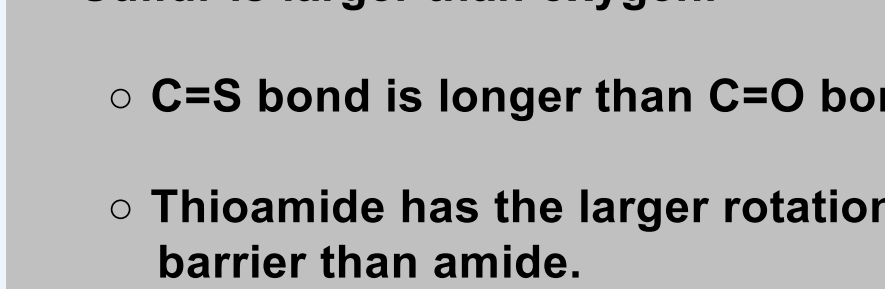


Graduate School of Pharmaceutical Sciences, Kyoto University

## 1. Introduction : About Thioamide



### Lawesson's Reagent



The chemical structure shows a cyclic peptide backbone (a 10-membered ring with four amide bonds). One of the nitrogen atoms in the backbone is substituted with a side chain. This side chain consists of a 4-aminobutyl group, which is further substituted with a Cbz (carboxybenzyl) group and a phenyl group. The Cbz group is represented as a benzene ring attached to a CH2 group, which is in turn attached to a carbonyl group (C=O) that is bonded to the nitrogen of the amide bond. The phenyl group is represented as a benzene ring attached to the nitrogen of the amide bond. The side chain is highlighted with a red circle and labeled 'X'.

**an 1000-fold increase in anticancer activity**  
H. Lin et al. *Cancer Cell*, 2016, 29, 297.

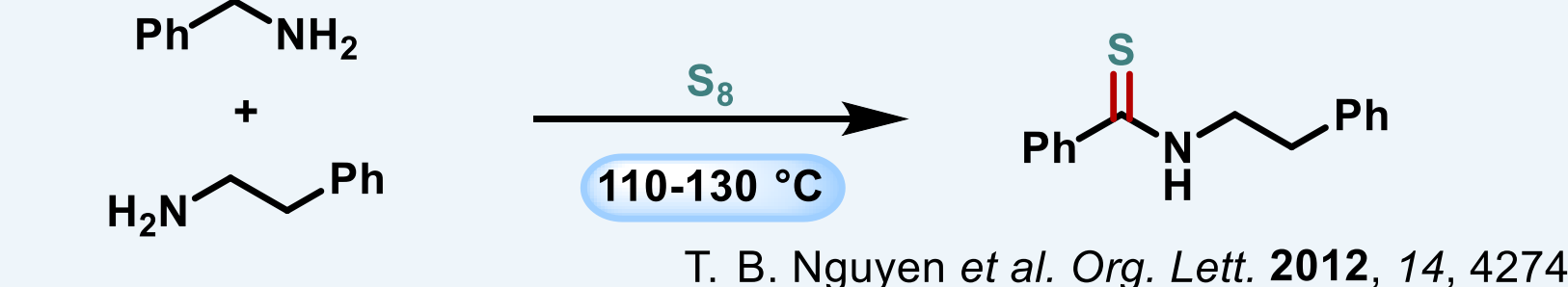
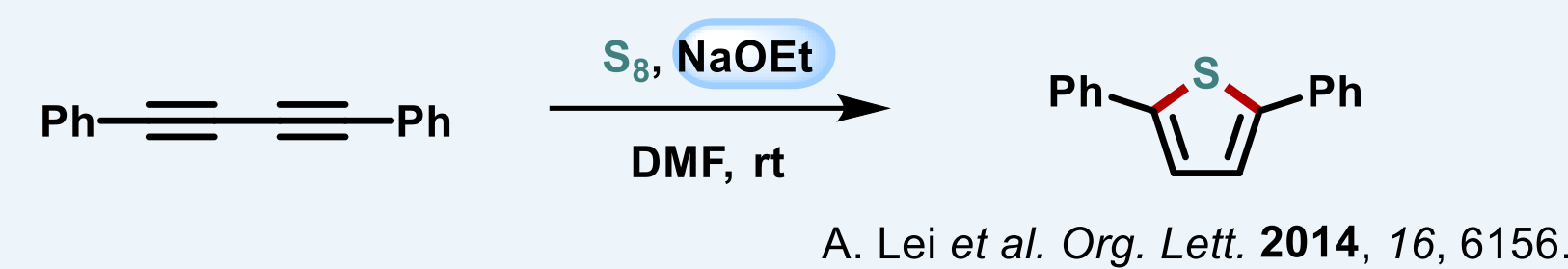
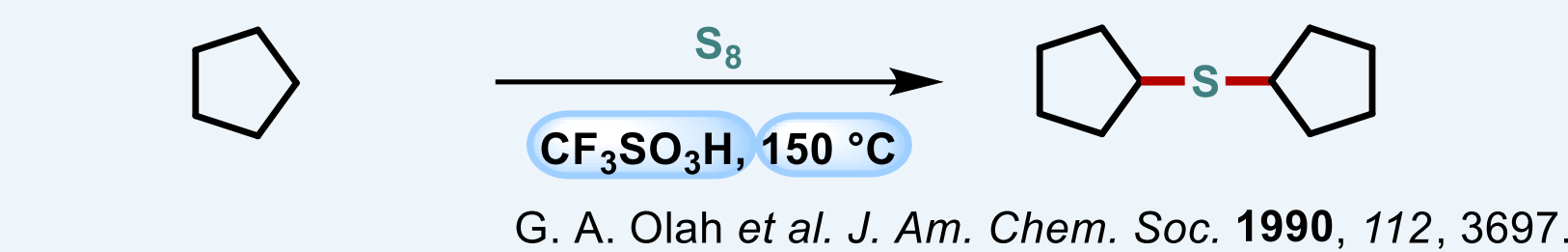
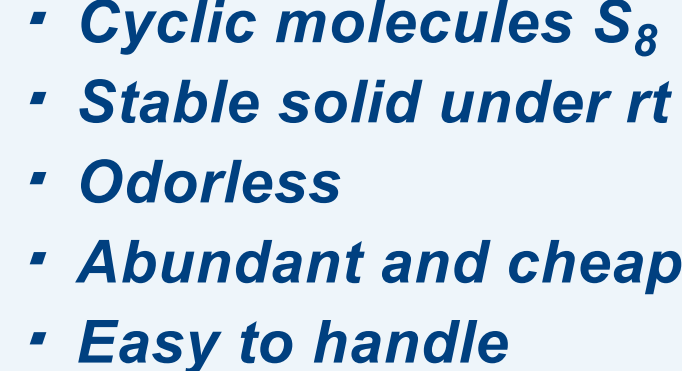
**O-S exchange**  
 $\text{X}=\text{O} \rightarrow \text{X}=\text{S}$

CC(=O)c1ccccc1 + S8 + R1NHR2  $\xrightarrow[\text{excess}]{\text{Willgerdt-Kindler Reaction}}$  CC(=O)c1ccccc1  $\xrightarrow[\text{excess}]{\text{Willgerdt-Kindler Reaction}}$  CC(=O)c1ccccc1

Harsh conditions ✓ Low functional group tolerance

K. Kindler et al. *Liebigs Ann. Chem.* **1923**, 431, 187.

## 2. Elemental Sulfur for Organic Synthesis



### 3. Strategy

✓ Harsh conditions    ✓ Low chemoselectivity    ✓ Low functional group tolerance

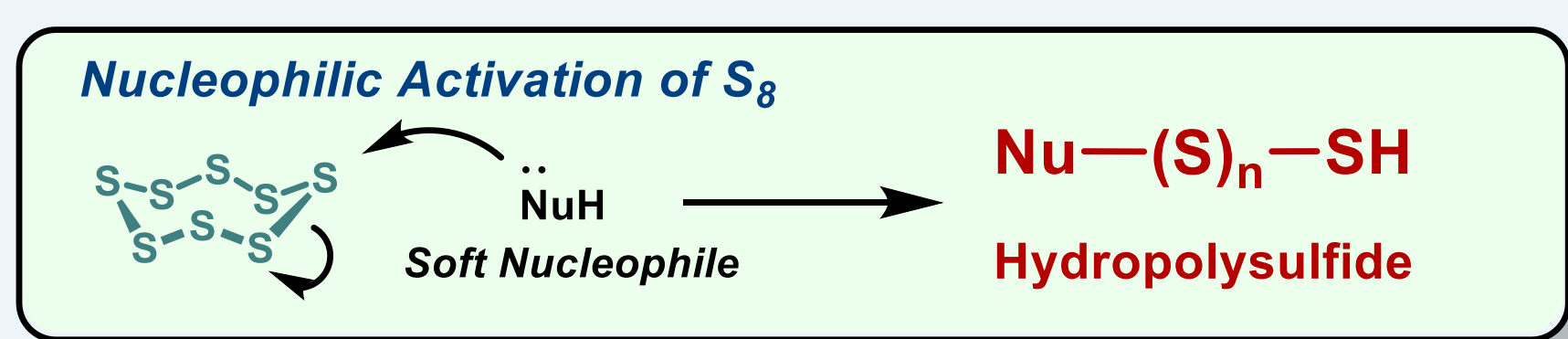
R. Grieco *et al.*, *Tetrahedron* **1988**, 44, 72

$$R^1-C(=O)CO_2H + H_2N-R^2 \longrightarrow \text{Intermediate} \xrightarrow[\text{TBHP}]{\text{tert-Bu-O-O-H}} \text{Intermediate} \xrightarrow[-CO_2]{-ROH} R^1-C(=O)NHR^2$$

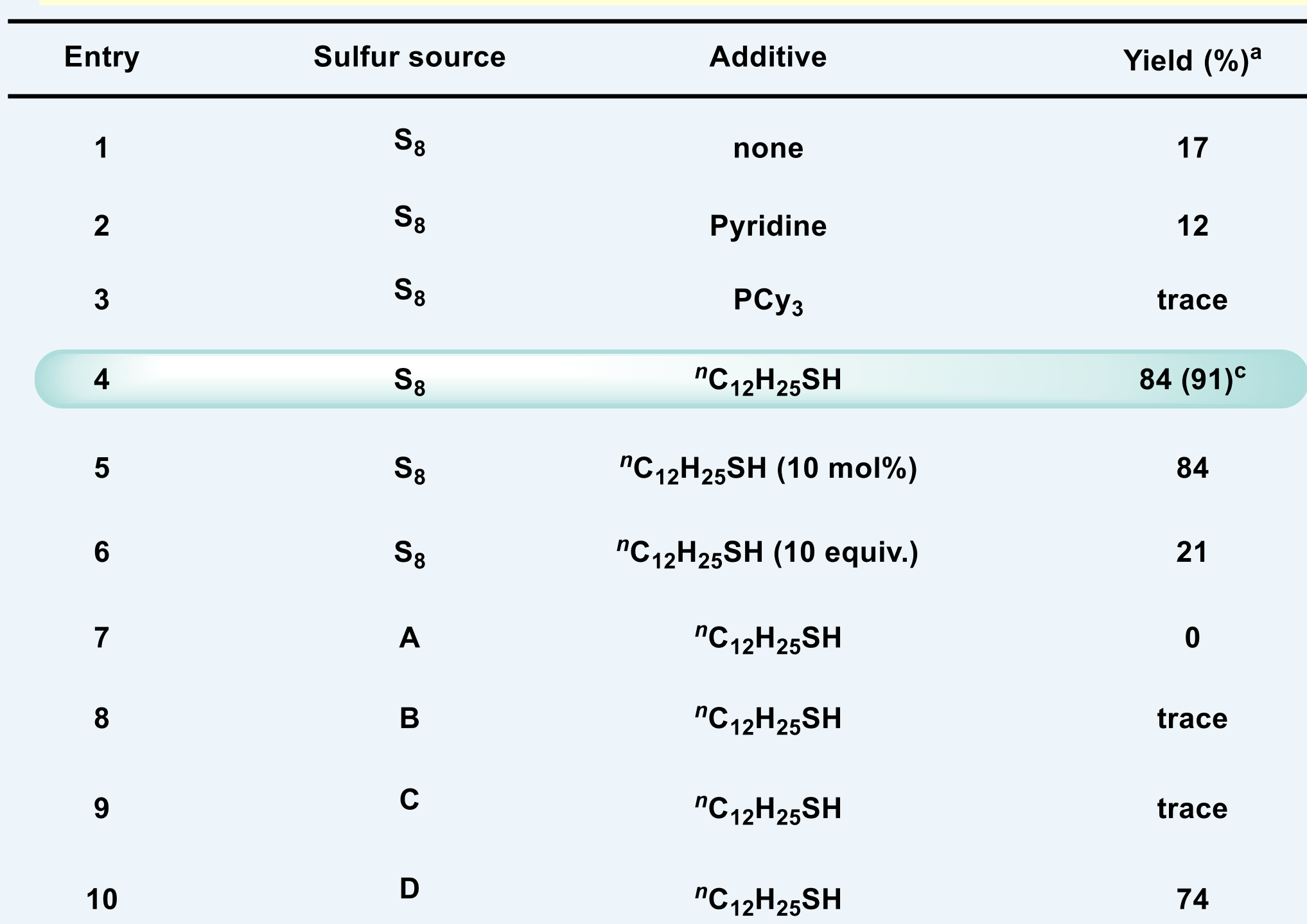
Y. Takemoto *et al.* *Chem. Eur. J.* 2019, 25, 15500

$$\text{R}^1\text{C}(=\text{O})\text{CO}_2\text{H} + \text{H}_2\text{N}-\text{R}^2 \longrightarrow \text{R}^1\text{C}(\text{NH}-\text{R}^2)(\text{CO}_2\text{H}) \xrightarrow[\text{Hydropolysulfide}]{\text{R}-\text{S}_n-\text{SH}} \text{R}-\text{S}-\text{S}-\text{NH}-\text{R}^2 \xrightarrow[-\text{RSH}]{-\text{CO}_2} \text{R}-\text{S}-\text{NH}-\text{R}^2$$

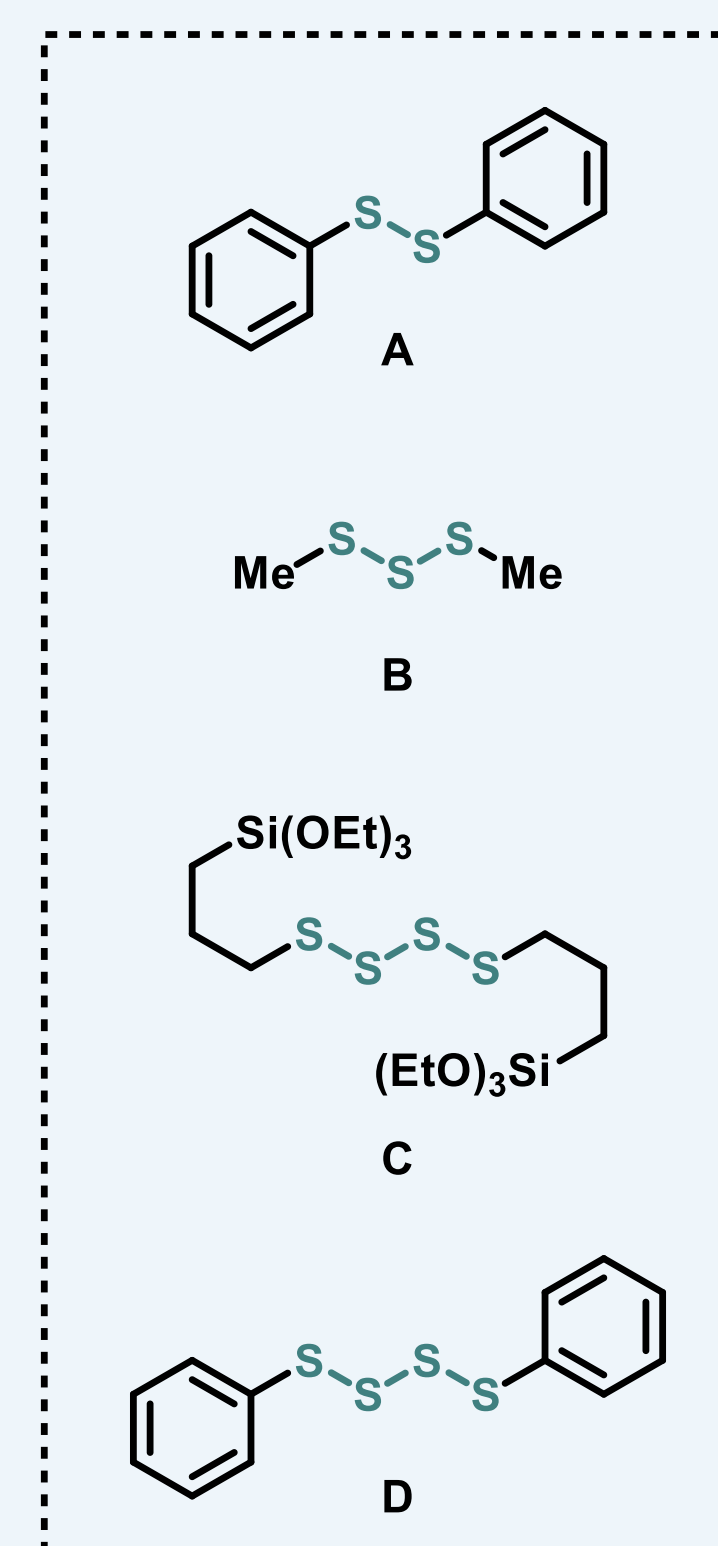
✓ Mild conditions    ✓ Broad scope    ✓ Site-specific    ✓ Pharmaceutical compounds



#### 4. Reaction Optimization



<sup>a</sup> The yield was determined by <sup>1</sup>H NMR spectroscopy using dimethyl terephthalate as the internal standard. <sup>b</sup>Equivalent was calculated as the number of S atoms. <sup>c</sup>Isolated yield.



## 5. Substrate Scope

<sup>a</sup>Isolated yields are shown. <sup>b</sup>The reaction was performed in DMF. <sup>c</sup>The reaction was performed at 50 °C. <sup>d</sup>Amine hydrochloride salt (0.10 mmol) and <sup>t</sup>Pr<sub>2</sub>NEt (0.10–0.20 mmol) were used. <sup>e</sup>α-Ketoacid (0.10 mmol), amine (0.12 mol), and 5-*t*-butyl-2-methylbenzenethiol (0.10 mmol) were reacted in DMF/CS<sub>2</sub> (9:1). <sup>f</sup>A solution of the amine and the thiol was added dropwise over 4 h at 80 °C.

84%

55%<sup>b,c,d</sup>

50% (dr 95 : 5)<sup>e,f</sup>

79% [2.9 g scale]<sup>b,c</sup>

82%<sup>b</sup>

Transcriptional antiestrogen S-analogue

ML390 S-analogue

## 6. Application

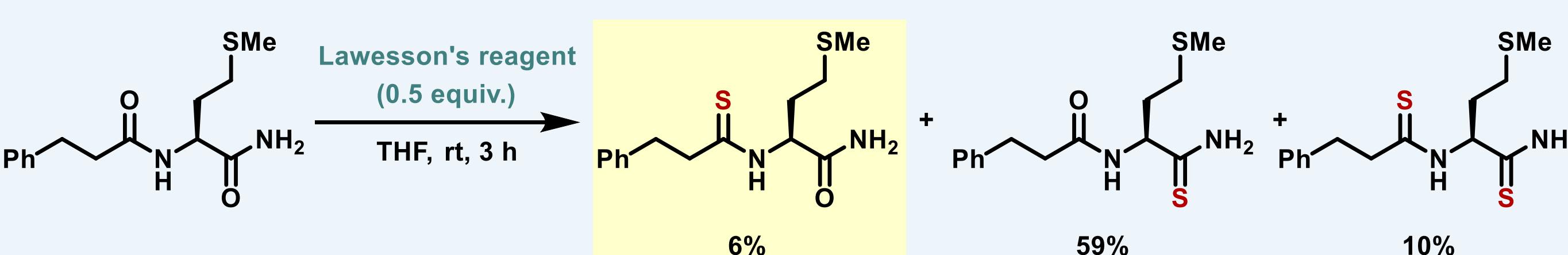
Reaction scheme showing the synthesis of various thionamide derivatives. The reaction involves the condensation of a carboxylic acid (R-CO<sub>2</sub>H) and a thionamide derivative (CbzHN-CH<sub>2</sub>-CH<sub>2</sub>-NH-C(=S)-NH-C(=O)-Ph) in the presence of S<sub>8</sub> (3.0 equiv.), <sup>n</sup>C<sub>12</sub>H<sub>25</sub>SH (1.0 equiv.), and Pr<sub>2</sub>NEt (1.0 equiv.) in DMF at room temperature for 2 hours. The products are thionamide derivatives with various R groups, including a long alkyl chain (TM, 80%), a 4-(trifluoromethyl)phenyl group (64%), a 4-(methoxy)phenyl group (76%), and a 4-(trifluoromethoxy)phenyl group (53%).

Site-specific thioamide formation of a primary amide containing molecule

PhCH2CH2C(=O)O + ClH2NCH2C(=O)NCCS
 $\xrightarrow[\text{DMF, rt, 2 h}]{\begin{array}{l} \text{S}_8 \text{ (3.0 equiv.)} \\ ^{13}\text{C}_{12}\text{H}_{25}\text{SH (1.0 equiv.)} \\ i\text{Pr}_2\text{NEt (1.0 equiv.)} \end{array}}$ 
PhCH2CH2C(=S)NCCS

[Site-specific]

64%



## 7. Mechanistic Analysis of the Reaction Intermediates

*Isolated as white solid*
  
**✓ Iminoacid is a possible intermediate of this reaction**

Figure 1 illustrates the synthesis of poly(1,2-ethanedithiolane)s. The reaction involves the ring-opening polymerization of 1,2-ethanedithiolane (a cyclic dithiolane) initiated by  $n\text{C}_{12}\text{H}_{25}\text{SH}$  in THF for 1 hour. The reaction is shown as:

$$\text{Cyclic dithiolane} \xrightarrow[\text{THF, 1 h}]{n\text{C}_{12}\text{H}_{25}\text{SH}} \text{Linear polymer}$$

The figure includes two photographs of test tubes. The left tube shows a precipitate, labeled "Not dissolved". The right tube shows a clear solution, labeled "Dissolved". A chemical structure of the polymer chain is shown, with a callout box indicating "Detected by ESI Mass  $R = n\text{C}_{12}\text{H}_{25}$ ".

Below the photographs, a chemical reaction scheme shows the ring opening of 1,2-ethanedithiolane with  $\text{RSH}$  in THF to form a linear polymer chain, with a red checkmark and the text "Ring opening" above the reaction arrow:

$$\text{Cyclic dithiolane} + \text{RSH} \xrightarrow[\text{THF}]{\text{Ring opening}} \text{R-S-S}_n\text{-SH} \xrightarrow{\text{RSH}} \text{R-S-S}_n\text{-S-R}$$

## 8. Proposed Mechanism

