Organic & Biomolecular Chemistry

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Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID	OB-ART-02-2022-000412.R1
Article Type:	Paper
Date Submitted by the Author:	07-Apr-2022
Complete List of Authors:	Zhang, Jin; Shaanxi University of Science & Technology, College of Chemistry & Chemical Engineering; Key Laboratory of Auxiliary Chemistry & Technology for Chemical Industry, Zhao, Hui; Shaanxi University of Science and Technology Li, Guangchen; Rutgers University, Department of Chemistry Zhu, Xinhao; Shaanxi University of Science and Technology Shang, Linqin; Shaanxi University of Science and Technology He, Yang; Shaanxi University of Science and Technology Liu, Xin; Shaanxi University of Science and Technology Ma, Yangmin; Shaanxi University of Science and Technology Szostak, Michal; Rutgers University, Department of Chemistry

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PAPER

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Jin Zhang,[a,b,*] Hui Zhao,[a] Guangchen Li,[b] Xinhao Zhu,[a] Linqin Shang,[a] Yang He,[a] Xin Liu,[a] Yangmin Ma,[a] and Michal Szostak[b,*]

Thioamides are 'single-atom' isosteres of amide bonds that have found broad applications in organic synthesis, biochemistry and drug discovery. In this *New Talent* themed issue, we present a general strategy for activation of N–C(S) thioamide bonds by ground-state-destabilization. This concept is outlined in the context of a full study on transamidation of thioamides with nucleophilic amines, and relies on (1) site-selective N-activation of the thioamide bond to decrease $n_N \rightarrow \pi^*_{C=S}$ resonance, (2) highly chemoselective nucleophilic acyl addition to the thioamide C=S bond. The follow-up collapse of the tetrahedral intermediate is favored by the electronic properties of the amine leaving group. The ground-state-destabilization concept of thioamides enables to weaken the N–C(S) bond and rationally modify the properties of valuable thioamide isosteres for the development of new methods in organic synthesis. We fully expect that in analogy to the burgeoning field of destabilized amides introduced by our group in 2015, the *thio*amide bond ground-state-destabilization activation manifold will find broad application in various facets of chemical science, including metal-free, metal-catalyzed and metal-promoted reaction pathways.

Introduction

In 2015, our group introduced ground-state-destabilization concept of amide N–C(O) bonds to enable chemoselective manipulation of amides by transition-metal-catalysis (Fig. 1).[1] The amide bond activation platform focusing on different aspects of activation was simultaneously reported in outstanding contributions by other groups,[2] then promptly extended to transition-metal-free reactions by tetrahedral intermediates,[3,4] and later significantly expanded to activation of amides via acyl radicals. At present, the area of ground-state-destabilization of amides is a burgeoning field of research, which is driven by the ubiquitous presence of amide bonds in organic chemistry, pharmaceuticals and biochemistry with amides representing the most fundamental functional group in chemistry and biology.[5-8]

In the meantime, a major thrust of research has been on the development of new activated amide bond precursors that enable the advancement of amide bond reactivity platform. As such, the discovery of decarbonylative cross-coupling of amides has been enabled by *N*-cyclic *N*-acyl-glutarimides that provide reactivity and stability advantages over other acyl precursors switched-on by twist and external N–C(O) conjugation outside the N–C(O) acyl bond in this important cross-coupling platform.[9] However, it is important to note that the synthetically most useful *N*-activated amides are those that can be directly derived from the corresponding 2° or 1° amides, thus enabling common amides to be rationally manipulated under mild and previously inaccessible reaction

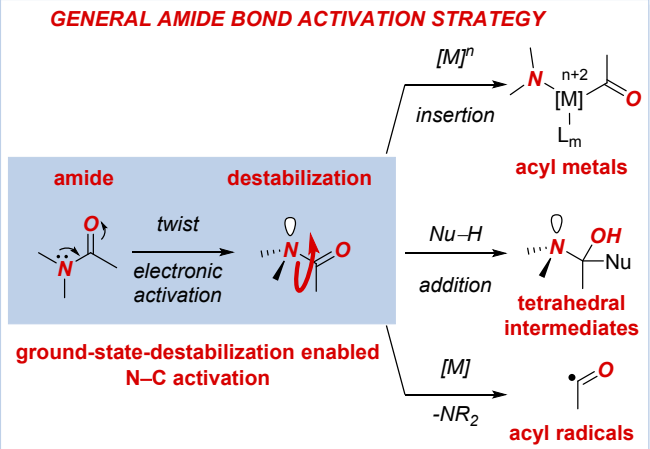


Fig. 1 Amide bond destabilization by twist and electronic activation.

[a]College of Chemistry and Chemical Engineering, Key Laboratory of Chemical Additives for China National Light Industry, Shaanxi University of Science and Technology, Xi'an 710021, China. E-mail: zhangjin@sust.edu.cn.
[b]Department of Chemistry, Rutgers University, 73 Warren Street, Newark, NJ 07102, USA. E-mail: michal.szostak@rutgers.edu.

†Electronic Supplementary Information (ESI) available: Experimental details and characterization data. See DOI: 10.1039/x0xx00000x

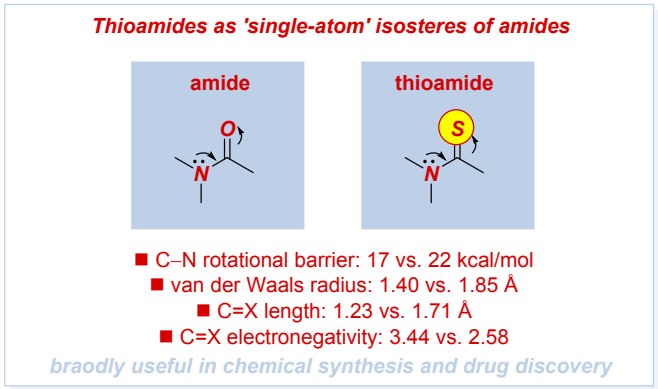


Fig. 2 Thioamides as 'single-atom' amide bond isosteres.

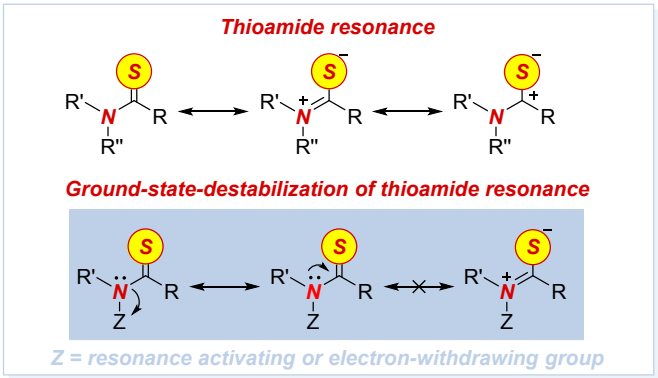


Fig. 3 Ground-state-destabilization of N–C(S) bond in thioamides.

conditions.[10] Indeed, the discoveries made by numerous research groups in the area of selective activation of N–C(O) amide bonds groups call for revision of the classical textbook definition of amides as stable and unreactive carboxylic acid derivatives (RE = 15-20 kcal/mol, RE = resonance energy)[11] with the amide bond as an easily modifiable functional group that covers the entire range of amidic $n_N \rightarrow \pi^*_{C=O}$ resonance (RE = 0-20 kcal/mol) enabled by *N*-substitution and the subsequent ground-state-destablization.[4] As such, this ground-state-destabilization concept enables a continuum of changes of amidic resonance, which in turn renders it possible to develop unprecedented reactions of amides by acyl-metals, tetrahedral intermediates, aryl-metals or acyl radicals.[8,12]

In this context, we were intrigued by the thioamide bond. Although thioamides have long been considered as ideal 'single-atom' isosteres of amide bonds and have found broad applications in organic synthesis, biochemistry and drug discovery,[13,14] direct activation of the N–C(S) bond has been notoriously difficult due to higher resonance stabilization of the thioamide bond (cf. amides) (Fig. 2).[15] Thioamides are characterized by an increase of the $n_N \rightarrow \pi^*_{C=S}$ resonance compared with the $n_N \rightarrow \pi^*_{C=O}$ resonance due to significantly higher contribution of the polar form. The large radius of sulfur (1.85 Å vs. oxygen, 1.40 Å) and low electronegativity of sulfur (2.58 vs. oxygen, 3.44) render the barrier to rotation around the N–C(S) bond in thioamides significantly higher than around the N–C(O) bond in amides by approximately 5-7 kcal/mol.[16] A telling example of the challenges in the direct activation of the N–C(S) bond in thioamides is the fact that the rate of hydrolysis of thioamides is 10-times slower than that of the corresponding amides.[17]

Despite the challenges, we realized that the advancement of the amide bond activation platform to thioamides would be significant in view of (1) the key role of thioamides as 'single-atom' isosteres of amide bonds, (2) the privileged role of sulfur in medicinal chemistry, where approximately 25% of APIs contain sulfur,[18] and (3) the opportunities opened up by the differential reactivity of the thioamide bond (cf. amide bond), including electrophilic addition at sulfur and desulfurization, which could be applied to the same manifolds as activation of ground-state-destabilized amides with vastly different chemoselectivity, geometry of precursors and intermediates, and electronic alteration of the reactive bonds.

In this *New Talent* themed issue, we present a general strategy for activation of N–C(S) thioamide bonds by ground-state-destabilization. (Fig. 3). This concept is outlined in the context of our full study on transamidation of thioamides with nucleophilic amines. In principle, there are two key considerations in this approach: (1) site-selective *N*-activation of the thioamide bond to decrease $n_N \rightarrow \pi^*_{C=S}$ resonance, (2) highly chemoselective nucleophilic acyl addition to the thioamide C=S bond (Fig. 4). The follow-up collapse of the tetrahedral intermediate is favored by the electronic properties of the amine leaving group.

Most broadly, the ground-state-destabilization concept of thioamides enables to weaken the N–C(S) bond and rationally modify the properties of thioamide-to-amide bond isosteres for the development of new methods in organic synthesis. We fully expect that in analogy to amides, *thio*amide bond ground-state-destabilization will find broad application in various facets of chemical science, including metal-free, metal-catalyzed and metal-promoted reaction pathways.

Results and discussion

Reaction discovery. Our laboratory has been interested in amide bond functionalization due to the potential to explore previously unknown reaction pathways of stable amide linkages.[19] Since one of the most successful and important reactions of activated amides developed to date are transamidations,[20-22] that is, processes that transform one amide bond ($R^1C(O)–NR^2R^3$) into another ($R^1C(O)–NR^4R^5$), we selected transamidation of thioamides as a model reaction to test the concept of ground-state-destabilization of thioamides. Recently, we reported transamidation of thioamides with non-nucleophilic amines, including preliminary results with nucleophilic amines.[23] Herein, we present full study on transamidation of thioamides with nucleophilic amines (Fig. 4). These processes differ by the mechanism of amine activation, where the use of non-nucleophilic amines requires strong bases and proceeds by deprotonation-addition pathway, while the use of nucleophilic amines follows the addition-deprotonation-collapse mechanism.[24,25]

Thioamide synthesis. The key consideration in the ground-state-destabilization platform is that N-activated thioamides

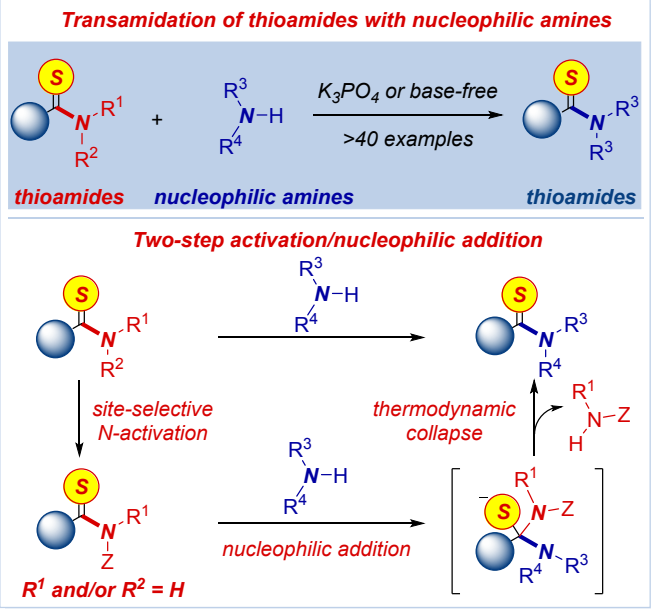
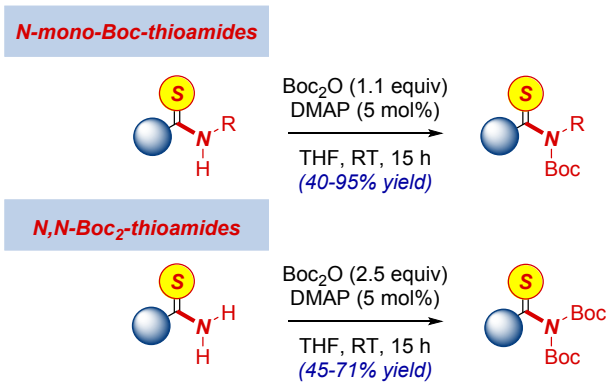


Fig. 4 Transamidation of thioamides with nucleophilic amines.

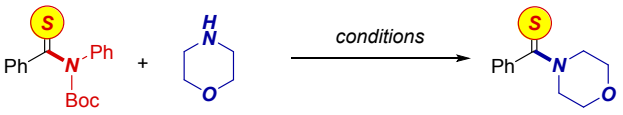


Scheme 1 Synthesis of ground-state-destabilized thioamides.

should be accessible directly from the corresponding 2° or 1° thioamides. After experimentation, we established that N-*tert*-butoxycarbonyl activation of the thioamide bond is possible with high site-selectivity for the nitrogen atom (Scheme 1). The reaction conditions involve Boc_2O (1.1-2.5 equiv), DMAP (5 mol%) as a catalyst in THF as a solvent. This reaction likely proceeds via S-*tert*-butoxycarbonylation, followed by S-to-N acyl transfer. Importantly, this activation method could be applied to both 2° and 1° thioamides to give *N*-mono-Boc and *N*,*N*-Boc_2-thioamides with broad reaction generality in 40-95% yields, including functional group tolerance to Lewis basic groups, halides and heterocycles. The capacity of 2° and 1° thioamides to engage in this N-activation method despite the presence of nucleophilic sulfur makes the subsequent N–C(S) activation step broadly useful.

Optimization of the reaction. During initial testing of the transamidation reaction, we found that transamidation of *N*-mono-Boc thioamides proceeds under optimal conditions in the presence of a weak phosphate base. Selected optimization reaction for the transamidation of *N*-mono-Boc thioamides are shown in Table 1. As expected, solvent choice has a significant

Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

Entry	Base	Solvent	Yield (%)
1	K_3PO_4	THF	86
2	K_3PO_4	CH_3CN	48
3	K_3PO_4	$CHCl_3$	47
4	K_3PO_4	Et_2O	54
5	K_3PO_4	dioxane	51
6	K_3PO_4	toluene	51
7	K_3PO_4	CH_2Cl_2	48
8	K_3PO_4	DMF	48
9	K_3PO_4	DMSO	22
10	K_3PO_4	EtOH	52
11	KO*t*Bu	THF	63
12	NaO*t*Bu	THF	60
13	LiO*t*Bu	THF	54
14	LiHMDS	THF	54
15	KHMDS	THF	64
16	NaHMDS	THF	76

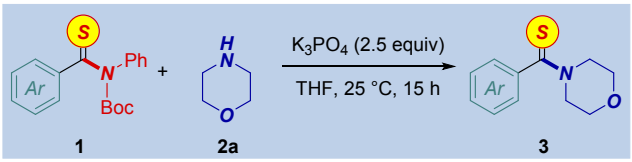
[a]Conditions: thioamide (1.0 equiv), amine (2.0 equiv), base (2.5 equiv), solvent (1.0 M), 25 °C, 15 h.

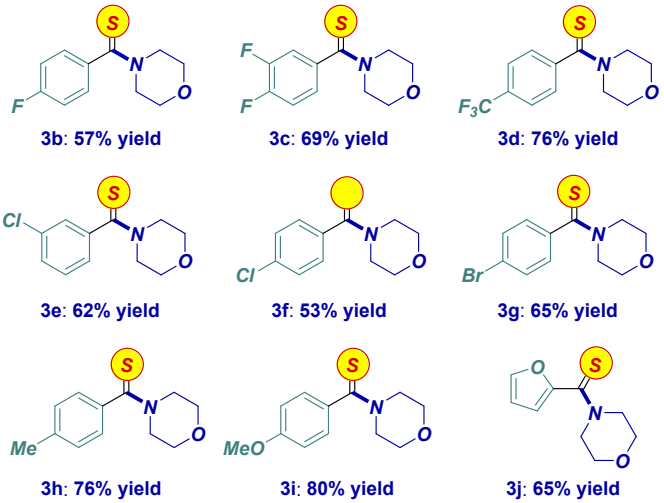
effect on the reaction (Table 1, entries 1-7). As such, THF was identified as optimal solvent (entry 1), while CH_3CN, $CHCl_3$, Et_2O, dioxane, toluene, CH_2Cl_2, DMF, DMSO and EtOH proved inferior to the reaction efficiency (entries 2-10). In particular, the use of more polar solvents resulted in significant decomposition of the thioamide bond. Furthermore, different bases were screened and although stronger bases, such as KO*t*Bu, NaO*t*Bu, LiO*t*Bu, LiHMDS, KHMDS, NaHMDS were found to promote the reaction (entries 11-16), their use is not recommended since the milder phosphate (entry 1) allows for broader functional group tolerance. Furthermore, we note that the use of organic bases (e.g. Et_3N) is not recommended since these reactions lack generality (not shown). Moreover, for transamidation of *N*,*N*-Boc_2-thioamides additional base was not required, while the addition of base did not increase the yield (vide infra), which is consistent with the higher electrophilicity of the thioamide bond in these derivatives.

Reaction scope. With the optimized conditions in hand, the reaction scope was next examined with respect to the thioamide component (Schemes 2-3).

In general, we found that for transamidation of *N*-mono-Boc-thioamides (Scheme 2), in addition to the neutral phenyl (**3a**) substitution (Table 1), substrates with medicinally-relevant fluoro-substitution, including single-substitution (**3b**) and multiple-substitution (**3c**) of the aromatic ring as well as trifluoromethyl-substitution (**3d**) were well tolerated. Importantly, halides, such as chloro (**3e-3f**) as well as bromo (**3g**) were found to be compatible substrates, providing handles for derivatization by cross-coupling. It is worth noting that especially bromides are often problematic using transition-metal-catalysis or strong base approaches, highlighting the synthetic advantage of the mild phosphate

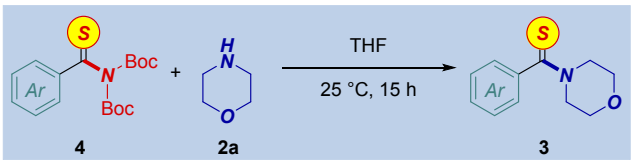
Scheme 2 Substrate scope of transamidation of *N*-mono-Boc-thioamides[a]

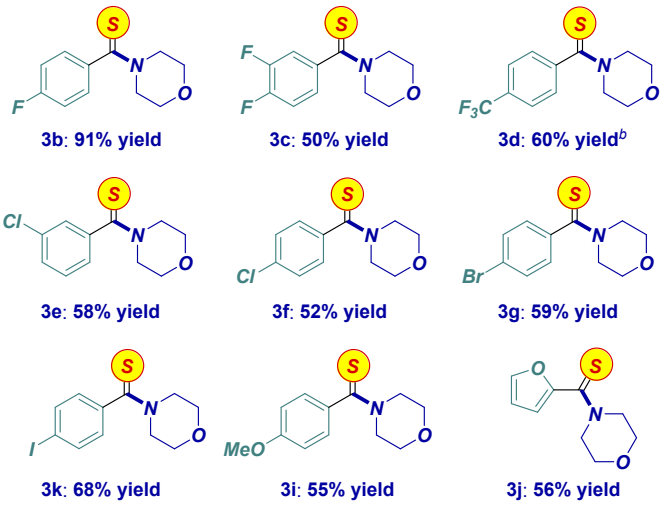




[a]Conditions: thioamide (1.0 equiv), **2a** (2.0 equiv), K_3PO_4 (2.5 equiv), THF (1.0 M), 25 °C, 15 h.

Scheme 3 Substrate scope of transamidation of *N*,*N*-Boc_2-thioamides[a]

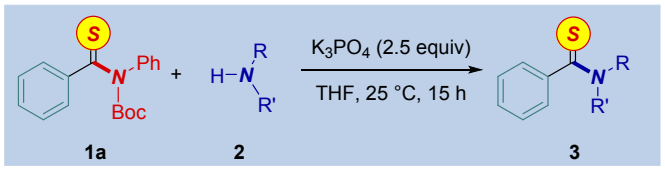


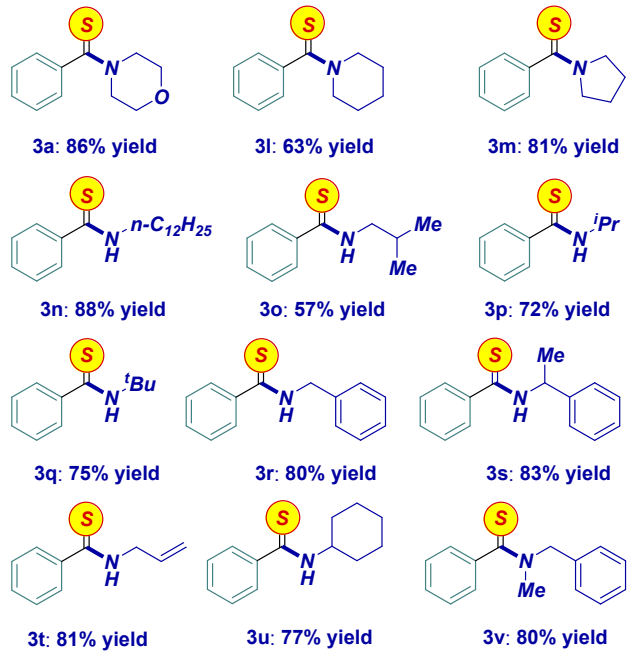


[a]Conditions: thioamide (1.0 equiv), **2a** (2.0 equiv), THF (1.0 M), 25 °C, 15 h. [b]NaHDMS (1.0 equiv).

base. Moreover, electron-rich substrates, such a 4-alkyl (**3h**) and 4-methoxy (**3i**) provided the transamidation products in high yields. Finally, we were pleased to find that this approach

Scheme 4 Amine scope of transamidation of *N*-mono-Boc-thioamides[a]





[a]Conditions: thioamide (1.0 equiv), **2a** (2.0 equiv), K_3PO_4 (2.5 equiv), THF (1.0 M), 25 °C, 15 h.

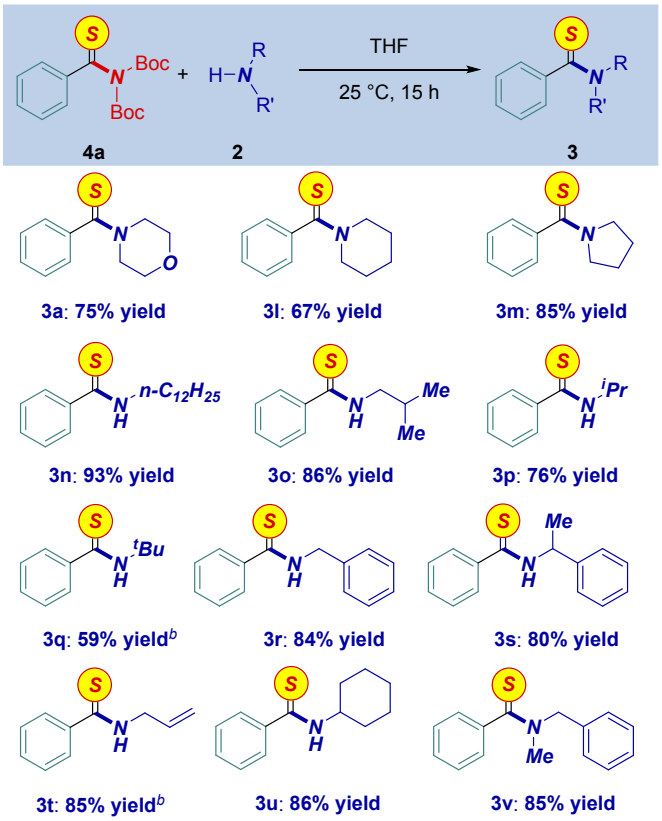
is also compatible with heterocycles, such as electronically-deactivated 2-furyl (**3j**).

Likewise, for transamidation of *N*,*N*-Boc_2-thioamides similar scope was established (Scheme 3), including fluorinated substrates (**3b-3d**) as well as chloro (**3e-3f**) and bromo (**3g**) containing substrates. Interestingly, in this case, we were also able to use 4-iodosubstitited thioamide (**3k**), which was not compatible with *N*-mono-Boc-thioamides. Finally, electron-rich methoxy (**3i**) and heterocyclic 2-furyl (**3j**) were also suitable substrates for this transamidation in analogy to *N*-mono-Boc-thioamides.

Next, the scope of different amines was evaluated using the electronically-neutral *N*-mono-Boc-thioamide (Scheme 4) and *N*,*N*-Boc_2-thioamide (Scheme 5) substrates. In general, a wide variety of amines are compatible with transamidation of *N*-mono-Boc-thioamides (Scheme 4), including cyclic amines, such as morpholine (**3a**), piperidine (**3l**), pyrrolidine (**3m**), simple unbranched 1° amines (**3n-3o**), sterically-hindered 1° amines (**3p-3q**), benzyl amines (**3r-3s**), allyl amines (**3t**), cyclohexylamines (**3u**) and 2° amines (**3v**).

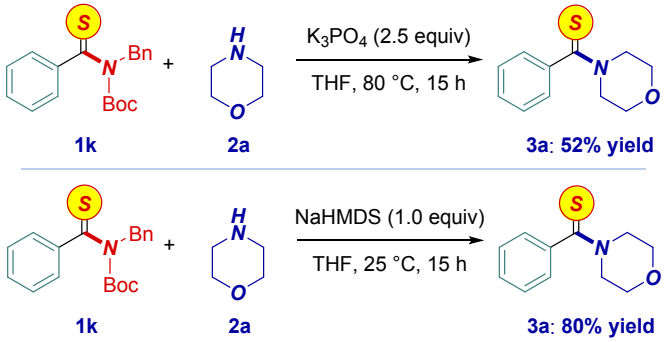
Likewise, the amine scope in transamidation of *N*,*N*-Boc_2-thioamides is also broad (Scheme 5) and encompasses the same variety of cyclic (**3a**, **3l-3m**), 1° acyclic (**3n-3o**), sterically-hindered (**3p-3q**), benzyl (**3r-3s**), allyl (**3t**), cyclohexyl (**3u**) and 2° amines (**3v**). It should be noted that conditions for nucleophilic transamidation using nucleophilic amines are

Scheme 5 Amine scope of transamidation of *N*,*N*-Boc$_2$-thioamides[a]



[a]Conditions: thioamide (1.0 equiv), **2a** (2.0 equiv), THF (1.0 M), 25 °C, 15 h. [b]NaHDMS (1.0 equiv).

Scheme 6 Transamidation of *N*-alkyl-*N*-Boc-thioamides[a]

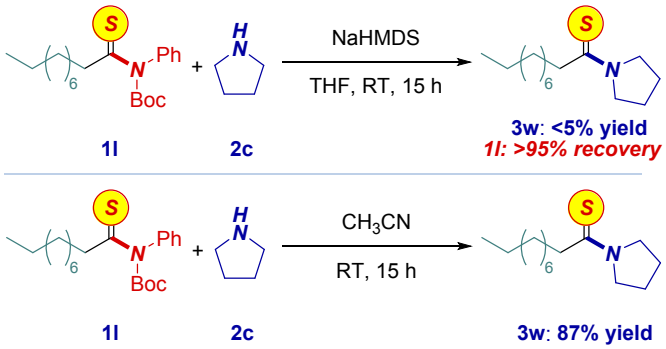


[a]Conditions: thioamide (1.0 equiv), **2a** (2.0 equiv), THF (1.0 M), A: K_3PO_4 (2.5 equiv), 80 °C, 15 h; B: NaHDMS (1.0 equiv), 25 °C, 15 h.

superior to the conditions using strong base conditions, which typically result incomplete conversions and side reactions when applied to electron-rich aliphatic amines. At present, chiral amines have not been tested. Studies are ongoing to expand the concept of N–C(S) activation to new substrates and reaction types. The scope of amines in Schemes 4-5 has been previously reported[23] and is included for comparison purposes.

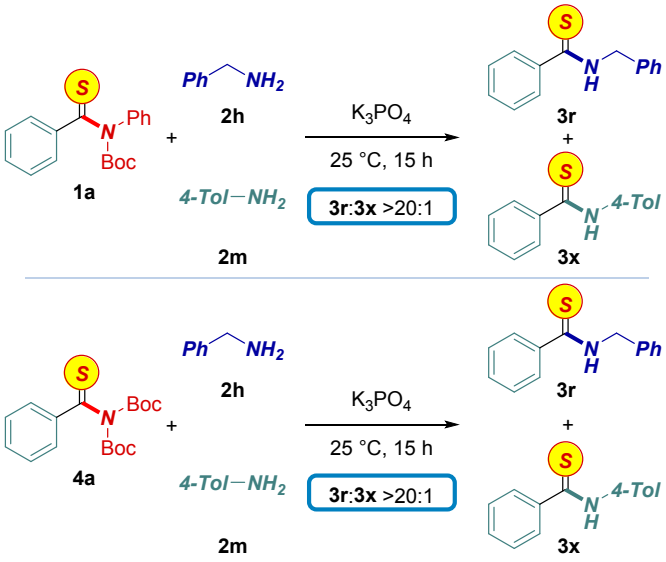
N-Variation. We were pleased to learn that these transamidation reactions are also compatible with N-aliphatic-*N*-mono-Boc-thioamides (Scheme 6). Two sets of conditions were developed, namely using K_3PO_4 as a base in THF at 80 °C (Scheme 6A) or using NaHMDS as a base in THF at RT (Scheme 6B). This N-variation with aliphatic substituents is significant as

Scheme 7 Transamidation of aliphatic *N*-mono-*N*-Boc-thioamides[a]



[a]Conditions: thioamide (1.0 equiv), **2c** (2.0 equiv), CH_3CN (1.0 M), 25 °C, 15 h.

Scheme 8 Selectivity in transamidation of *N*-mono-*N*-Boc and *N*,*N*-Boc$_2$-thioamides[a]



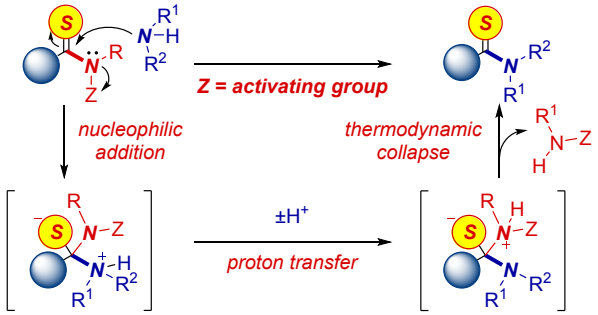
[a]Conditions: thioamide (1.0 equiv), amine (2.0 equiv each), K_3PO_4 (2.5 equiv), THF (1.0 M), 25 °C, 15 h.

it shows compatibility of the thioamide activation platform to both N-Ar and N-alkyl 2° thioamides.

Aliphatic thioamides. Another important consideration involves aliphatic thioamides. Although strong base conditions used for transamidation with non-nucleophilic amines are incompatible with aliphatic *N*-Boc-thioamides, resulting in competing α-deprotonation and thioamide recovery, we were pleased to find that aliphatic thioamides are compatible substrates for nucleophilic transamidation (Scheme 7). This reactivity represents another potential advantage of the direct nucleophilic addition to ground-state-activated thioamides, resulting in a net thioamide bond exchange of aliphatic thioamides.

Selectivity studies. Intermolecular competition experiments between different amines were conducted to gain insight into the proposed mechanism (Scheme 8).

Scheme 9 Mechanism of transamidation of ground-state-activated thioamides with nucleophilic amines



As shown, the reaction is exquisitely selective for the addition of nucleophilic amines in the presence of non-nucleophilic amines for both *N*-mono-Boc thioamides (Scheme 8A) ($PhCH_2NH_2$:4-Tol-NH_2 >20:1) and *N*,*N*-Boc_2-thioamides (Scheme 8B) ($PhCH_2NH_2$:4-Tol-NH_2 >20:1). This finding is consistent with our proposed mechanism and indicates nucleophilic addition to the ground-state destabilized thioamide bond governed by amine nucleophilicity.

Mechanism. The proposed mechanism for nucleophilic addition to N-activated thioamides involves two steps: (1) site-selective N-activation of the thioamide bond, (2) chemoselective nucleophilic addition to the N–C(S) bond to give tetrahedral intermediate (Scheme 9). The driving force is two-fold: (1) switched-on electrophilicity of the ground-state-activated thioamide bond, (2) thermodynamic collapse of the tetrahedral intermediate favored by the electronic properties of the leaving amine. The availability of *N*-mono-Boc and *N*,*N*-Boc_2-thioamides from common 2° and 1° thioamides renders this activation manifold broadly useful for manipulation of thioamide bonds by a variety of synthetic pathways.

Conclusions

In summary, we have outlined a general strategy for activation of N–C(S) thioamide bonds by ground-state-destabilization. This method exploits site-selective N-activation of the thioamide bond to decrease $n_N \rightarrow \pi^*_{C=S}$ resonance to enable broadly useful acyl nucleophilic addition of amines to the thioamide C=S bond. The method tolerates a wide range of thioamides and amines, affording important thioamide to thioamide interconversion products in high yields.

In a broader context, thioamides represent the most important 'single-atom' isosteres of amide bonds that are essential structural motifs in organic synthesis, biochemistry and drug discovery. Although direct activation of the thioamide N–C(S) bond has been a major challenge due to higher $n_N \rightarrow \pi^*_{C=S}$ resonance stabilization of the thioamide bond, the ground-state-destabilization of thioamides permits to weaken the N–C(S) bond and perform acyl addition under remarkably mild and chemoselective conditions. In light of the prominent role of thioamides in organic synthesis and drug discovery, we fully expect that ground-state-destabilization of thioamides will find broad application in chemistry by metal-free, metal-catalyzed and metal-promoted reaction pathways.

Acknowledgements

Rutgers University and the NSF (CAREER CHE-1650766, M.S.) are gratefully acknowledged for support. J.Z. thanks the National Natural Science Foundation of China (22179075) and the China Scholarship Council (201808610096). Supplement funding for this project was provided by the Rutgers University – Newark Chancellor's Research Office.

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