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# Ynamide-Mediated Thionoester and Dithioester Syntheses

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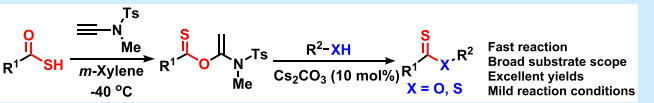
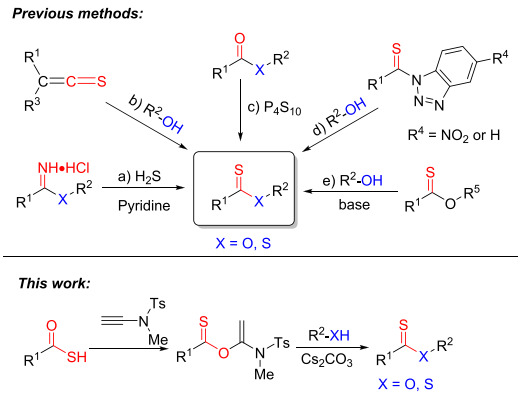
**ABSTRACT:** A novel ynamide-mediated synthesis of thionoesters and dithioesters is described. The selective addition reactions of various monothiocarboxylic acids with ynamide furnish $\alpha$-thioacyloxyenamides, which undergo transesterification with nucleophilic −OH or −SH species to afford thionoesters and dithioesters, respectively. The broad substrate scope, mild reaction conditions, and excellent yields make this method an attractive synthetic approach to thionoesters and dithioesters.






Thionoesters and dithioesters are important compounds due to the presence of a thiocarbonyl group, which imparts them with unique properties and reactivities.[1] Both of these classes of esters have been used as intermediates in a broad range of organic transformations.[2] For example, thionoesters can be readily transformed into difluoroalkyl ethers[3] or thioamides.[4] Thionoesters can also serve as the precursors for ethers[5] and 1,4,2-oxathiazoles.[6] Very recently, Pluth and co-workers have demonstrated that thionoesters and dithioesters could function as cysteine-selective $H_2S$ donors.[7] Although thionoesters and dithioesters are ester analogs, their syntheses are more complicated and challenging than those of esters.[2] Thionoesters and dithioesters are typically prepared from Pinner intermediates (Scheme 1, eq a).[8] Unfortunately, the coformation of thioamide side products is often a major concern in this strategy.[9] Dithioacids are ideal starting materials for thionoester and dithioester syntheses but are unstable and difficult to prepare, particularly aliphatic dithioacids.[10] The addition reaction of alcohols or thiols with thioketenes offers an attractive alternative approach to thionoesters and dithioesters (Scheme 1, eq b). However, thioketenes are unstable and can only be isolated at very low temperatures.[11] A general strategy for direct conversion of esters into the corresponding thiocarbonyl esters involves the use of thionating reagents such as $P_4S_{10}$[12] and Lawesson's reagent (Scheme 1, eq c).[13] While this strategy provides a wide range of thionoesters, the poor reactivity of the ester functionality leads to low reaction efficiency, a long reaction time, and poor chemoselectivity between ester and amide functional groups.[14,15] Alternatively, the use of thioacylating reagents and transesterification reactions has provided more convenient synthetic approaches to thionoesters (Scheme 1, eq d[16] and e[2,17]). However, most thioacylating reagents are highly reactive and unstable.[18] Additionally, the preparation of thioacylating reagents requires tedious multiple-step reactions and the use of malodorous thionating reagents. Considering the versatile applications of thionoesters and dithioesters, highly efficient strategies for their syntheses are in great demand. Herein, we report a novel ynamide-mediated synthetic approach to thionoesters and dithioesters, in which $\alpha$-thioacyloxyenamides act as the thioacylating reagents.

**Scheme 1. Syntheses of Thionoesters and Dithioesters**




Over the past three decades, ynamides have been widely used in a broad range of organic transformations because of their versatile reactivity.[19] We previously demonstrated that ynamides could serve as racemization-free coupling reagents for amide bond formation.[20] Later, we found that $\alpha$-thioacyloxyenamides formed from the selective addition reaction of monothiocarboxylic amino acids with ynamides could be used as the efficient racemization-free thioacylating reagents for site-specific incorporation of a thioamide substituent into a growing peptide backbone.[21] Notably, the protection of hydroxyl groups in the side chain of Ser, Thr, and Tyr is not necessary during thioamide bond formation which is mainly attributed to the lower nucleophilicity of the hydroxyl group compared to that of the

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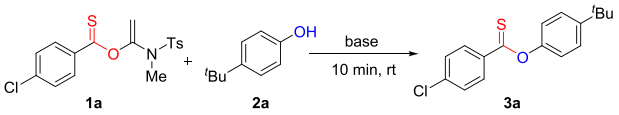
free amino group. Transesterifications can be promoted by acid or base catalysts,[15,17] and this strategy has been successfully applied to the transesterification of α-acyloxyenamides with alcohol and phenol derivatives.[22] Based on these advances, we hypothesized that α-thioacyloxyenamide could act as a thioacyl donor for thionoesters. Our preliminary study revealed that transesterification of α-thioacyloxyenamide **1a** with 4-*tert*-butylphenol **2a** proceeded smoothly in acetonitrile ($CH_3CN$) at room temperature using *N*,*N*-diisopropylethylamine (DIPEA) as the base (Table 1, entry 1). Further, the reaction

**Table 1. Optimization of the Reaction Conditions**[a]



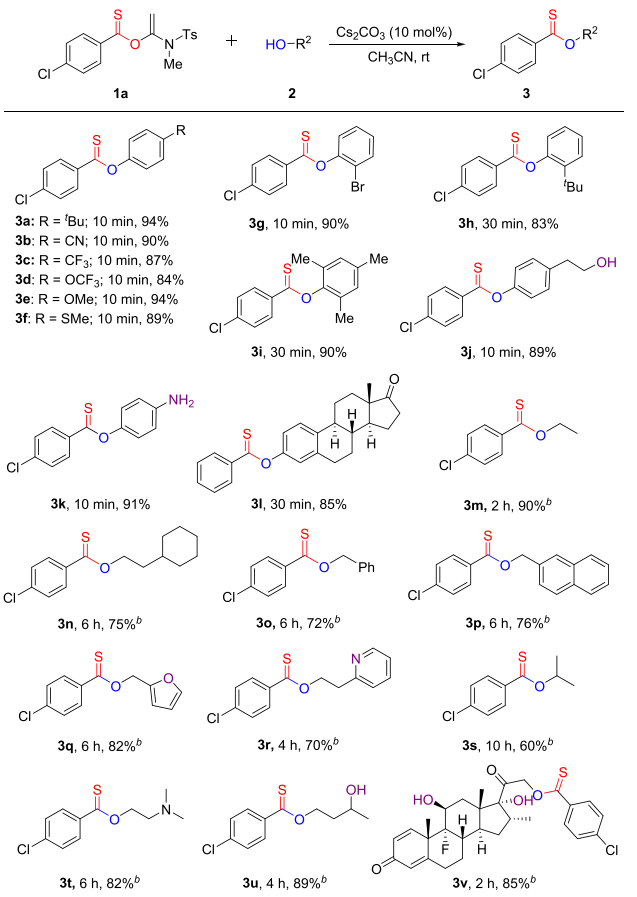

| entry | solvent | base | yield (%) |
|---|---|---|---|
| 1[b] | $CH_3CN$ | DIPEA | 68 |
| 2[b] | $CH_3CN$ | $Et_3N$ | 72 |
| 3 | $CH_3CN$ | DMAP | 85 |
| 4 | $CH_3CN$ | $Cs_2CO_3$ | 91 |
| 5 | DCM | $Cs_2CO_3$ | 80 |
| 6 | DMF | $Cs_2CO_3$ | 85 |
| 7 | Acetone | $Cs_2CO_3$ | 82 |
| 8 | THF | $Cs_2CO_3$ | 81 |
| **9**[c] | **$CH_3CN$** | **$Cs_2CO_3$** | **90** |
| 10[d] | $CH_3CN$ | $Cs_2CO_3$ | 72 |

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol, 2 equiv), base (0.02 mmol, 0.2 equiv), solvent (1 mL), rt, 10 min, isolated yield. [b]2 h. [c]$Cs_2CO_3$ (0.01 mmol, 0.1 equiv). [d]$Cs_2CO_3$ (0.005 mmol, 0.05 equiv), 50 min.

conditions were optimized to establish a robust protocol for the thionoester synthesis (Table 1). The base catalyst played a crucial role in this transesterification reaction (Table 1, entries 1−4). $CH_3CN$ was identified to be the optimal solvent system (Table 1, entries 4−8). Reducing the loading of $Cs_2CO_3$ from 20 mol % to 10 mol % had no detrimental effect on the reaction efficiency (Table 1, entries 4 and 9). However, further decreasing the $Cs_2CO_3$ loading to 5 mol % led to a reduced yield, even with a prolonged reaction time (Table 1, entry 10).

With the optimized reaction conditions in hand, we next investigated the scope of phenols and alcohols **2** using α-thioacyloxyenamide **1a** as a model thioacyl donor (Scheme 2). Phenols containing both electron-donating (*p*-$^t$Bu, *p*-$OCF_3$, *p*-OMe, *p*-SMe) and electron-withdrawing (*p*-CN, *p*-$CF_3$, *o*-Br) substituents reacted smoothly to afford the desired products in good to excellent yields (84%−94%). Transesterification products of trisubstituted (**3i**) and sterically hindered phenols (**3h**) could also be obtained in excellent yields under the standard reaction conditions. Additionally, a complex substrate, such as estrone, could also serve as a nucleophile to provide the desired product in good yield (**3l**). Although the reaction efficiency of alcohols was lower than that of phenols, all the thionoesters of various alcohols could be obtained in good to excellent yields albeit with an excess amount of alcohols. Excellent selectivity was observed for the transesterifications of polyfunctionalized phenols, such as 4-(2-hydroxyethyl)phenol and 4-aminophenol (**3j** and **3k**). A variety of primary and secondary alcohols were compatible with this protocol (**3m**−**t**). Interestingly, the primary hydroxyl group could be selectively

**Scheme 2. Substrate Scope of the Hydroxyl Species**[a]




[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol, 2 equiv), $Cs_2CO_3$ (0.01 mmol, 0.1 equiv), $CH_3CN$ (1.0 mL), rt, isolated yield. [b]**2** (2.0 mmol, 20 equiv).

thioacylated in the presence of secondary and tertiary hydroxyl groups (**3u** and **3v**).

We subsequently extended our methodology to the dithioesters, which are important but have received less attention than thioamides and thionoesters due to the lack of synthetic strategies. Under the standard reaction conditions, the transesterification reaction between **1b** and **4a** offered the expected compound **5a** in only 40% yield (data not shown). To our delight, an excellent yield of compound **5a** (90%) was obtained when the reaction was carried out under a nitrogen atmosphere with 1.2 equiv of **1b** (Scheme 3). Exploring the substrate scope of thiophenols revealed that both electron-donating and electron-withdrawing substituents were compatible with the reaction, providing the target dithioesters in good to excellent yields (**5a**−**5g**). Interestingly, transesterification of alkyl thiols was also viable without the requirement of excess thiols or long reaction times (**5h**−**5j**). Notably, dithioester was produced exclusively when 2-mercaptoethanol was used as the substrate due to the stronger nucleophilicity of −SH compared to −OH (**5k**). Sterically bulky substrates, such as cyclohexanethiol and *tert*-butyl mercaptan, were also compatible with this strategy (**5l** and **5m**). The sulfhydryl group of Cys can also react with α-thioacyloxyenamide to give the corresponding dithioesters (**5n**), thus providing an opportunity for the chemical modification of peptides and proteins. This transesterification reaction could also be extended to a seleno nucleophile, with phenylselenol reacting with α-thioacyloxy-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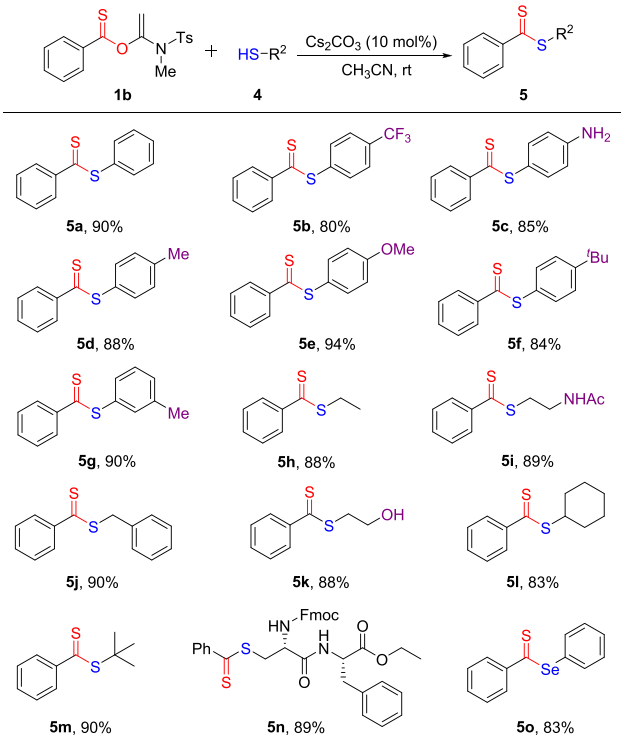
**Scheme 3. Substrate Scope of the Sulfhydryl Species**[a]




[a]Reaction conditions: **1b** (0.12 mmol, 1.2 equiv), **4** (0.1 mmol), $Cs_2CO_3$ (0.01 mmol, 0.1 equiv), $CH_3CN$ (1.0 mL), $N_2$, rt, 5 min, isolated yield.

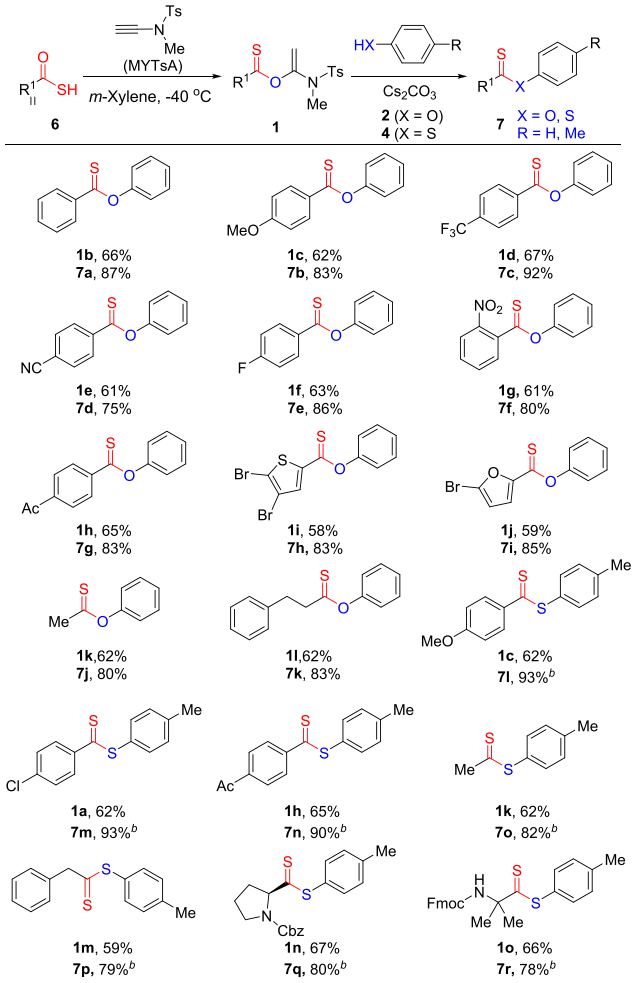
enamide to produce Se-phenyl benzoselenothioate (**5o**) in 83% yield. This preliminary result is promising for the development of a general synthetic approach to thioselenoesters.

These encouraging results prompted us to extend the reaction to other α-thioacyloxyenamides, which could be easily prepared in good yields by the selective addition reaction of monothiocarboxylic acids with ynamide (MYTsA) (for details, see Supporting Information).[21] As shown in Scheme 4, a broad range of α-thioacyloxyenamides reacted with alcohol and thiol derivatives smoothly to give the desired products in good to excellent yields. Heterocyclic aromatic moieties, such as furan and thiophene, could also be tolerated to produce the corresponding thionoesters (**7h** and **7i**). Note that thionoesters **7g** and **7n**, which cannot be prepared by using thionating reagents and methylthionobenzoate methods, can be obtained in excellent yields under the standard reaction conditions.[17] Additionally, α-thioacyloxyenamides derived from aliphatic monothiocarboxylic acids are also valid substrates for the synthesis of thionoesters (**7j** and **7k**) and dithioesters (**7o**−**7r**).

To further illustrate the utility of this method, gram-scale synthesis was performed, and 1.12 g of thionoester **3m** was obtained in 80% yield. In addition, **3m** was successfully transformed into a series of valuable compounds according to the reported methods (for details, see the Supporting Information).

In conclusion, we have developed a novel and efficient synthetic strategy for thionoesters and dithioesters with α-thioacyloxyenamides, which could be prepared easily from the selective addition reaction of monothiocarboxylic acids with ynamide (MYTsA), as the thioacyl donor. A broad range of nucleophilic −OH and −SH species and monothiocarboxylic acids were compatible with the reaction conditions and afforded

**Scheme 4. Substrate Scope of α-Thioacyloxyenamides**[a]




[a]Reaction conditions for the first step: **6** (0.45 mmol), **MYTsA** (0.3 mmol), *m*-xylene (2.0 mL), $N_2$, −40 °C, 8 h. Reaction conditions for the second step: **1** (0.1 mmol), **2** (0.2 mmol, 2 equiv), $Cs_2CO_3$ (0.01 mmol, 0.1 equiv), $CH_3CN$ (1.0 mL), rt, 10 min, isolated yield. [b]**1** (0.12 mmol, 1.2 equiv) and **4** (0.1 mmol), $Cs_2CO_3$ (0.01 mmol, 0.1 equiv), $CH_3CN$ (1.0 mL), $N_2$, rt, 5 min.

the target thionoesters and dithioesters in good to excellent yields. Undoubtedly, this simple and efficient strategy for the synthesis of thionoesters and dithioesters will find broad application in the field of organic chemistry.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02402.

Experimental procedures, compound characterization data, and copies of NMR spectra (PDF)

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## Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

(1) (a) Tan, W.; Jansch, N.; Ohlmann, T.; Meyer-Almes, F. J.; Jiang, X. Thiocarbonyl Surrogate via Combination of Potassium Sulfide and Chloroform for Dithiocarbamate Construction. *Org. Lett.* **2019**, *21*, 7484−7488. (b) Tan, W.; Jiang, X. Construction of Thiocarbonyl (C = S) with Inorganic Sulfur. *Phosphorus, Sulfur Silicon Relat. Elem.* **2019**, *194*, 731−734. (c) Metzner, P. Thiocarbonyl Compounds as Specific Tools for Organic Synthesis. In *Organosulfur Chemistry I*; Page, P. C. B., Ed.; Springer Berlin Heidelberg: Berlin, Heidelberg, 1999; pp 127−181. (d) Liu, C.; Fang, Y.; Wang, S. Y.; Ji, S. J. Highly Regioselective Rh(III)-Catalyzed Thiolation of N-Tosyl Acrylamides: General Access to (Z)-β-Alkenyl Sulfides. *Org. Lett.* **2018**, *20*, 6112−6116.

(2) Jones, B. A.; Bradshaw, J. S. Synthesis and Reduction of Thiocarboxylic O-esters. *Chem. Rev.* **1984**, *84*, 17−30.

(3) Newton, J.; Driedger, D.; Nodwell, M. B.; Schaffer, P.; Martin, R. E.; Britton, R.; Friesen, C. M. A Convenient Synthesis of Difluoroalkyl Ethers from Thionoesters Using Silver(I) Fluoride. *Chem. - Eur. J.* **2019**, *25*, 15993−15997.

(4) (a) Ried, W.; von der Emden, W. Aminosäure-thionester und Endothiopeptide. *Angew. Chem.* **1960**, *72*, 268−268. (b) Lajoie, G.; Lépine, F.; Maziak, L.; Belleau, B. Facile Regioselective Formation of Thiopeptide Linkages from Oligopeptides with New Thionation Reagents. *Tetrahedron Lett.* **1983**, *24*, 3815−3818.

(5) (a) Bradshaw, J. S.; Jones, B. A.; Gebhard, J. S. Formation of Ethers by the Reductive Desulfurization of Thiono Esters. *J. Org. Chem.* **1983**, *48*, 1127−1129. (b) Nicolaou, K. C.; Sato, M.; Theodorakis, E. A.; Miller, N. D. Conversion of Thionoesters and Thionolactones to Ethers - a General and Efficient Radical Desulfurization. *J. Chem. Soc., Chem. Commun.* **1995**, *15*, 1583−1585.

(6) (a) Couture, A.; Grandclaudon, P.; Huguerre, E. Nouvelle Méthode de Synthèse de Thiazolopyridines. *J. Heterocycl. Chem.* **1987**, *24*, 1765−1769. (b) Lu, F. L.; Keshavarz-K, M.; Srdanov, G.; Jacobson, R. H.; Wudl, F. A New Preparation of 5-(Alkylthio)-1,2-dithiole-3-thiones and a Highly Functionalized 1,3-Dithiole-2-thione. *J. Org. Chem.* **1989**, *54*, 2165−2169.

(7) Cerda, M. M.; Zhao, Y.; Pluth, M. D. Thionoesters: A Native Chemical Ligation-Inspired Approach to Cysteine-Triggered $H_2S$ Donors. *J. Am. Chem. Soc.* **2018**, *140*, 12574−12579.

(8) Marvel, C. S.; De Radzitzky, P.; Brader, J. J. An Improved Preparation of Dithioesters and Some Reactions and Spectral Properties of These Compounds. *J. Am. Chem. Soc.* **1955**, *77*, 5997−5999.

(9) Ried, W.; Emden, W. V. D. Aminosäure-thionester und Endothiopeptide, II. *Liebigs Ann. Chem.* **1961**, *642*, 128−133.

(10) Latif, K. A.; Ali, M. Y. Reaction of Thiobenzoyldisulphides with Bases Synthesis of Thion-esters. *Tetrahedron* **1970**, *26*, 4247−4249.

(11) Bühl, H.; Seitz, B.; Meier, H. Thermolyse von 1,2,3-Thiadiazolen. *Tetrahedron* **1977**, *33*, 449−452.

(12) Loiseau, F.; Kholod, I.; Neier, R. Thione Esters as Substrates for the Stereoselective Alkylation of Model Compounds of Nonactic Acids. *Eur. J. Org. Chem.* **2010**, *2010*, 4642−4661.

(13) (a) Davy, H. A Direct Conversion of Carboxylic Acids into Dithioesters. *J. Chem. Soc., Chem. Commun.* **1982**, *8*, 457−458. (b) Hewitt, R. J.; Ong, M. J. H.; Lim, Y. W.; Burkett, B. A. Investigations of the Thermal Responsiveness of 1,4,2-Oxathiazoles. *Eur. J. Org. Chem.* **2015**, *2015*, 6687−6700.

(14) Carey, F. A.; Dailey, O. D. Regioselectivity of Metalation of 1,3-Dithiolanes and 1,3-Dithiolane 1-Oxides. *Phosphorus Sulfur Relat. Elem.* **1981**, *10*, 169−174.

(15) Shalaby, M. A.; Rapoport, H. A General and Efficient Route to Thionoesters via Thionoacyl Nitrobenzotriazoles. *J. Org. Chem.* **1999**, *64*, 1065−1070.

(16) Yeo, S. K.; Choi, B. G.; Kim, J. D.; Lee, J. H. A Convenient Method for the Synthesis of Thiobenzamide Derivatives and O-Thiobenzoates by Use of 2-Benzothiazolyl Dithiobenzoate as Effective Thiobenzoylation Reagent. *Bull. Korean Chem. Soc.* **2002**, *23*, 1029−1030.

(17) Newton, J. J.; Britton, R.; Friesen, C. M. Base-Catalyzed Transesterification of Thionoesters. *J. Org. Chem.* **2018**, *83*, 12784−12792.

(18) Levesque, G.; Arsene, P.; Fanneau-Bellenger, V.; Pham, T. N. Protein thioacylation. 1. Reagents Design and Synthesis. *Biomacromolecules* **2000**, *1*, 387−399.

(19) (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. Ynamides: a Modern Functional Group for the New Millennium. *Chem. Rev.* **2010**, *110*, 5064−5106. (b) Evano, G.; Coste, A.; Jouvin, K. Ynamides: Versatile Tools in Organic Synthesis. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840−2859. (c) Pan, F.; Li, X.-L.; Chen, X.-M.; Shu, C.; Ruan, P.-P.; Shen, C.-H.; Lu, X.; Ye, L.-W. Catalytic Ynamide Oxidation Strategy for the Preparation of α-Functionalized Amides. *ACS Catal.* **2016**, *6*, 6055−6062. (d) Pan, F.; Shu, C.; Ye, L.-W. Recent Progress Towards Gold-Catalyzed Synthesis of N-containing Tricyclic Compounds Based on Ynamides. *Org. Biomol. Chem.* **2016**, *14*, 9456−9465. (e) Huang, B.; Zeng, L.; Shen, Y.; Cui, S. One-Pot Multicomponent Synthesis of β-Amino Amides. *Angew. Chem., Int. Ed.* **2017**, *56*, 4565−4568. (f) Chen, R.; Zeng, L.; Huang, B.; Shen, Y.; Cui, S. Decarbonylative Coupling of α-Keto Acids and Ynamides for Synthesis of β-Keto Imides. *Org. Lett.* **2018**, *20*, 3377−3380. (g) Zhou, B.; Tan, T. D.; Zhu, X. Q.; Shang, M. Z.; Ye, L. W. Reversal of Regioselectivity in Ynamide Chemistry. *ACS Catal.* **2019**, *9*, 6393−6406. (h) Peng, B.; Huang, X.; Xie, L. G.; Maulide, N. A Bronsted Acid Catalyzed Redox Arylation. *Angew. Chem., Int. Ed.* **2014**, *53*, 8718−8721. (i) Baldassari, L. L.; de la Torre, A.; Li, J.; Ludtke, D. S.; Maulide, N. Ynamide Preactivation Allows a Regio- and Stereoselective Synthesis of α, β-Disubstituted Enamides. *Angew. Chem., Int. Ed.* **2017**, *56*, 15723−15727.

(20) (a) Hu, L.; Xu, S.; Zhao, Z.; Yang, Y.; Peng, Z.; Yang, M.; Wang, C.; Zhao, J. Ynamides as Racemization-Free Coupling Reagents for Amide and Peptide Synthesis. *J. Am. Chem. Soc.* **2016**, *138*, 13135−13138. (b) Hu, L.; Zhao, J. F. Ynamide: A New Coupling Reagent for Amide and Peptide Synthesis. *Synlett* **2017**, *28*, 1663−1670.

(21) (a) Yang, J.; Wang, C.; Xu, S.; Zhao, J. Ynamide-Mediated Thiopeptide Synthesis. *Angew. Chem., Int. Ed.* **2019**, *58*, 1382−1386. (b) Yang, J.; Wang, C.; Yao, C.; Chen, C.; Hu, Y.; He, G.; Zhao, J. Site-Specific Incorporation of Multiple Thioamide Substitutions into a Peptide Backbone via Solid Phase Peptide Synthesis. *J. Org. Chem.* **2020**, *85*, 1484−1494.

(22) (a) Yang, M.; Wang, X.; Zhao, J. Ynamide-Mediated Macrolactonization. *ACS Catal.* **2020**, *10*, 5230−5235. (b) Wang, X.; Yang, Y.; Zhao, Y.; Wang, S.; Hu, W.; Li, J.; Wang, Z.; Yang, F.; Zhao, J. Ynamide-Mediated Intermolecular Esterification. *J. Org. Chem.* **2020**, *85*, 6188−6194.