Esterification of Thioamides via Selective N–C(S) Cleavage under Mild Conditions

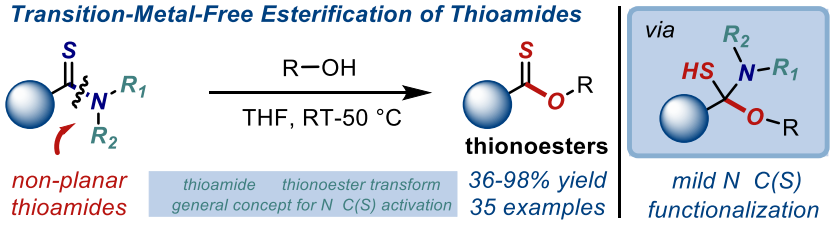
Xinhao Zhu,[†,‡] Kerou Wan,[§,‡] Jin Zhang,[*,†] Hui Zhao,[†] Yang He,[†] Yangmin Ma,[†] Xiufang Yang,[*,†] and Michal Szostak[*,Δ]

[†]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

[§]Kaili Catalyst & New Materials CO., LTD, Shaanxi Key Laboratory of Catalytic Materials and Technology, Xi'an 710299, China

[Δ]Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States

Supporting Information



ABSTRACT: Herein, we report an exceedingly mild method for direct, transition-metal-free esterification of thioamides through the selective generation of tetrahedral intermediates. The method represents the first transition-metal-free approach to direct thioamide to thionoester transform in organic synthesis. This reactivity has been accomplished through *N,N*-Boc$_2$-thioamides that engage ground-state-destabilization of the $n_N \rightarrow \pi^*_{C=S}$ conjugation. The ground-state-destabilization of "single-atom" bioisosteric thioamides will expand the arsenal of valuable amide bond functionalization reactions.

The direct transformation of carboxylic acid derivatives represents one of the most fundamental processes in organic synthesis.[1] In recent years, particular attention has been given to direct transformations of amides owing to the pivotal role of amide bonds in chemistry and biology,[2] where amides represent the most common functional group in pharmaceuticals and the key linkages in peptides and proteins.[3]

In this regard, two generic pathways have been developed, (1) transition-metal-catalyzed cross-coupling via acyl-metal intermediates,[4] and (2) transition-metal-free reactions via tetrahedral intermediates (Figure 1A).[5] Both reactivity frameworks are underpinned by the development of ground-state-destabilization concept of the acyclic amide bond,[6] where the amidic resonance (15-20 kcal/mol, $n_N \rightarrow \pi^*_{CO}$ conjugation) is tailored by steric and electronic substitution in common amides.[7] The transition-metal-free manifold of activating amide bonds is significantly useful due to inherent advantages of transition-metal-free reactions, such as operational-simplicity, scalability, the use of readily-available and non-toxic reagents as well as the environmental and practical benefits.[8]

In contrast to amide bonds, the direct activation of thioamides has been a major challenge. Thioamides represent the closest amide bond bioisosteres in the strictest sense, where the replacement of the N–C(O) linkage with its N–C(S) counterpart brings about important structural and electronic alterations (Figure 1B).[9] As a consequence, thioamides have found a host of major applications in organic synthesis[10] and medicinal chemistry,[11] including as conformational probes,[12] photoswitches,[13] coordination complexes,[14] and bioactive molecules.[15] However, the direct addition to the thioamide bond is even more challenging than to amides due to higher barrier to rotation around the N–C(S) bond vs. N–C(O) bond (by approximately 5-7 kcal/mol).[16] The difficulty of the direct addition to the thioamide bond is highlighted by the fact that the rate of hydrolysis of planar thioamides is ten-times slower than that of corresponding amides, which itself is regarded as an exceedingly slow process in organic synthesis.

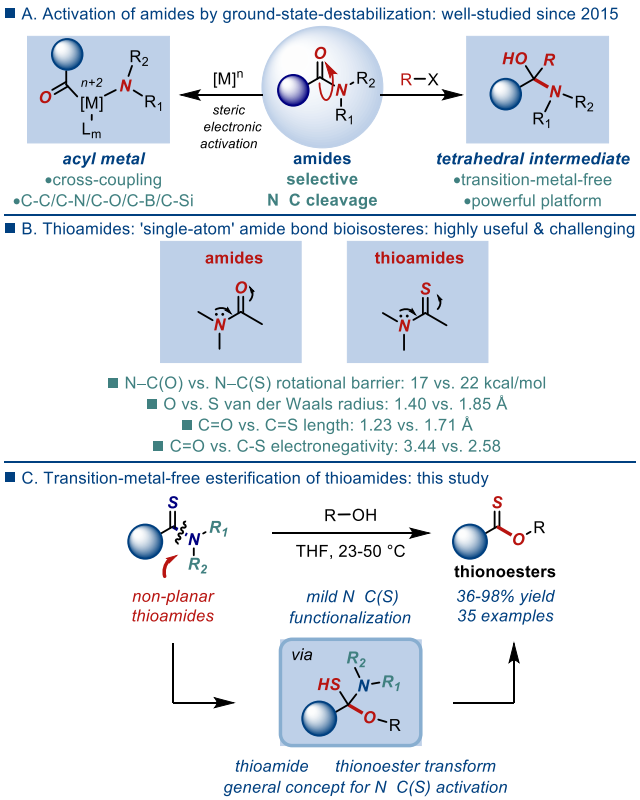


Figure 1. Context of this work: direct esterification of thioamides by N–C(S) activation.

Within our program on amide bond activation[17], herein, we report a mild method for direct, transition-metal-free esterification of thioamides through the selective generation of tetrahedral intermediates (Figure 1C). The method represents the first transition-metal-free approach to direct thioamide to thionoester transform in organic synthesis. The challenge of direct esterification of thioamides has been addressed through the implementation of *N,N*-Boc_2-thioamides that engage ground-state-destabilization of the $n_N \rightarrow \pi^*_{C=S}$ conjugation. The method is characterized by broad scope and excellent functional group tolerance inherent to transition-metal-free protocols. We have demonstrated the potential of this mild esterification in late-stage functionalization. We anticipate that the ground-state-destabilization of bioisosteric thioamides will expand the arsenal of valuable amide bond functionalization reactions.

In particular, the present method permits for thioamide to thionoester disconnection, while the classical methods involve the use of Lawesson's or Curphey's reagents for ester to thionoester disconnection.[18] More generally, the method represents the first transformation of thioamides to thionoesters, demonstrating that ground-state-destabilization of thioamides is suitable for oxygen nucleophiles.[8] Thionoesters are broadly useful intermediates in organic synthesis.[9,10] The reaction is significantly more challenging than transamidation owing to the lower nucleophilicity of alcohols.[5,9,16]

Our studies commenced with optimization of the reaction between *N,N*-Boc_2-thiobenzamide (**1a**) and 4-methoxyphenol (**2a**) (see SI). After very extensive optimization, we established that the combination of K_3PO_4 as a base and THF as a solvent provided optimal results, affording the desired thionic acid ester in 98% yield at room temperature. It is worthwhile to note that THF was found superior to other solvents, including CH_3CN, CH_2Cl_2, EtOH, hexane, $CHCl_3$ and toluene. Furthermore, a decrease of the reaction yield was observed at higher temperatures. Moreover, the crucial importance of K_3PO_4 was highlighted by the fact that other bases, including K_2CO_3, NaO*t*Bu, NaHMDS, NaOH, Et_3N, Na_2CO_3, KOH, provided inferior results. Finally, it should be noted that the *N,N*-Boc_2-thiobenzamide is prepared directly from the corresponding 1° thioamide by a site- and chemoselective *tert*-butoxycarbonylation process, which enables to engage generic thioamides in this mild esterification.

With the optimized conditions in hand, the scope of this novel esterification method with respect to the phenol component was examined (Scheme 1). As shown, we found that the reaction is broad in scope and readily tolerates various electronically-differentiated alcohols. As such, electron rich (**3a**), electron-neutral (**3b**), alkyl-substituted (**3c–3d**) and conjugated biaryl (**3e**) phenols afforded the desired thionoesters in excellent yields. Furthermore, halogen substitution was well-compatible (**3f–3h**), including even sensitive chloro and bromo functionalities that would be problematic in transition-metal-catalyzed protocols and provide handles for further derivatization. Finally, more sterically-demanding phenols could also be employed as demonstrated by 1-naphthol, furnished the desired product in 94% yield (**3i**).

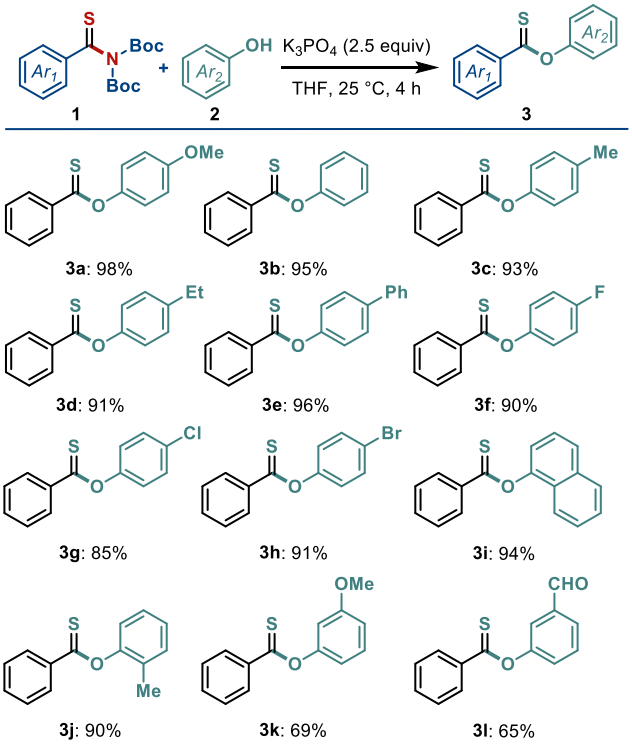
Next, the scope with respect to the thioamide component was evaluated (Scheme 2). The critical aspect is the availability of *N,N*-Boc_2-thioamides from the corresponding benzthioamides. We established that this esterification method is compatible with electronically-differentiated thioamides, such as electron-rich (**3j**), alkyl-substituted (**3k–3l**) and halogen-substituted (**3m–3p**) thioamides. It is noteworthy that even very sensitive halides, such as chloro (**3n**), bromo (**3o**) and iodo (**3p**) are compatible, albeit in slightly decreased yields. Finally, we found that the reaction is not limited to electron-rich thioamides and also encompasses challenging electron-deficient thioamides, such as 4-CF_3 (**3q**), that are prone to N–Boc deprotection.

Having established the scope of this novel esterification reaction using aromatic alcohols, we next became intrigued to test aliphatic alcohols as substrates in this process (Scheme 3). Although the standard conditions used for aromatic alcohols proved unsuccessful, we found that the combination of KHMDS as a base and THF as a solvent at 50 °C proved suitable for esterification with aliphatic alcohols (see SI). We were pleased to find that these conditions were general and accommodated various aliphatic alcohols. As such, simple aliphatic alcohols (**4a–4b**), β-branched (**4c**), more sterically-demanding α-branched (**4d–4e**) and long aliphatic chain alcohols (**4g–4j**) performed well in this reaction. Furthermore, activated benzyl (**4k**) and even bromo-substituted (**4l**) could be employed as well, providing the thionoester products in high yields. It is worth noting that meta-substitution in both phenol (**3k**, **3l**) and thioamide (**3u**) component is well-tolerated. Of note, these substrates contain sensitive functional groups, such as formyl and bromide. Furthermore, ortho-substituted phenols are well-tolerated (**3j**, **3v**, **3aa**). In contrast, ortho-substituted thioamides are not compatible due to steric hindrance. At present, aliphatic thioamides are not tolerated. These reactions

result in recovery of starting materials. Likewise, tertiary alcohols are not tolerated, resulting in decomposition. Nitrogen nucleophiles are also suitable for the reaction manifold involving ground-state-destabilized thioamides.[8a] Carbon nucleophiles have not been tested at present; however, precedents from the twisted amide chemistry are known.[8c]

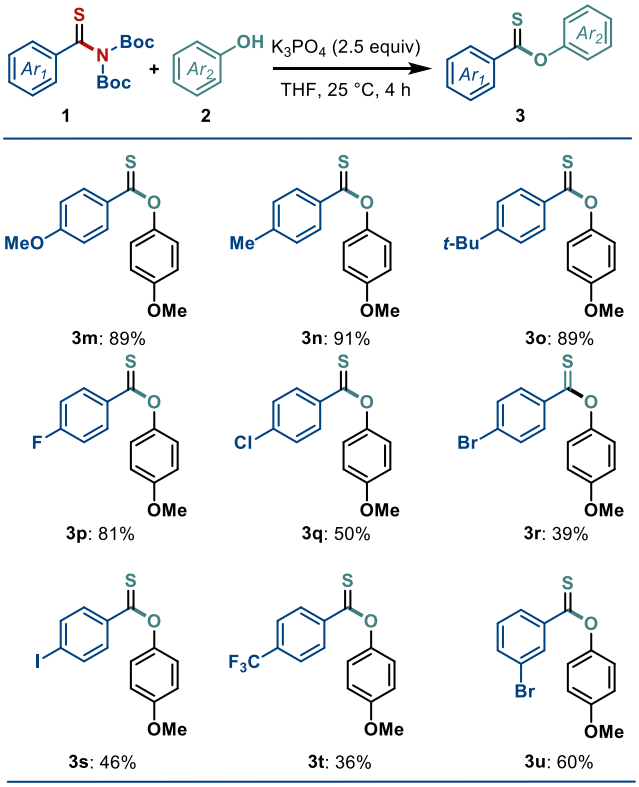
We performed late-stage functionalization of complex alcohols to highlight the synthetic utility of this process (Scheme 4). In the event, the reaction of *eugenol*, a fragrance containing allyl bond (**3r**), as well as *estradiol*, a steroid hormone containing aliphatic and aromatic alcohols (**3s**), and *ethinylestradiol*, an estrogen drug containing sensitive propargyl alcohol and terminal alkyne (**3t**), proceeded in good to high yields demonstrating the potential use of the method in derivatization of complex substrates. The reactions using KHMDS resulted in decomposition. Notably, (**3s**) and (**3t**) were fully characterized by x-ray crystallography, confirming the chemoselective esterification of the aromatic alcohols (*vide infra*).

Scheme 1. Phenol Scope of the Esterification of *N,N*-Boc$_2$-Thioamides [a,b]



[a]Conditions: **1** (1.0 equiv), **2** (2.0 equiv), K_3PO_4 (2.5 equiv), THF (1.0 M), 25 °C, 4 h. [b]Isolated yields.

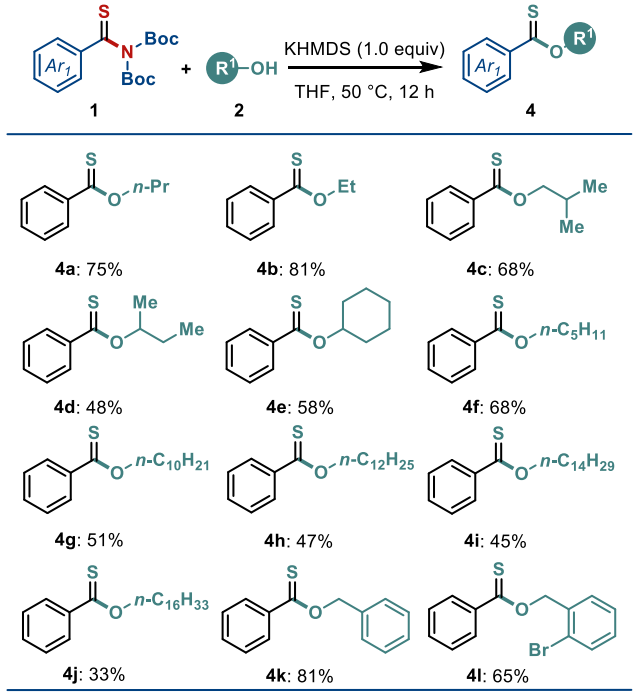
Scheme 2. Thioamide Scope of the Esterification of *N,N*-Boc$_2$-Thioamides [a,b]



[a,b]See Scheme 1.

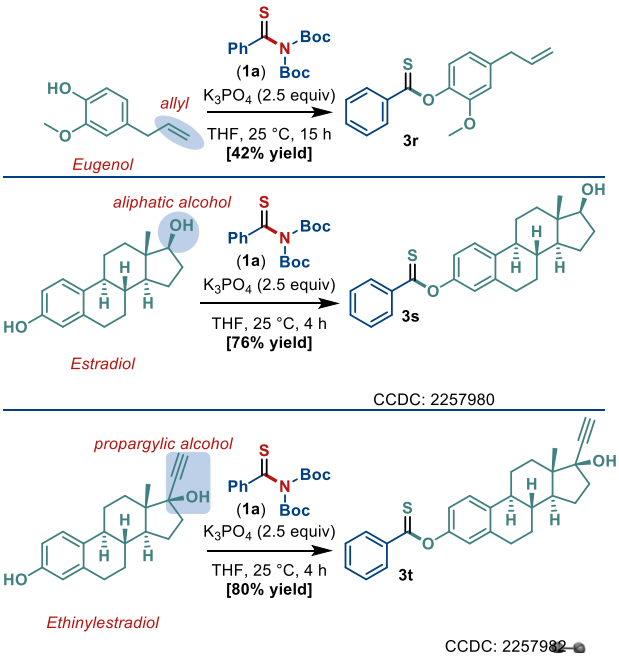
Considering the versatility of the method, we also tested the capacity of *N,N*-Boc$_2$ thioamides to participate in direct thioesterification (Scheme 5). Pleasingly, the ditioester product (**6**) was formed, showcasing that the approach could be used for a thioamide-to-*S*-thioester transform.

Scheme 3. Alcohol Scope of the Esterification of *N,N*-Boc$_2$-Thioamides [a,b]



[a]Conditions: **1** (1.0 equiv), **2** (5.0 equiv), KHMDS (1.0 equiv), THF (1.0 M), 50 °C, 12 h. [b]Isolated yields.

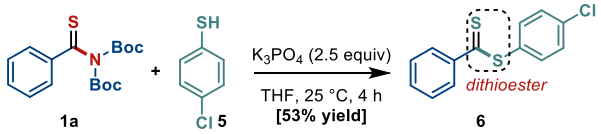
Scheme 4. Late-Stage Functionalization



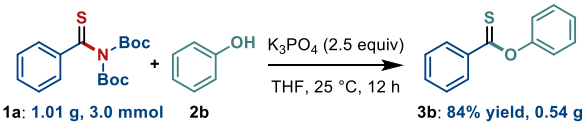
To assess the scalability, the reaction was performed on a gram scale (Scheme 6). Gratifyingly, the reaction afforded the desired product in 84% yield without any modification, attesting to the scalability of the protocol.

Mechanistic studies were performed to gain insight into the selectivity of this method (Scheme 7). First, by subjecting different N-Boc thioamides, we established than *N,N*-Boc_2 thioamides are preferred substrates (Scheme 7A). This finding is consistent with the high amidic resonance of the thioamide bond requiring double *N,N*-Boc_2-activation. From the synthetic standpoint, this reactivity enables for selective functionalization of 1° thioamides. Next, competition experiments were conducted (Scheme 7B–7E). We found that electron-deficient thioamides were inherently more reactive (4-CF_3:4-*t*-Bu = 71:29) (Scheme 7B). This is consistent with the relative electrophilicity of the thioamide bond. Furthermore, electron-rich phenols were found to react preferentially using K_3PO_4 conditions (4-MeO:4-F = 80:20) (Scheme 7C). This is consistent with addition-deprotonation mechanism under these conditions. In contrast, electron-deficient phenols and aliphatic alcohols were found to be more reactive under the KHMDS conditions (4-F:4-MeO >95:5) (Scheme 7D) and (*n*PrOH:PhOH >95:5) (Scheme 7E), consistent with deprotonation-first mechanism under these conditions.

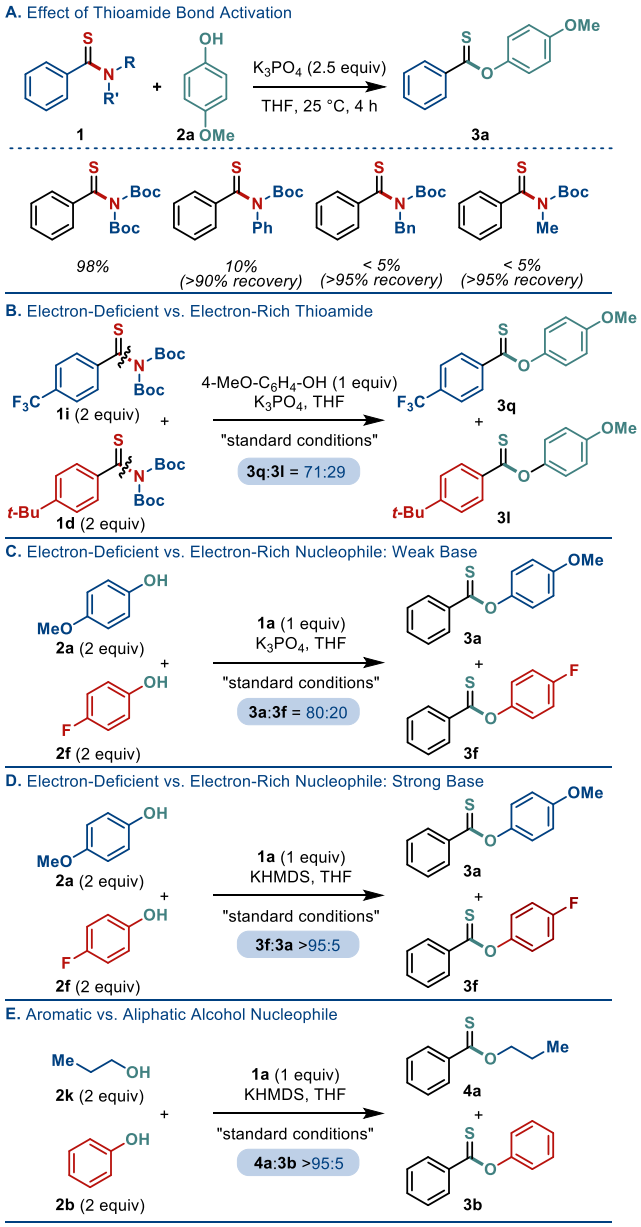
Scheme 5. Thioesterification of *N,N*-Boc_2-Thioamides



Scheme 6. Gram Scale Esterification

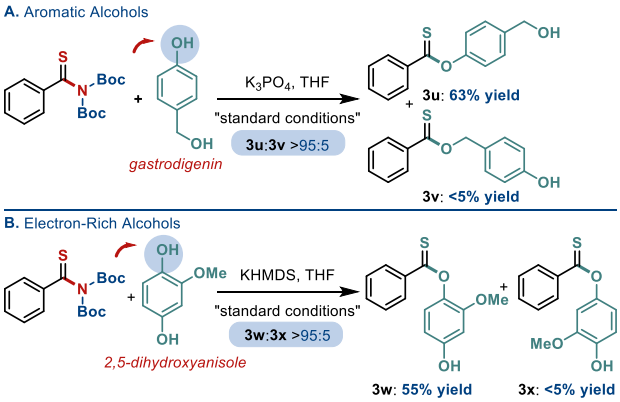


Scheme 7. Mechanistic Studies



This divergence represents a rare example of synthetically useful selectivity control by the choice of reaction conditions in the direct addition to amide derivatives. This reactivity could be exploited in selective esterification using the naturally-occurring 4-hydroxybenzyl alcohol (*gastrodigenin*), which underwent selective reactivity at the aromatic oxygen, and naturally-occurring 2-methoxyhydroquinone (*2,5-dihydroxyanisol*), which reacted selectively at the more electron-rich oxygen (Scheme 8). The higher reactivity of aromatic alcohols is consistent with deprotonation/addition mechanism and the reactivity of more nucleophilic oxygen in these cases. The reaction mechanism is consistent with the nucleophilic addition to the activated thioamide bond to furnish tetrahedral intermediate and collapse.[17b]

Scheme 8. Chemoselective Esterification



In conclusion, we have reported the first direct, transition-metal-free esterification of thioamides through the selective generation of tetrahedral intermediates. The method represents a selective thioamide to thionoester transform by engaging *N,N*-Boc$_2$-thioamides to enable ground-state-destabilization of the thioamide bond. The potential of this mild esterification was highlighted by the broad scope involving aromatic and aliphatic alcohols. We demonstrated the utility of this method in the direct late-stage functionalization of complex molecules. We expect that the concept of ground-state-destabilization of thioamides as the closest amide bond bioisosteres will enable direct derivatization of thioamides in organic synthesis.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

Procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

‡X.Z. and K.W. contributed equally to this work.

Corresponding Author

zhangjin@sust.edu.cn
yangxf@sust.edu.cn
michal.szostak@rutgers.edu

ACKNOWLEDGMENT

J.Z. thanks the National Natural Science Foundation of China (22179075), the Scientific Research Project of Shaanxi Province Education Department (No. 22JC018) and the CSC (201808610096). M.S. thanks Rutgers University and the NSF (CAREER CHE-1650766).

REFERENCES

(1) (a) Rodriguez, N.; Goossen, L. J., Decarboxylative coupling reactions: a modern strategy for C-C-bond formation. *Chem. Soc. Rev.* **2011**, *40*, 5030-5048. (b) Larrosa, I.; Cornella, J., Decarboxylative Carbon-Carbon Bond-Forming Transformations of (Hetero)aromatic Carboxylic Acids. *Synthesis* **2012**, *44*, 653-676.

(2) (a) Pattabiraman, V. R.; Bode, J. W., Rethinking amide bond synthesis. *Nature* **2011**, *480*, 471-479. (b) Tani, K.; Stoltz, B. M., Synthesis and structural analysis of 2-quinuclidonium tetrafluoroborate. *Nature* **2006**, *441*, 731-734. (c) Lei, C.; Liu, Z.; Chen, H.; Ye, D., Transamidation of N-Benzyl-N-Boc-amides under Transition Metal-Free and Base-Free Conditions. *Chinese J. Org. Chem.* **2021**, *41,* 1658-1669. (d) El-Faham, A.; Albericio, F., Peptide coupling reagents, more than a letter soup. *Chem. Rev.* **2011**, *111*, 6557-6602.

(3) (a) Elashal, H. E.; Cohen, R. D.; Raj, M., modified peptides by formation of a backbone cyclic urethane moiety. *Chem. Commun.* **2016**, *52*, 9699-9702. (b) Mahesh, S.; Tang, K. C.; Raj, M., Amide Bond Activation of Biological Molecules. *Molecules* **2018**, *23,* 2615. (c) Greenberg, A.; Breneman, C. M.; Liebman, J. F., Eds. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; Wiley: New York, 2000.

(4) (a) Hie, L.; Baker, E. L.; Anthony, S. M.; Desrosiers, J. N.; Senanayake, C.; Garg, N. K., Nickel-Catalyzed Esterification of Aliphatic Amides. *Angew. Chem., Int. Ed.* **2016**, *55*, 15129-15132. (b) Dander, J. E.; Garg, N. K., Breaking Amides using Nickel Catalysis. *ACS Catal.* **2017**, *7*, 1413-1423. (c) Liu, Y.; Mo, X.; Majeed, I.; Zhang, M.; Wang, H.; Zeng, Z. An efficient and straightforward approach for accessing thionoesters via palladium-catalyzed C-N cleavage of thioamides. *Org. Biomol. Chem.* **2022**, *20,* 1532-1537.

(5) (a) Li, G.; Szostak, M., Highly selective transition-metal-free transamidation of amides and amidation of esters at room temperature. *Nat. Commun.* **2018**, *9*, 4165. (b) Zong, C.; Cheung-Lee, W. L.; Elashal, H. E.; Raj, M.; Link, A. J., Albusnodin: an acetylated lasso peptide from Streptomyces albus. *Chem. Commun.* **2018**, *54*, 1339-1342. (c) Ye, D.; Liu, Z.; Chen, H.; Sessler, J. L.; Lei, C., Cesium Carbonate Catalyzed Esterification of N-Benzyl-N-Boc-amides under Ambient Conditions. *Org. Lett.* **2019**, *21*, 6888-6892. (d) Ghosh, T.; Jana, S.; Dash, J., KO^{t}Bu-Promoted Transition-Metal-Free Transamidation of Primary and Tertiary Amides with Amines. *Org. Lett.* **2019**, *21*, 6690-6694.

(6) Pauling, L. *The Nature of the Chemical Bond*; Oxford University Press: London, 1940.

(7) (a) Szostak, R.; Shi, S.; Meng, G.; Lalancette, R.; Szostak, M. Ground-State Distortion in N-Acyl-tert-butyl-carbamates (Boc) and N-Acyl-tosylamides (Ts): Twisted Amides of Relevance to Amide N-C Cross-Coupling. *J. Org. Chem.* **2016**, *81*, 8091-8094. (b) Pace, V.; Holzer, W.; Meng, G.; Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. Structures of Highly Twisted Amides Relevant to Amide N-C Cross-Coupling: Evidence for Ground-State Amide Destabilization. *Chem. - Eur. J.* **2016**, *22*, 14494-14498. (c) Szostak, R.; Meng, G.; Szostak, M. Resonance Destabilization in N-Acylanilines (Anilides): Electronically-Activated Planar Amides of Relevance in N-C(O) Cross-Coupling. *J. Org. Chem.* **2017**, *82*, 6373-6378. (d) Meng, G.; Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. Reversible Twisting of Primary Amides via Ground State N-C(O) Destabilization: Highly Twisted Rotationally Inverted Acyclic Amides. *J. Am. Chem. Soc.* **2018**, *140*, 727-734. (e) Kemnitz, C. R.; Loewen, M. J. "Amide Resonance" Correlates with a Breadth of C-N Rotation Barriers. *J. Am. Chem. Soc.* **2007**, *129*, 2521-2528. (f) Mujika, J. I.; Mercero, J. M.; Lopez, X. Water-Promoted Hydrolysis of a Highly Twisted Amide: Rate Acceleration Caused by the Twist of the Amide Bond. *J. Am. Chem. Soc.* **2005**, *127*, 4445-4453. (g) Glover, S. A.; Rosser, A. A. Reliable Determination of Amidicity in Acyclic Amides and Lactams. *J. Org. Chem.* **2012**, *77*, 5492-5502.

(8) (a) Li, G.; Xing, Y.; Zhao, H.; Zhang, J.; Hong, X.; Szostak, M., Chemoselective Transamidation of Thioamides by Transition-Metal-Free N-C(S) Transacylation. *Angew. Chem., Int. Ed.* **2022**, *61*, e202200144. (b) Zhang, J.; Zhao, H; Li, G.; Zhu, X.; Shang, L.; He, Y.; Liu, X.; Ma, Y.; Szostak, M. Transamidation of thioamides with nucleophilic amines: thioamide N–C(S) activation by ground-state-destabilization. *Org. Biomol. Chem.* **2022**, *20*, 5981-5988. (c) Li, G.; Szostak, M. Kinetically-Controlled, Highly Chemoselective Acylation of Functionalized Grignard Reagents with Amides by N–C Cleavage. *Chem. Eur. J.* **2020**, *26*, 611-615.

(9) (a) Mahanta, N.; Szantai-Kis, D. M.; Petersson, E. J.; Mitchell, D. A., Biosynthesis and Chemical Applications of Thioamides. *ACS Chem. Biol.* **2019**, *14*, 142-163. (b) Choudhary, A.; Raines, R. T., An evaluation of peptide-bond isosteres. *ChemBioChem* **2011**, *12*, 1801-1807. (c) Cao, W.; Dai, F.; Hu, R.; Tang, B. Z., Economic Sulfur Conversion to Functional Polythioamides through Catalyst-Free Multicomponent Polymerizations of Sulfur, Acids, and Amines. *J. Am. Chem. Soc.* **2020**, *142*, 978-986. (d) Miele, M.; D'Orsi, R.; Sridharan, V.; Holzer, W.; Pace, V., Highly chemoselective difluoromethylative homologation of iso(thio)cyanates: expeditious access to unprece-

dented alpha,alpha-difluoro(thio)amides. *Chem. Commun.* **2019**, *55*, 12960-12963.

(10) (a) Liao, Y. Zhang, S. Jiang, X. Construction of Thioamide Peptides from Chiral Amino Acids. *Angew. Chem., Int. Ed.* **2023**, *62*, e202303625. (b) Fukagawa, S.; Kato, Y.; Tanaka, R.; Kojima, M.; Yoshino, T.; Matsunaga, S., Enantioselective C(sp^3)-H Amidation of Thioamides Catalyzed by a $Cobalt^{III}$ /Chiral Carboxylic Acid Hybrid System. *Angew*. *Chem*., *Int*. *Ed*. **2019**, *58*, 1153-1157.

(11) Beno, B. R.; Yeung, K. S.; Bartberger, M. D.; Pennington, L. D.; Meanwell, N. A., A Survey of the Role of Noncovalent Sulfur Interactions in Drug Design. *J. Med. Chem.* **2015**, *58*, 4383-4438.

(12) Soares, P.; Lucas, X.; Ciulli, A., Thioamide substitution to probe the hydroxyproline recognition of VHL ligands. *Bioorg. Med. Chem.* **2018**, *26*, 2992-2995.

(13) Helbing, J.; Bregy, H.; Bredenbeck, J.; Pfister, R.; Hamm, P.; Huber, R.; Wachtveitl, J.; De Vico, L.; Olivucci, M., A Fast Photoswitch for Minimally Perturbed Peptides: Investigation of the trans → cis Photoisomerization of N-Methylthioacetamide. *J. Am. Chem. Soc*. **2004**, *126*, 8823 – 8834.

(14) Thomas, J., Metal ion directed self-assembly of sensors for ions, molecules and biomolecules. *Dalton Trans.* **2011**, *40*, 12005-12016.

(15) (a) Artis, D. R.; Lipton, M. A., Conformations of Thioamide-Containing Dipeptides: A Computational Study. *J. Am. Chem. Soc.* **1998**, *120*, 12200-12206. (b) Newberry, R. W.; VanVeller, B.; Guzei, I. A.; Raines, R. T., n→π* Interactions of Amides and Thioamides: Implications for Protein Stability. *J. Am. Chem. Soc.* **2013**, *135*, 7843-7846. (c) Walters, C. R.; Szantai-Kis, D. M.; Zhang, Y.; Reinert, Z. E.; Horne, W. S.; Chenoweth, D. M.; Petersson, E. J., The effects of thioamide backbone substitution on protein stability: a study in alpha-helical, beta-sheet, and polyproline II helical contexts. *Chem. Sci.* **2017**, *8*, 2868-2877.

(16) K. B. Wiberg, D. J. Rush, Solvent Effects on the Thioamide Rotational Barrier: An Experimental and Theoretical Study. *J. Am. Chem. Soc.* **2001**, *123*, 2038 – 2046.

(17) (a) Li, G.; Lei, P.; Szostak, M., Transition-Metal-Free Esterification of Amides via Selective N-C Cleavage under Mild Conditions. *Org. Lett.* **2018**, *20*, 5622-5625. (b) G..Li,.M. Szostak, C. L. Ji, X. Hong, M. Szostak, Highly Chemoselective, Transition-Metal-Free Transamidation of Unactivated Amides and Direct Amidation of Alkyl Esters by N–C/O–C Cleavage.*J. Am. Chem. Soc.* **2019**, *141*, 11161–11172.

(18) Curphey, T. J. Thionation with the Reagent Combination of Phosphorus Pentasulfide and Hexamethyldisiloxane. *J. Org. Chem.* **2002**, *67*, 6461–6473.