chlorides are known to react with (vinylogous) heteroaromatic amidines at the azine/azole nitrogen first and therefore consume at least 2 equiv of reagent.[15]

Considering our initial goal, we subsequently investigated the applicability of our protocol for the synthesis of very challenging amides from the point of view of sterics and electronics. First, reaction of **1d** with carboxylic acids even more sterically hindered than pivalic acid (**2a**) were screened. However, initial tests with 2,4,6-trimethylbenzoic acid (**3r**) revealed the formation of a significant amount of urea **10** under the standard conditions (Table S5). Interestingly, when 2-butanol instead of 2-propanol was used as solvent at 98 °C, a selective transformation of **1d** and 91% of **7a** were achieved (Scheme 4). Under these conditions, sterically hindered aliphatic carboxylic acids (2,2,2-triphenylacetic acid (**2j**), 2,2-diphenylpropanoic acid (**2k**), 2,2-diphenylacetic acid (**2l**), 1-adamantanecarboxylic acid (**2m**), and abietic acid (**2i**)) all reacted with **1d** to provide the corresponding amides **7b–f** in generally very high yields. Even a combination of a carboxylic acid and an isothiourea which, are both sterically hindered, was found to be well tolerated in the reaction. Reaction of **2a** or **3r** with *N*-aryl-*N*′-*tert*-butyl-*S*-phenylisothiourea featuring a 2,6-Me_2 (**1v**), 2,4,6-Me_3 (**1w**), and 2,6-(isopropyl)$_2$ (**1x**) phenyl substitution pattern did not affect the overall efficiency, and the corresponding products **7g–l** were obtained in 81–89% yield. In addition, a combination of a sterically hindered carboxylic acid (**2j**) and an isothiourea derived from an electron-deficient (hetero)aromatic amine (4-aminopyridine (**1s**), 4-CF_3 (**1p**)) smoothly gave the desired amides **7m** and **7n**.

When we attempted to synthesize the challenging amides of Scheme 4 via classical reaction of amine and carboxylic acid with DCC, no or only a low amount of the target amides was obtained. The new amide synthesis disclosed is therefore complementary with classical protocols. While both protocols will provide standard amides, only the new protocol gives efficient access to the challenging representatives.

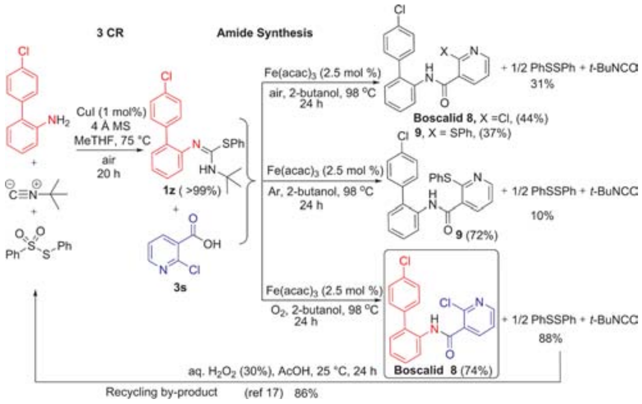
In order to demonstrate the potential of the new methodology, we applied it to the synthesis of the fungicide boscalid (Scheme 5).[16] It is classically synthesized by acylation of 2-chloronicotinyl chloride with 4′-chlorobiphenyl-2-ylamine. Our approach started from *N*-*tert*-butyl-*N*′-[4′-chloro-(1,1′-biphenyl)-2-yl]-*S*-phenylisothiourea (**1z**) and 2-chloronicotinic acid (**3s**) to give a 74% yield of boscalid (Scheme 5).

Scheme 4. Synthesis of Challenging *N*-(Hetero)arylamides 7[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** or **3** (0.36 mmol), Fe(acac)$_3$ (2.5 mol %), 2-butanol (2 mL), 98 °C, air, 24 h; (a) *N*-*tert*-butyl-*N*′-(hetero)aryl-*S*-methylisothiourea and Fe(acac)$_3$ (15 mol %). Classical method starting from (Het)ArNH_2: carboxylic acid **2** or **3** (1.05 mmol), 1,3-dicyclohexylcarbodiimide (DCC) (1.08 mmol), 4-(dimethylamino)pyridine (DMAP) (0.25 mmol), (Het)ArNH_2 (1.0 mmol), CH_2Cl_2 (10 mL), 0–25 °C, 24 h.

Scheme 5. Synthesis of Boscalid



Compound **1z** can be prepared in very high yield from commercially available 4′-chlorobiphenyl-2-ylamine, *S*-phenyl benzenethiosulfonate, and *tert*-butyl isocyanide via the 3CR.[10] It is important to note that the amide synthesis is in this case executed under oxygen atmosphere; otherwise, additional S_NAr on the C2–Cl occurs with the thiophenol formed in situ. Under oxygen instead of air, the rate of its oxidation to PhSSPh is increased, allowing the desired chemoselectivity to be achieved. Notably, the PhSSPh byproduct formed from PhSH under the amide-forming reaction conditions could be isolated in high yield. Interestingly, it can be transformed back into *S*-phenyl benzenethiosulfonate reagent for the 3CR.[17] For the model system **4a** (Scheme 2), this recovery procedure was successfully applied (Table S4, entry 7).

In conclusion, we have developed a novel amide synthesis based on rarely explored amine rather than carboxylic acid activation. (Hetero)arylamines are easily activated as bench-stable *N*-*tert*-butyl-*N*′-(hetero)aryl-*S*-phenylisothiourea via a three-component reaction (3CR) with commercially available reagents, *tert*-butyl isocyanide, and *S*-phenyl benzenethiosulfonate. *N*-(Hetero)arylamides can be obtained in high selectivity and yield from these isothioureas via reaction with carboxylic acids under iron catalysis, showing a broad functional group compatibility. The protocol allows for the synthesis of very challenging amides, from the point of view of sterics and electronics, not (or only in poor yield) accessible via classical coupling agents. The further exploration of the potential of this new methodology as well as the study of its mechanism are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02247.

> Optimization data, experimental procedures, characterization of new compounds, and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bert.maes@uantwerpen.be.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work has been supported by the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement 657883, the Research Foundation-Flanders (FWO), the UAntwerp (BOF), and the Hercules Foundation. The research leading to these results has also received funding from the Innovative Medicines Initiative (www.imi.europa.eu) Joint Undertaking project CHEM21 under Grant Agreement 115360, resources of which are composed of financial contributions from the European Union's Seventh Framework Programme and EFPIA companies' in-kind contributions.

■ REFERENCES

(1) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606.

(2) Subirós-Funosas, R.; Prohens, R.; Barbas, R.; El-Faham, A.; Albericio, F. *Chem. - Eur. J.* **2009**, *15*, 9394.

(3) Lundberg, H.; Tinnis, F.; Selander, N.; Adolfsson, H. *Chem. Soc. Rev.* **2014**, *43*, 2714.

(4) (a) Lanigan, R. M.; Sheppard, T. D. *Eur. J. Org. Chem.* **2013**, *2013*, 7453. (b) Al-Zoubi, R. M.; Marion, O.; Hall, D. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 2876. (c) Lundberg, H.; Adolfsson, H. *ACS Catal.* **2015**, *5*, 3271. (d) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471.

(5) (a) Fang, X.; Li, H.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* **2014**, *136*, 16039. (b) Fang, X.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 14089. (c) Xu, T.; Sha, F.; Alper, H. *J. Am. Chem. Soc.* **2016**, *138*, 6629. (d) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. - Eur. J.* **2010**, *16*, 9750. (e) Zhang, F.-L.; Wang, Y.-F.; Lonca, G. H.; Zhu, X.; Chiba, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 4390. (f) Tang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 6528. (g) Schäfer, G.; Matthey, C.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9173. (h) Schäfer, G.; Bode, J. W. *Org. Lett.* **2014**, *16*, 1526. (i) Noda, H.; Bode, J. W. *Chem. Sci.* **2014**, *5*, 4328. (j) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 1229712. (k) Jin, X.; Kataoka, K.; Yatabe, T.; Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 7212. (l) Zultanski, S. L.; Zhao, J.; Stahl, S. S. *J. Am. Chem. Soc.* **2016**, *138*, 6416. (m) Krause, T.; Baader, S.; Erb, B.; Goossen, L. J. *Nat. Commun.* **2016**, *7*, 11732. (n) Kang, B.; Fu, Z.; Hong, S. H. *J. Am. Chem. Soc.* **2013**, *135*, 11704. (o) Liu, J.; Liu, Q.; Yi, H.; Qin, C.; Bai, R.; Qi, X.; Lan, Y.; Lei, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 502. (p) Liu, Z.; Zhang, J.; Chen, S.; Shi, E.; Xu, Y.; Wan, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 3231. (q) Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027. (r) Wang, T.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 11708. (s) Debnath, P.; Baeten, M.; Lefèvre, N.; Daele, S. V.; Maes, B. U. W. *Adv. Synth. Catal.* **2015**, *357*, 197.

(6) (a) Ju, X.; Liu, Z. Chinese Patent CN101701016A, 2011, 20091103. (b) Zhang, Y.; Feng, J.; Liu, C.; Fang, H.; Xu, W. *Bioorg. Med. Chem.* **2011**, *19*, 4437. (c) MacMillan, D. S.; Murray, J.; Sneddon, H. F.; Jamieson, C.; Watson, A. J. B. *Green Chem.* **2013**, *15*, 596. (d) Junkers, M. *Aldrich ChemFiles* **2007**, *7.2*, 8−9. (e) Larrivée-Aboussafy, C.; Jones, B. P.; Price, K. E.; Hardink, M. A.; McLaughlin, R. W.; Lillie, B. M.; Hawkins, J. M.; Vaidyanathan, R. *Org. Lett.* **2010**, *12*, 324.

(7) (a) Top USA pharmaceutical products of 2013: http://njardarson.lab.arizona.edu/content/top-pharmaceuticals-poster, accessed June 2016. (b) Jarvis, L. M. *Chem. Eng. News* **2016**, *94*, 12−17.

(8) Michael, F. W. *The Agrochemical and Pesticides Safety Handbook*; CRC Press LLC: New York, 1998.

(9) For a book describing the use of Fe catalysts as Lewis acids, see: Plietker, B. *Iron Catalysis Fundamentals and Applications, in Topics in Organometallic Chemistry*; Springer: Heidelberg, 2011; Vol. 33.

(10) Mampuys, P.; Zhu, Y.; Vlaar, T.; Ruijter, E.; Orru, R. V. A.; Maes, B. U. W. *Angew. Chem., Int. Ed.* **2014**, *53*, 12849.

(11) (a) Wu, X.; Stockdill, J. L.; Park, P. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 2378. (b) Li, X.; Yuan, Y.; Kan, C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 13225.

(12) (a) Suppo, J.-S.; Subra, G.; Bergès, M.; Marcia de Figueiredo, R.; Campagne, J.-M. *Angew. Chem., Int. Ed.* **2014**, *53*, 5389. (b) Grzyb, J. A.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 7485.

(13) Kosal, A. D.; Wilson, E. E.; Ashfeld, B. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12036. Hegarty, A. F.; McCormack, M. T.; Ferguson, G.; Roberts, P. J. *J. Am. Chem. Soc.* **1977**, *99*, 2015.

(14) Urea **10** is presumably formed via reaction of an *O*-acylisourea intermediate with 2-propanol (solvent). *O*-Acylisourea is obtained via reaction of carboxylic acid with isothiourea.

(15) Joule, J. A. *Heterocyclic Chemistry*; VCH: Weinheim, 2010; pp 125−138.

(16) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Syntheses, Patents, Applications of the most relevant APIs*; Thieme: Stuttgart, 2008.

(17) Okumura, S.; Takeda, Y.; Kiyokawa, K.; Minakata, S. *Chem. Commun.* **2013**, *49*, 9266.