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The Dynamic Kinetic Resolution of Azlactones with Thiol Nucleophiles Catalyzed by Arylated, Deoxygenated Cinchona Alkaloids

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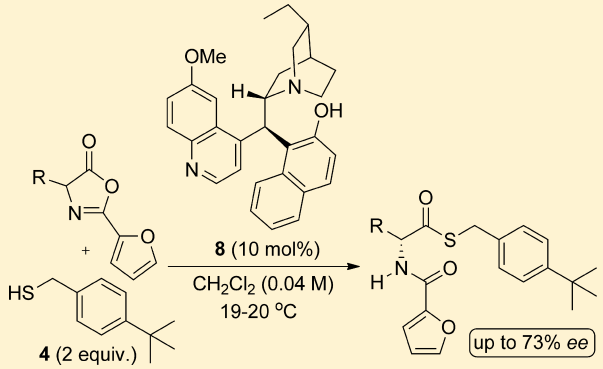
Supporting Information

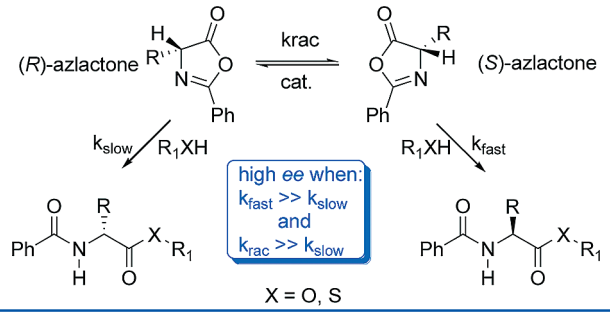
ABSTRACT: A significant improvement of the available organocatalytic methods (in terms of product substrate scope and product enantiomeric excess) for the generation of enantioenriched α-amino acid thioesters via the dynamic kinetic resolution of azlactones is reported. C-9 arylated cinchona alkaloid catalysts have been found to be considerably superior to other bifunctional alkaloid catalysts as the promoters of this asymmetric process.



INTRODUCTION

The catalytic dynamic kinetic resolution (DKR) of α-substituted azlactones by alcoholysis is a valuable route for the facile, enantioselective synthesis of N-protected α-amino acid derivatives.[1] In this process, one enantiomer of the racemic azlactone reacts preferentially (in the presence of a chiral catalyst) with the alcohol. The acidity of the α-hydrogen of the azlactone ($pK_a \sim 9$, H_2O, 25 °C)[2] allows the continuous regeneration of the fast reacting azlactone enantiomer, if the catalyst is capable of accelerating the rate of racemization to a greater degree than the alcoholysis of the slow reacting azlactone enantiomer (i.e., $k_{fast} \gg k_{slow}$ and $k_{rac} \gg k_{slow}$, Scheme 1).

Scheme 1. DKR of Azlactones



Whereas the selective DKR of azlactones with alcohols has been widely studied, leading to the disclosure of several examples of very efficient processes, including the use of enzymes,[3] Ti-complexes,[4] and organocatalysts,[5−7] *the thiolysis of azlactones still remains relatively unexplored*. While thiols and alcohols are ostensibly quite similar, the considerably higher acidity and longer bond lengths associated with thiols make them considerably more challenging substrates in this reaction. However, it is still perhaps surprising that no highly effective method of thiolysis has been established, given the potential application of such a process to the synthesis of enantioenriched peptide thioesters for native chemical ligation (NCL), a well-established coupling technique used to construct large peptide structures through the coupling of two smaller peptides via the reaction between N-terminal cysteine and C-terminal thioester units (usually derived from either aromatic or primary alkyl thiols), followed by an $S \rightarrow N$ acyl shift.[8] One of the challenges associated with NCL is the synthesis of the peptidic thioesters,[9] which is sometimes accompanied by epimerization at the amino acid derived α-chiral center via either azlactone formation or enolization of the relatively acidic (when compared to ester or amide analogues) thioester.[10,11] This compromises the process and limits the practical application of the archetypal NCL reaction to coupling at faster reacting, less hindered amino acid thioesters (e.g., Ala or the achiral Gly) at the *C*-terminal partner. Undoubtedly, the synthesis of peptide thioesters for use in NCL is still an unsolved problem, and numerous examples aimed at the circumvention of this issue have recently appeared.[8d−i,9]

Exploratory attempts to perform DKR on azlactones by thiolysis were performed in 2008 using urea-based catalyst **2** (Scheme 2).[6e,12] Under optimized conditions (which result in

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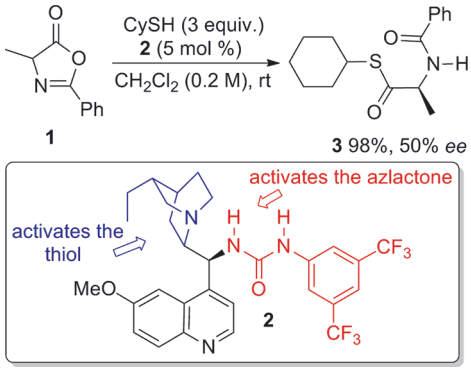
Scheme 2. The First Example of the DKR of Azlactones Mediated by Thiols

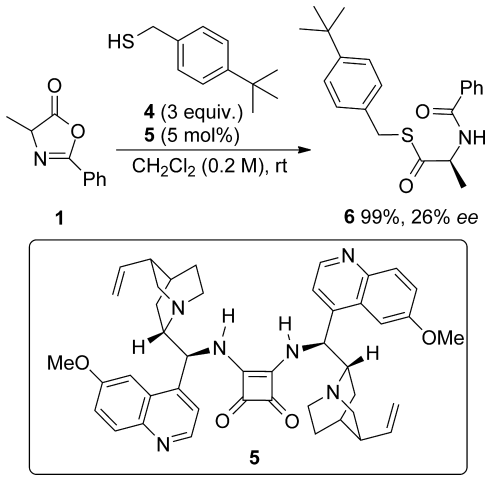


high levels of product ee in the corresponding alcoholysis reactions), the DKR of alanine-derived azlactone **1** with cyclohexanethiol catalyzed by the bifunctional urea-based catalyst **2** resulted in the formation of thioester **3** in 50% ee at ambient temperature (64% ee was possible at −30 °C). This represented the first example of this class of reaction. However, the requirement for the use of a secondary thiol (lower enantioselectivity resulted with more synthetically useful primary thiol nucleophiles) and low reaction temperatures limited possible future application of the method.

RESULTS AND DISCUSSION

In a preliminary attempt to improve the efficacy of this process, we evaluated the DKR of azlactone **1** with the benzyl thiol **4** catalyzed by **5**: the benchmark literature catalyst developed by Song et al.[6f] for the DKR of azlactones by alcoholysis (Scheme 3).

Scheme 3. DKR by Thiolysis Catalyzed by Squaramide 5

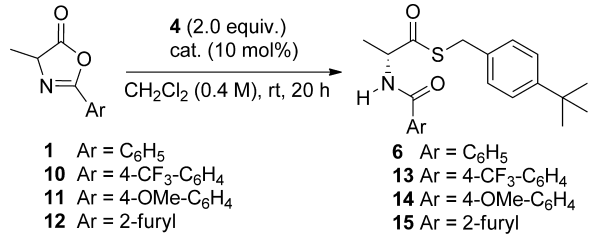


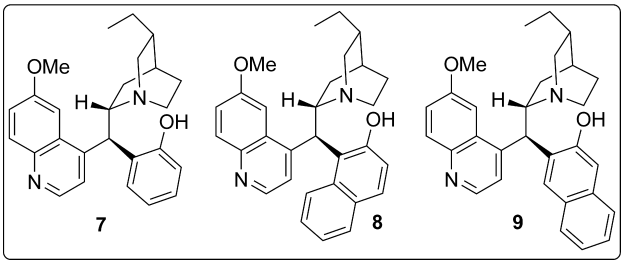
Under identical conditions to those outlined in Scheme 2, efficient, but largely unselective, catalysis was observed. Given the failure of the known (thio)urea and squaramide-based bifunctional organocatalysts for alcoholysis reactions to mediate the analogous thiolysis chemistry selectively, it seemed clear that, in order to improve the utility of the thiolysis protocol, a significant departure in terms of catalyst design was required.

Recently, we developed a small library (nine members) of cinchona alkaloid-based catalysts. These are characterized by the presence of a phenolic substituent at C-9 (in which the distance/relative orientations of the quinuclidine base and the hydrogen-bond-donating phenolic hydroxyl groups can be systematically varied), of which **7**, **8**, and **9** are representative. These materials were found to be capable of promoting the selective DKR of azlactones using allyl alcohol as the nucleophile, with levels of product ee up to 92% possible.[6g] Since these promoters possess distinct steric- and hydrogen-bond-donating/accepting characteristics to either **2** or **5**, yet have been shown to be catalytically competent in azlactone DKR processes, we were encouraged to investigate their potential for application to the formation of enantiomerically enriched thioesters by DKR.

The catalysts were evaluated in the addition of the primary thiol **4** to the alanine-derived azlactone **1** in dichloromethane. This has traditionally proven to be a particularly challenging substrate due to the relatively small steric requirement of the methyl moiety at the acidic α-carbon. In our previous alcoholysis study,[6g] we observed that the steric and electronic nature of the product N-protecting group[13] has a profound influence over both the rate and the enantioselectivity of the DKR process catalyzed by amines, such as **7**–**9**. It was, therefore, considered prudent to include azlactones **10**, **11**, and **12** (which incorporate relatively electron-deficient, electron-rich, and heterocyclic aromatic functionalities, respectively) in our preliminary survey (Table 1).

Table 1. Initial Substrate and Catalyst Screening





entry	azlactone	catalyst	conv. (%)[a]	ee (%)[b]	abs. config.
1	**1**	**7**	>98	25	*S*
2	**1**	**8**	>98	20	*R*
3	**1**	**9**	>98	17	*S*
4	**10**	**7**	>98	16	*S*
5	**10**	**8**	>98	35	*R*
6	**10**	**9**	>98	8	*S*
7	**11**	**7**	>98	20	*S*
8	**11**	**8**	>98	15	*R*
9	**11**	**9**	>98	11	*S*
10	**12**	**7**	>98	0	
11	**12**	**8**	>98	43	*R*
12	**12**	**9**	>98	4	*S*
13	**12**	**5**	>98	10	*S*
14[c]	**12**	**8**	>98	53	*R*

[a]Determined by ^{1}H NMR spectroscopy. [b]Determined by CSP-HPLC. [c]Reaction carried out at an equilibrated temperature of 19–20 °C.

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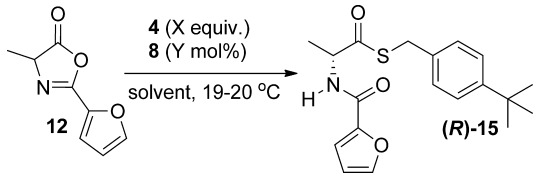
The thiolysis of **1** with **4** (which does not occur in the absence of catalyst) proceeded smoothly and cleanly to full conversion in the presence of 10 mol % **7**–**9** with low levels of enantiomeric excess (entries 1–3). We were pleased to observe that (as was the case in the alcoholysis study) that a degree of conformational control over the stereochemical outcome of the reaction was possible:[6g] that is, catalysts **7** and **8** (both quinine-derived) promote the thiolysis reaction to furnish **6** with similar levels of product ee; however, while **7** favors (*S*)-**6** (entry 1), catalysis involving the 1,2-substituted naphthol derivative **8** leads to preferential formation of the (*R*)-product antipode (entry 2). While the same trends were observed in reactions involving the activated and deactivated azlactones **10** and **11**, respectively, no significant general increase in the enantioselectivity of the process was discernible (entries 4–9). However, the analogous reactions involving the *N*-furyl-substituted azlactone **12** were intriguing. While catalysts **7** and **9** appear not to efficiently differentiate between the enantiomers of (*rac*)-**12** (entries 10 and 12), the 1,2-naphthol **8** promoted the same reaction with 43% ee. Interestingly, this recognition appears to be confined to catalyst **8**: the same reaction promoted by the squaramide catalyst **5** resulted in poor product ee (entry 13). We also observed that the enantioselectivity of the reaction of **12** with **4** catalyzed by **8** exhibited subtle temperature dependence—careful equilibration of the temperature between 19 and 20 °C led to an increase in product ee from 43 to 53% (entries 11 and 14).

With the optimum catalyst and N-protecting group identified, the optimization of the reaction conditions was then undertaken (Table 2). Starting with the best conditions identified in our preliminary study (entry 1), it was found that carrying out the reaction at either lower or higher temperatures reduces the enantioselectivity of the process (entries 2–4). Using fewer equivalents of the nucleophile led to slower conversion and slightly lower product ee (entry 5), while variation of either the catalyst loading (entries 6–7) or the reaction solvent (entries 8–10) also failed to impact the enantioselectivity positively. Dilution of the reaction did allow for more effective DKR (entries 11–14): the product ee increased significantly from 53% at 0.4 M in dichloromethane solvent (entry 1) to 73% ee at 0.04 M (entry 12). This concentration proved optimal—further dilution resulted in longer reaction times (entries 13–14). It is noteworthy that, under these optimized conditions, the thiolysis process is considerably more enantioselective (using a more NCL compatible thiol at lower loadings) at ambient temperature than the literature benchmark reaction, which was carried out at −30 °C.

The scope of the method was next probed through the thiolytic DKR of other amino acid derived azlactones (Table 3). Emphasis was placed on the investigation of substrates derived from α-unbranched amino acids more usually employed at the C-terminus of a peptide coupling partner in NCL processes. Gratifyingly, the thiolysis of azlactones derived from racemic versions of the naturally occurring amino acids alanine, phenylalanine, methionine, and leucine resulted in the formation of the *N*-furoyl amino acid thioesters **15**–**18**, respectively, in good to excellent isolated yield and 66–73% ee (entries 1–4). The synthesis of thioesters **19**–**21** formally derived from unnatural amino acids was also possible (entries 5–7) with similar enantioselectivity. We also evaluated the considerably more hindered (and less practical from the standpoint of application to NCL) valine-derived azlactone variant—this served as a very poor substrate, which converted to **22** slowly and with low levels of enantiodiscrimination (entry 8).

While the absolute configuration at the stereocenter in these thiolysis products is the same as that obtained in our earlier alcoholysis study, it is interesting to note that the sensitivity of the catalyst to steric bulk at the α-carbon (i.e., higher levels of product ee from less-hindered substrates) is the opposite of that observed with an allyl alcohol as the nucleophile. This strongly suggests that the pretransition state assemblies of the thiolysis and alcoholysis DKR processes catalyzed by **8** may be analogous, but far from identical,[15] which leads to the conclusion that these two reactions must be studied separately.

Table 2. Optimization of the Reaction Conditions



entry	concn (M)	solvent	*X* (equiv)	*Y* (mol %)	time (h)	conv. (%)[a]	ee (%)[b]
1	0.4	CH_2Cl_2	2	10	20	>98	53
2[c]	0.4	CH_2Cl_2	2	10	26	>98	12
3[d]	0.4	CH_2Cl_2	2	10	21	>98	36
4[e]	0.4	CH_2Cl_2	2	10	21	>98	45
5	0.4	CH_2Cl_2	1	10	20	80	42
6	0.4	CH_2Cl_2	2	5	20	>98	38
7	0.4	CH_2Cl_2	2	20	20	>98	42
8	0.4	MTBE	2	10	21	85	21
9	0.4	PhMe	2	10	48	23	35
10	0.4	$CDCl_3$	2	10	48	50	21
11	0.1	CH_2Cl_2	2	10	20	93	56
12	0.04	CH_2Cl_2	2	10	70	72	73
13	0.02	CH_2Cl_2	2	10	120	50	71
14	0.01	CH_2Cl_2	2	10	120	30	69

[a]Determined by ^{1}H NMR spectroscopy. [b]Determined by CSP-HPLC. [c]Reaction at −25 °C. [d]Reaction at 0 °C. [e]Reaction at 30 °C.

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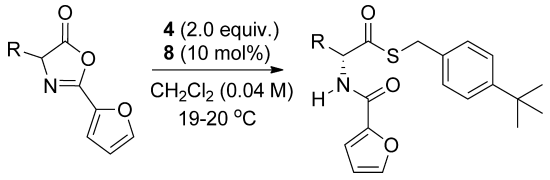
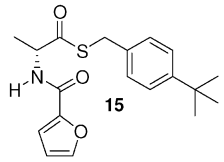
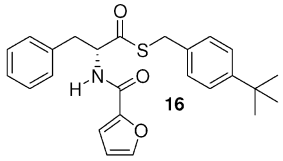
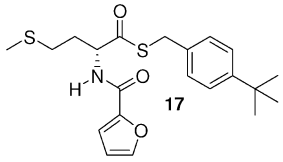
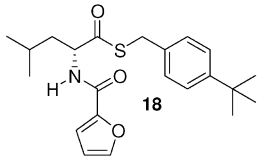
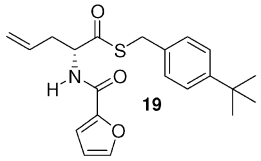
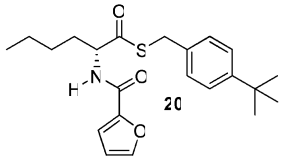
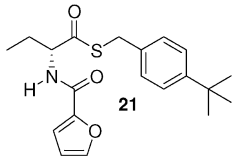
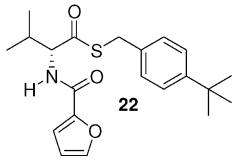
Table 3. Substrate Scope Evaluation



entry	product	time (d)	yield (%)[a]	*ee* (%)[b]
1	 **15**	3	86	73
2	 **16**	5	96	66
3	 **17**	3	96	73
4	 **18**	8	97	70
5	 **19**	5	95	72
6	 **20**	15	91	65
7	 **21**	11	80	71
8	 **22**	28	82	23

[a]Isolated yields. [b]Determined by CSP-HPLC.

To eliminate the possibility that the catalyst is capable of influencing the product absolute configuration through thioester deprotonation/reprotonation, (*rac*)-**15** was exposed to the catalyst (10 mol %) and the thiol **4** (1.0 equiv) in CH_2Cl_2 (0.04 M) for 70 h at ambient temperature: no change in the thioester ee was detected. Thus, it can be inferred that the asymmetric induction derives only from the DKR addition process. It, therefore, seems likely that, if the enantioselectivity of these reactions can be improved, catalysts, such as **8**, could hold promise for the in situ generation of thioesters for the synthesis of hydrophobic proteins via NCL in organic solvents.[14]

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CONCLUSION

Where "traditional" urea- and squaramide-based cinchona alkaloid derived organocatalysts—which mediate highly selective DKR reactions of azlactones with alcohol nucleophiles—failed to promote the DKR of azlactones by thiolysis (with unhindered thiols) with synthetically useful levels of product ee, it has been found that the recently reported C-9 arylated phenolic variants are capable of promoting the most enantioselective DKR reactions of azlactones by thiolysis to date. Other significant improvements over the literature benchmark include the possibility of using primary thiol nucleophiles (essential if the technology is eventually to be applied to NCL processes) at lower loadings than previously required, and a catalyst that operates optimally at ambient temperature in conjunction with azlactones derived from less-hindered amino acids most suitable for selection as the C-terminal peptide thioester coupling partner in NCL reactions. The levels of enantioselectivity associated with the DKR reactions (65−73% ee) are lower than those usually obtained in the corresponding alcoholysis reactions. An investigation to uncover the origins of this discrepancy with a view toward the design of one-pot NCL-type coupling reactions (which will naturally involve the use of a more easily cleaved N-protecting group) involving azlactones is underway.

EXPERIMENTAL SECTION

General Methods. All the DKR reactions were carried out in oven-dried glassware and under an argon atmosphere. Unless otherwise stated, all chemicals were commercially sourced and used without purification. The 4-*tert*-butylbenzyl mercaptan was distilled under low pressure prior to use. The catalyst **8** was prepared following literature procedures.[6g] The azlactones were immediately used after preparation. NMR spectra were internally referenced to residual solvent signals ($CHCl_3$ or DMSO).

General Procedure for the Synthesis of the *N*-2-Furoyl Amino Acids. The commercially available racemic amino acid (5 mmol) was dissolved or suspended in an aqueous solution of NaOH (25 mL, 0.93 M, 11.6 mmol, 2.33 equiv.) and the solution or suspension cooled down to 0 °C with an ice/water bath. 2-Furoyl chloride (0.5 mL, 5 mmol, 1.00 equiv) was added slowly via a syringe. The resulting mixture was allowed to warm to room temperature and stirred overnight.

For alanine, phenylalanine, methionine, and valine: a solution of aqueous HCl (approx. 1 mL, 36% conc.) was added until a precipitate was formed and the pH of the solution was approximately 2. The mixture was filtered (frit nb 3) and solids extensively washed with cold water (15 mL) and Et_2O (15 mL). The resulting white solids were dried under high vacuum.

For leucine, nor-leucine, allylglycine, and 2-aminobutiric acid: a solution of aqueous HCl (approx. 1 mL, 36% conc.) was added until a precipitate was formed and the pH of the solution was approximately 2. The precipitate formed an oily residue that was dissolved with CH_2Cl_2 (10 mL). The aqueous layer was then extracted with more CH_2Cl_2 (15 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford oils that solidified (hygroscopic) after drying under high vacuum.

*N-2-Furoylalanine (**23**):* White solid (0.46 g, 51%), mp 173−174 °C; ^{1}H NMR (400 Hz, d^6-DMSO) δ 1.40 (d, 3H, J_2 = 7.4 Hz), 4.40 (app. qn, 1H), 6.67 (dd, 1H, J_2 = 3.5, 1.5 Hz), 7.20 (d, 1H, J_2 = 3.5 Hz), 7.89 (m, 1H), 8.56 (d, 1H, J_2 = 7.5 Hz), 12.65 (bs, 1H); ^{13}C NMR (100 Hz, d^6-DMSO) δ 17.9, 48.4, 112.8, 114.7, 146.1, 148.5 (C), 158.5 (C), 175.0 (C); IR (neat) ν_{max}/cm^{-1} 3316, 2497, 1713, 1592, 1564, 1525, 1471, 1219, 1190, 1162, 1123, 937, 884, 761; HRMS (ESI) m/z calculated for $C_8H_9NNaO_4$, $[M + Na]^+$ 206.0429; found, 206.0424.

*N-2-Furoylphenylalanine (**24**):* White solid (0.88 g, 68%), mp 153−154 °C; ^{1}H NMR (400 Hz, d^6-DMSO) δ 3.10 (dd, 1H, J_1 = 14.0 Hz, J_2 = 4.51 Hz), 3.21 (dd, 1H, J_1 = 14.0 Hz, J_2 = 10.4 Hz), 4.59−4.65 (m, 1H), 6.64 (dd, 1H, J_2 = 3.4, 1.5 Hz), 7.15 (d, 1H, J_2 = 3.4 Hz), 7.20−7.23 (m, 1H), 7.26−7.34 (m, 4H), 7.87 (bs, 1H), 8.58 (d, 1H, J_2 = 8.3 Hz), 12.90 (bs, 1H); ^{13}C NMR (100 Hz, d^6-DMSO) δ 37.0, 54.3, 112.8, 114.8, 127.4, 129.2, 130.0, 139.0 (C), 146.2, 148.3 (C), 158.7 (C), 173.9 (C); IR (neat) ν_{max}/cm^{-1} 3328, 2820, 2516, 1916, 1727, 1608, 1593, 1566, 1530, 1353, 1253, 1232, 1196, 988, 763, 752, 697; HRMS (ESI) m/z calculated for $C_{14}H_{13}NNaO_4$, $[M + Na]^+$ 282.0742; found, 282.0737.

*N-2-Furoylmethionine (**25**):* Cream solid (0.90 g, 75%), mp 128−130 °C; ^{1}H NMR (400 Hz, d^6-DMSO) δ 2.04−2.12 (m, 5H), 2.47−2.64 (m, 2H), 4.48−4.55 (dd, 1H, J_2 = 14.5, 7.7 Hz), 6.66−6.69 (m, 1H), 7.21 (d, 1H, J_2 = 3.4 Hz), 7.90 (bs, 1H), 8.59 (d, 1H, J_2 = 8.0 Hz), 12.78 (bs, 1H); ^{13}C NMR (100 Hz, d^6-DMSO) δ 15.5, 31.0 (2 × CH_2), 51.8, 112.8, 114.8, 146.2, 148.4 (C), 158.9 (C), 174.3 (C); IR (neat) ν_{max}/cm^{-1} 3414, 2922, 1729, 1639, 1597, 1529, 1476, 1188, 1009, 880, 765, 746; HRMS (ESI) m/z calculated for $C_{10}H_{13}NO_4SNa$, $[M + Na]^+$ 266.0463; found, 266.0461.

*N-2-Furoylleucine (**26**):* Off-white hygroscopic solid (0.71 g, 63%), mp 75−77 °C; ^{1}H NMR (400 Hz, d^6-DMSO) δ 0.89 (d, 3H, J_2 = 6.3 Hz), 0.94 (d, 3H, J_2 = 6.4 Hz), 1.54−1.73 (m, 2H), 1.75−1.84 (m, 1H), 4.39−4.47 (m, 1H), 6.65−6.68 (m, 1H), 7.21 (d, 1H, J_2 = 3.4 Hz), 7.89 (bs, 1H), 8.51 (d, 1H, J_2 = 8.1 Hz); ^{13}C NMR (100 Hz, d^6-DMSO) δ 22.0, 23.9, 25.4, 40.3, 51.03, 112.8, 114.8, 146.1, 148.4 (C), 158.8 (C), 175.0 (C); IR (neat) ν_{max}/cm^{-1} 3415, 3118, 2959, 1737, 1645, 1595, 1532, 1472, 1397, 1182, 1148, 1004, 926, 841, 754, 748, 657; HRMS (ESI) m/z calculated for $C_{11}H_{15}NO_4Na$, $[M + Na]^+$ 248.0899; found, 248.0894.

*N-2-Furoylallylglycine (**27**):* White hygroscopic solid (0.93 g, 89%), mp 79−81 °C; ^{1}H NMR (400 Hz, d^6-DMSO) δ 2.55−2.67 (m, 2H), 4.42−4.49 (m, 1H), 5.07 (d, 1H, J_{cis} = 10.2 Hz), 5.15 (d, 1H, J_{trans} = 17.2 Hz), 5.76−5.88 (m, 1H), 6.63−6.67 (m, 1H), 7.20 (d, 1H, J_2 = 3.4 Hz), 7.87 (bs, 1H), 8.43 (d, 1H, J_2 = 7.4 Hz); ^{13}C NMR (100 Hz, d^6-DMSO) δ 36.0, 52.7, 113.0, 115.0, 118.7, 135.5, 146.3, 148.5 (C), 158.8 (C), 174.0 (C); IR (neat) ν_{max}/cm^{-1} 3374, 2895, 2549, 1721, 1594, 1528, 1473, 1234, 1209, 1191, 1017, 993, 943, 919, 885, 756, 695; HRMS (ESI) m/z calculated for $C_{10}H_{11}NO_4Na$, $[M + Na]^+$ 232.0586; found, 232.0589.

*N-2-Furoylnorleucine (**28**):* Off-white solid (0.95 g, 83%), mp 94−96 °C; ^{1}H NMR (400 Hz, d^6-DMSO) δ 0.86 (t, 3H, J_2 = 7.2 Hz), 1.22−1.39 (m, 4H), 1.69−1.85 (m, 2H), 4.27−4.35 (m, 1H), 6.64 (dd, 1H, J_2 = 1.8, 3.5 Hz), 7.19 (dd, 1H, J_2 = 3.5 Hz, J_3 = 0.8 Hz), 7.86 (dd, 1H, J_2 = 1.8 Hz, J_3 = 0.8 Hz), 8.44 (d, 1H, J_2 = 8.2 Hz); ^{13}C NMR (100 Hz, d^6-DMSO) δ 13.8, 21.7, 27.9, 30.2, 51.8, 111.8, 113.8, 145.2, 147.4 (C), 157.9 (C), 173.7 (C); IR (neat) ν_{max}/cm^{-1} 3370, 2952, 2870, 1734, 1715, 1625, 1596, 1530, 1479, 1416, 1288, 1200, 1151, 1007, 870, 790, 748; HRMS (ESI) m/z calculated for $C_{11}H_{15}NO_4Na$, $[M + Na]^+$ 248.0899; found, 248.0905.

*N-2-Furoyl-2-aminobutiric acid (**29**):* Off-white hygroscopic solid (0.93 g, 95%), mp 105−108 °C; ^{1}H NMR (400 Hz, d^6-DMSO) δ 0.95 (app t, 3H, J_2 = 7.4 Hz), 1.72−1.83 (m, 1H), 1.85−1.95 (m, 1H), 4.25−4.33 (m, 1H), 6.65−6.68 (m, 1H), 7.23 (d, 1H, J_2 = 3.4 Hz), 7.88 (bs, 1H), 8.43 (d, 1H, J_2 = 7.7 Hz); ^{13}C NMR (100 Hz, d^6-DMSO) δ 11.8, 24.9, 54.4, 112.9, 114.8, 146.2, 148.5 (C), 158.9 (C), 174.5 (C); IR (neat) ν_{max}/cm^{-1} 3339, 2973, 1731, 1636, 1592, 1528, 1473, 1414, 1294, 1182, 1128, 1076, 1013, 885, 757, 748, 670; HRMS (ESI) m/z calculated for $C_9H_{11}NO_4Na$, $[M + Na]^+$ 220.0586; found, 220.0582.

*N-2-Furoylvaline (**30**):* Bright white solid (0.61 g, 58%), mp 113−114 °C; ^{1}H NMR (400 Hz, d^6-DMSO) δ 0.96 (d, 3H, J_2 = 2.9 Hz), 0.97 (d, 3H, J_2 = 2.9 Hz), 2.15−2.26 (m, 1H), 4.25−4.31 (m, 1H), 6.67 (dd, 1H, J_2 = 3.5, 1.8 Hz), 7.28 (d, 1H, J_2 = 3.5 Hz), 7.89 (m, 1H), 8.21 (d, 1H, J_2 = 8.3 Hz), 12.78 (bs, 1H); ^{13}C NMR (100 Hz, d^6-DMSO) δ 18.6, 19.3, 29.6, 57.5, 111.8, 114.0, 145.3, 147.3 (C), 158.0 (C), 173.0 (C); IR (neat) ν_{max}/cm^{-1} 3363, 2961, 1708, 1618, 1593, 1532, 1478, 1394, 1328, 1295, 1228, 1196, 1020, 926, 885, 803, 770, 758, 740; HRMS (ESI) m/z calculated for $C_{10}H_{13}NO_4Na$, $[M + Na]^+$ 234.0742; found, 234.0740.

General Procedure for the Synthesis of the *N*-2-Furoyl Azlactones. A solution of *N*,*N*′-dicyclohexylcarbodiimide (DCC, 0.95 mmol, 0.95 equiv) in CH_2Cl_2 (2 mL) was added slowly via a syringe

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to a solution/suspension of the corresponding *N*-2-furoyl amino acid (1 mmol) in dry CH_2Cl_2 (10 mL). The reaction was stirred overnight at room temperature under an Ar atmosphere. The resulting suspension was filtered and the solids washed with CH_2Cl_2 (10 mL × 2). The filtrate was concentrated in vacuo to afford an oily residue that was passed through a short silica column and eluted with a mixture of 10−20% EtOAc in hexane. The solvent was removed and the products dried under high vacuum to afford either waxy solids or clear oils that were used immediately in the next step.

*N-2-Furoylalanine Azlactone (**12**):* Off-white waxy solid (136.5 mg, 87%), mp 54−56 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 1.59 (d, 3H, J_2 = 7.6 Hz), 4.44, (q, 1H, J_2 = 7.6 Hz), 6.58 (m, 1H), 7.11 (d, 1H, J_2 = 3.4 Hz), 7.66 (bs, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.9, 60.3, 112.1, 117.0, 140.8 (C), 146.9, 153.8 (C), 177.9 (C); IR (neat) ν_{max}/cm^{-1} 3146, 3122, 3086, 1820, 1808, 1675, 1661, 1556, 1478, 1402, 1323, 1255, 1179, 1147, 1106, 1079, 1067, 1026, 1002, 933, 906, 882, 869, 852, 807, 774, 728, 714, 658; HRMS (ESI) *m*/*z* calculated for $C_8H_6NO_3$, $[M - H]^-$ 164.0348; found, 164.0340.

*N-2-Furoylphenylalanine Azlactone (**31**):* Off-white waxy solid (139.8 mg, 61%), mp 88−89 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 3.21 (dd, 1H, J_1 = 14.0 Hz, J_2 = 6.45 Hz), 3.36 (dd, 1H, J_1 = 14.0 Hz, J_2 = 5.0 Hz), 4.68 (app t, 1H, J = 5.6 Hz), 6.52−6.55 (m, 1H), 7.00 (d, 1H, J_2 = 3.4 Hz), 7.19−7.33 (m, 5H), 7.63 (bs, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 37.2, 65.8, 112.0, 117.0, 127.2, 128.5, 129.6, 134.9 (C), 140.6 (C), 146.9, 153.8 (C), 176.4 (C); IR (neat) ν_{max}/cm^{-1} 3123, 3092, 2923, 1813, 1800, 1665, 1559, 1477, 1401, 1320, 1268, 1246, 1169, 1145, 1078, 1049, 1017, 972, 925, 882, 841, 778, 734, 715, 698, 658; HRMS (ESI) *m*/*z* calculated for $C_{14}H_{10}NO_3$, $[M - H]^-$ 240.0661; found, 240.0662.

*N-2-Furoylmethionine Azlactone (**32**):* Off-white waxy solid (139.1 mg, 65%), mp 45−46 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 2.11 (s, 3H), 2.12−2.18 (m, 1H), 2.28−2.36 (m, 1H), 2.74 (app t, 2H), 4.60 (app t, 1H), 6.59 (m, 1H), 7.12 (bs, 1H), 7.26 (bs, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 15.0, 30.0, 30.3, 62.9, 112.1, 117.1, 140.8 (C), 147.0, 154.2 (C), 177.3 (C); IR (neat) ν_{max}/cm^{-1} 3121, 2913, 1806, 1660, 1553, 1575, 1446, 1401, 1325, 1251, 1167, 1089, 1065, 1041, 1014, 977, 927, 903, 883, 857, 798, 773, 718, 654; HRMS (ESI) *m*/*z* calculated for $C_{10}H_{11}NO_3S$, $[M - H]^-$ 224.0381; found, 224.0378.

*N-2-Furoylleucine Azlactone (**33**):* Off-white waxy solid (128.0 mg, 61%), mp 39−42 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 0.99 (d, 3H, J_2 = 6.6), 1.23 (d, 3H, J_2 = 6.6 Hz), 1.63−1.72 (m, 1H), 1.77−1.86 (m, 1H), 2.02−2.14 (m, 1H), 4.40 (dd, 1H, J_2 = 9.2, 5.4 Hz), 6.56−6.59 (m, 1H), 7.10 (d, 1H, J_2 = 3.4 Hz), 7.65 (bs, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 21.8, 22.8, 25.0, 40.8, 63.1, 112.0, 116.8, 140.9 (C), 146.8, 153.7 (C), 177.9 (C); IR (neat) ν_{max}/cm^{-1} 3112, 2964, 1821, 1668, 1557, 1474, 1398, 1321, 1275, 1236, 1179, 1144, 1055, 1007, 922, 894, 771, 720, 654; HRMS (ESI) *m*/*z* calculated for $C_{11}H_{12}NO_3$, $[M - H]^-$ 206.0817; found, 206.0813.

*N-2-Furoylallylglycine Azlactone (**34**):* Clear oil (167.1 mg, 92%); ^{1}H NMR δ (400 Hz, $CDCl_3$) 2.58−2.67 (m, 1H), 2.75−2.83 (m, 1H), 4.47 (app t, 1H), 5.15 (d, 1H, J_{cis} = 10.0 Hz), 5.23 (dd, 1H, J_{trans} = 17.0 Hz), 5.70−5.84 (m, 1H), 6.56 (dd, 1H, J_2 = 3.4, 1.7 Hz), 7.09 (1H, d, J_2 = 3.4 Hz), 7.64 (bs, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 35.2, 64.6, 112.0, 117.0, 119.9, 131.1, 140.6 (C), 146.9, 153.9 (C), 176.5 (C); IR (neat) ν_{max}/cm^{-1} 3288, 2926, 2855, 1824, 1673, 1624, 1530, 1476, 1400, 1314, 1235, 1045, 1011, 918, 884, 756, 715, 674; HRMS (ESI) *m*/*z* calculated for $C_{10}H_8NO_3$, $[M - H]^-$ 190.0504; found, 190.0504.

*N-2-Furoylnorleucine Azlactone (**35**):* Off-white waxy solid (120.2 mg, 58%), mp 48−50 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 0.94 (t, 3H, J_2 = 7.2 Hz), 1.35−1.57 (m, 4H), 1.82−1.93 (m, 1H), 2.00−2.11 (m, 1H), 4.42 (dd, 1H, J_2 = 5.5, 7.3 Hz), 6.61 (dd, 1H, J_2 = 1.7, 3.4 Hz), 7.13 (d, 1H, J_2 = 3.4 Hz), 7.69 (d, 1H, J_2 = 1.7 Hz); ^{13}C NMR (100 Hz, $CDCl_3$) δ 13.3, 21.8, 26.9, 30.9, 64.2, 111.6, 116.5, 140.4 (C), 146.4, 153.4 (C), 177.0 (C); IR (neat) ν_{max}/cm^{-1} 3284, 2959, 2872, 1742, 1649, 1516, 1467, 1299, 1184, 1011, 885, 748; HRMS (ESI) *m*/*z* calculated for $C_{11}H_{14}NO_3$, $[M + H]^+$ 208.974; found, 208.0979.

*N-2-Furoyl-2-aminobutyric acid Azlactone (**36**):* Off-white waxy solid (119.1 mg, 70%), mp 52−55 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 1.06 (app t, 3H), 1.87−2.0 (m, 1H), 2.02−2.14 (m, 1H), 4.37 (app t, 1H), 6.57−6.60 (m, 1H), 7.11 (d, 1H, J_2 = 3.4 Hz), 7.66 (bs, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 9.5, 24.9, 65.7, 112.0, 116.9, 140.8 (C), 146.8, 153.9 (C), 177.2 (C); IR (neat) ν_{max}/cm^{-1} 3288, 3136, 3113, 2938, 2878, 2856, 1830, 1806, 1681, 1661, 1555, 1471, 1400, 1235, 1179, 1146, 1111, 1074, 1065, 1042, 1008, 976, 909, 869, 767, 723, 715; HRMS (ESI) *m*/*z* calculated for $C_9H_8NO_3$, $[M - H]^-$ 178.0504; found, 178.0506.

*N-2-Furoylvaline Azlactone (**37**):* Off-white waxy solid (139.5 mg, 76%), mp 72−74 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 1.02 (d, 3H, J_2 = 6.8 Hz), 1.15 (d, 1H, J_2 = 6.8 Hz), 2.33−2.44 (m, 1H), 4.26−4.29 (m, 1H), 6.57−6.60 (m, 1H), 7.11 (d, 1H, J_2 = 3.3 Hz), 7.66 (bs, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 17.5, 18.8, 31.2, 70.0, 112.0, 116.9, 140.8 (C), 146.8, 153.9 (C), 176.7 (C); IR (neat) ν_{max}/cm^{-1} 3123, 3095, 2982, 2931, 1813, 1669, 1559, 1477, 1398, 1336, 1326, 1234, 1172, 1145, 1077, 1063, 1036, 1014, 918, 882, 873, 850, 774, 719; HRMS (ESI) *m*/*z* calculated for $C_{10}H_{10}NO_3$, $[M - H]^-$ 192.0661; found, 192.0666.

Dynamic Kinetic Resolution Using 4-*tert*-Butylbenzyl Mercaptan. *General Procedure for Table 1.* The freshly made azlactone (0.2 mmol) was placed into a dry graduated reaction vial previously flushed with Ar and equipped with a magnetic stirring bar. 4-*tert*-Butylbenzyl mercaptan (75 μL, 0.4 mmol, 2.0 equiv) was added, and the volume of the reaction was completed with dry CH_2Cl_2 up to 0.5 mL (0.4 M). After 10 min, the corresponding catalyst (**5**, **7**−**9**) (0.02 mmol, 0.1 equiv) was added, and the reaction was stirred at room temperature and under Ar for 20 h. The reaction was directly poured onto a column of silica gel and the product purified by flash chromatography using a mixture of 12−15% EtOAc in hexane as eluent. Stereochemical assignment for **15** was determined after hydrolysis to the corresponding acid (see the Determination of the Absolute Configuration at the end of the section). Compound **6** was assigned according to the literature.[6e] **13** and **14** were assigned by analogy.

General Procedure for Table 2. The freshly prepared azlactone **12** (0.2 mmol) was placed in a dry graduated reaction vial previously flushed with Ar and equipped with a magnetic stirring bar. The rest of the experimental procedure is analogous to the one described in the section above, but adjusting the relative amounts of catalyst **8**, 4-*tert*-butylbenzyl mercaptan, and the various solvents according to the levels indicated in Table 2.

General Procedure for Table 3. The freshly made azlactone (0.4 mmol) was placed into a dry reaction vial previously flushed with Ar and equipped with a magnetic stirring bar. 4-*tert*-Butylbenzyl mercaptan (150 μL, 0.8 mmol, 2.0 equiv) was added, and the volume of the reaction was made up with dry CH_2Cl_2 to 10 mL (0.04 M). This solution was warmed to 19−21 °C. After 10 min, catalyst **8** (18.10 mg, 0.04 mmol, 0.1 equiv) was added, and the reaction was stirred at 19−21 °C under Ar for the times indicated in Table 3. The reaction was quenched with an aqueous solution of HCl (2 M, 5 mL), and the aqueous phase was extracted with CH_2Cl_2 (5 mL × 2). The combined organic layers were successively washed with an aqueous saturated solution of $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford an oily residue. The residue was purified by silica flash chromatography using a mixture of 12−15% EtOAc in hexane as eluent.

*N-2-Furoylalanine, 4-tert-Butylbenzyl Thioester (**15**):* White solid (56.6 mg, 86%, 73% ee), mp 99−101 °C; $[\alpha]^{20}_{546}$ −47.6 (*c* 0.105, $CHCl_3$); ^{1}H NMR (400 Hz, $CDCl_3$) δ 1.29 (s, 9H), 1.52 (d, 3H, J_2 = 7.1 Hz), 4.07−4.17 (m, 2H), 4.88−4.97 (m, 1H), 6.49−6.62 (m, 1H), 6.84 (d, 1H, J_2 = 7.8 Hz), 7.15 (d, 1H, J_2 = 3.5 Hz), 7.21 (d, 2H, J_2 = 8.2 Hz), 7.31 (d, 2H, J_2 = 8.2 Hz), 7.46 (bs, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 19.0, 31.2, 32.9, 34.4 (C), 54.4, 112.2, 115.03, 125.6, 128.5, 133.5 (C), 144.3, 147.2 (C), 150.4 (C), 157.7 (C), 200.2 (C); IR (neat) ν_{max}/cm^{-1} 3351, 2958, 1678, 1651, 1517, 1294, 1200, 1100, 1027, 967, 939, 905, 827, 763, 702, 659; HRMS (ESI) *m*/*z* calculated for $C_{19}H_{23}NO_3SNa$, $[M + Na]^+$ 368.1296; found, 368.1291. CSP-HPLC analysis: Chiralcel OD-H (4.6 mm × 25 cm), 90:10 hexane/IPA, 1 mL/min, 254 nm; t_R = 12.8 min (major enantiomer) and 17.1 min (minor enantiomer).

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*N-2-Furoylphenylalanine, 4-tert-Butylbenzyl Thioester (**16**):* White solid (162.0 mg, 96%, 66% ee), mp 121−126 °C; $[\alpha]_{346}^{20}$ +13.95 (*c* 1.62, $CHCl_3$); ^1H NMR (400 Hz, $CDCl_3$) δ 1.31 (s, 9H), 3.23 (app d, 2H), 4.10 (bs, 2H), 5.12−5.21 (m, 1H), 6.46−6.50 (dd, 1H, J_2 = 3.4, 1.8 Hz), 6.70 (d, 1H, J_2 = 8.6 Hz), 7.08−7.13 (m, 3H), 7.19 (d, 2H, J_2 = 8.2 Hz), 7.22−7.26 (m, 3H), 7.32 (d, 2H, J_2 = 8.2 Hz), 7.42 (d, 1H, J_2 = 1.3 Hz); ^{13}C NMR (100 Hz, $CDCl_3$) δ 31.3, 33.0, 34.5 (C), 38.4, 58.9, 112.2, 115.1, 125.5, 127.1, 128.6 (2 × CH), 129.4, 133.6 (C), 135.2 (C), 144.4 (C), 147.1 (C), 150.4 (C), 157.8 (C), 199.2 (C); IR (neat) ν_{max}/cm^{-1} 3375, 2960, 1661, 1592, 1518, 1475, 1279, 1177, 1070, 1009, 928, 884, 839, 761, 751, 703; HRMS (ESI) *m*/*z* calculated for $C_{25}H_{27}NO_3SNa$, $[M + Na]^+$ 444.1609; found, 444.1608. CSP-HPLC analysis: Chiralcel OD-H (4.6 mm × 25 cm), 95:5 hexane/IPA, 1 mL/min, 254 nm; t_R = 22.0 min (major enantiomer) and 25.3 min (minor enantiomer).

*N-2-Furoylmethionine, 4-tert-Butylbenzyl Thioester (**17**):* Clear oil (156.2 mg, 96%, 73% ee); $[\alpha]_{546}^{20}$ −7.49 (*c* 1.56, $CHCl_3$); ^1H NMR (400 Hz, $CDCl_3$) δ 1.29 (s, 9H), 2.02−2.13 (m, 4H), 2.24−2.35 (m, 1H), 2.54−2.59 (m, 2H), 4.12 (bs, 2H), 5.01−5.08 (m, 1H), 6.51 (dd, 1H, J_2 = 3.4, 2.0 Hz), 7.09 (d, 1H, J_2 = 8.4 Hz), 7.15 (d, 1H, J_2 = 3.4 Hz), 7.20 (d, 2H, J_2 = 8.3 Hz), 7.31 (d, 2H, J_2 = 8.3 Hz), 7.47 (bs, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 15.4, 29.9, 31.2, 32.0, 33.0, 34.4 (C), 57.8, 112.3, 115.2, 125.5, 128.5, 133.4 (C), 144.4, 147.1 (C), 150.4 (C), 157.9 (C), 199.2 (C); IR (neat) ν_{max}/cm^{-1} 3240, 2963, 1682, 1639, 1592, 1568, 1535, 1471, 1312, 1015, 934, 885, 833, 783, 760; HRMS (ESI) *m*/*z* calculated for $C_{21}H_{27}NO_3S_2Na$, $[M + Na]^+$ 428.1330; found, 428.1326. CSP-HPLC analysis: Chiralcel OD-H (4.6 mm × 25 cm), 90:10 hexane/IPA, 1 mL/min, 254 nm; t_R = 9.6 min (major enantiomer) and 11.6 min (minor enantiomer).

*N-2-Furoylleucine, 4-tert-Butylbenzyl Thioester (**18**):* Yellow oil (150.0 mg, 97%, 70% ee); $[\alpha]_{546}^{20}$ −18.6 (*c* 1.50, $CHCl_3$); ^1H NMR (400 Hz, $CDCl_3$) δ 0.95 (bs, 3H), 0.97 (bs, 3H), 1.29 (s, 9H), 1.58−1.87 (m, 3H), 4.10 (bs, 2H), 4.89−4.96 (m, 1H), 6.50−6.53 (m, 1H), 6.63 (d, 1H, J_2 = 8.8 Hz), 7.16 (d, 1H, J_2 = 3.9 Hz), 7.20 (d, 2H, J_2 = 8.0 Hz), 7.31 (d, 2H, J_2 = 8.0 Hz), 7.47 (bs, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 21.5, 23.1, 24.8, 31.3, 33.0, 34.5 (C), 41.9, 57.1, 112.3, 115.1, 125.6, 128.5, 133.6 (C), 144.3, 147.2 (C), 150.3 (C), 158.0 (C), 200.3 (C); IR (neat) ν_{max}/cm^{-1} 3285, 2958, 1649, 1592, 1516, 1471, 1365, 1289, 1183, 1074, 1009, 933, 884, 834, 758; HRMS (ESI) *m*/*z* calculated for $C_{22}H_{29}NO_3SNa$, $[M + Na]^+$ 410.1766; found, 410.1746. CSP-HPLC analysis: Chiralcel OD-H (4.6 mm × 25 cm), 90:10 hexane/IPA, 1 mL/min, 254 nm; t_R = 7.3 min (major enantiomer) and 8.2 min (minor enantiomer).

*N-2-Furoylallylglycine, 4-tert-Butylbenzyl Thioester (**19**):* Yellowish oil (142.2 mg, 95%, 72% ee); $[\alpha]_{546}^{20}$ −5.77 (*c* 0.711, $CHCl_3$); ^1H NMR (400 Hz, $CDCl_3$) δ 1.29 (s, 9H), 2.63−2.71 (m, 2H), 4.12 (bs, 2H), 4.97 (dd, 1H, J_2 = 14.0, 6.8 Hz), 5.15 (bs, 1H), 5.19 (br. d, 1H), 5.65−5.79 (m, 1H), 6.50−6.52 (m, 1H), 6.77 (bd, 1H, J_2 = 8.3 Hz), 7.15 (d, 1H, J_2 = 3.3 Hz), 7.20 (d, 2H, J_2 = 7.5 Hz), 7.31 (d, 2H, J_2 = 7.5 Hz), 7.46 (s, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 31.2, 33.0, 34.5 (C), 37.0, 57.5, 112.3, 115.1, 119.8, 125.6, 128.5, 131.7, 133.5 (C), 144.3, 147.2 (C), 150.4 (C), 157.8 (C), 199.2 (C); IR (neat) ν_{max}/cm^{-1} 3282, 2948, 1670, 1649, 1593, 1515, 1475, 1392, 1057, 1004, 917, 882, 833, 751; HRMS (ESI) *m*/*z* calculated for $C_{21}H_{25}NO_3SNa$, $[M + Na]^+$ 394.1453; found, 394.1462. CSP-HPLC analysis: Chiralcel OD-H (4.6 mm × 25 cm), 90:10 hexane/IPA, 1 mL/min, 254 nm, t_R = 8.1 min (major enantiomer) and 9.8 min (minor enantiomer).

*N-2-Furoylnorleucine, 4-tert-Butylbenzyl Thioester (**20**):* Yellow oil (136.0 mg, 91%, 65% ee); $[\alpha]_{546}^{20}$ −9.29 (*c* 0.42, $CHCl_3$); ^1H NMR (400 Hz, $CDCl_3$) δ 0.91 (t, 3H, J_2 = 7.2 Hz), 1. 30−1.43 (m, 13H), 1.71−1.82 (m, 1H), 1.98−2.08 (m, 1H), 4.14 (s, 2H), 4.91 (dt, 1H, J_2 = 4.8, 8.4 Hz), 6.54 (dd, 1H, J_2 = 1.8, 3.6 Hz), 6.76 (d, 1H, J_2 = 8.4 Hz), 7.18 (d, 1H, J_2 = 3.6 Hz), 7.23 (d, 2H, J_2 = 8.4 Hz), 7.33 (d, 2H, J_2 = 8.4 Hz), 7.49 (d, 1H, J_2 = 1.8 Hz); ^{13}C NMR (100 Hz, $CDCl_3$) δ 13.4, 21.9, 26.9, 30.9, 32.2, 32.5, 34.1 (C), 58.2, 111.9, 114.7, 125.2, 128.1, 133.3 (C), 143.9, 146.9 (C), 149.4 (C), 157.6 (C), 199.5 (C); IR (neat) ν_{max}/cm^{-1} 3289, 2958, 1865, 1651, 1591, 1568, 1515, 1473, 1302, 1180, 1009, 934, 884,756; HRMS (ESI) *m*/*z* calculated for $C_{22}H_{29}NO_3SNa$, $[M + Na]^+$ 410.1766; found, 410.1773. CSP-HPLC analysis: Chiralcel OD-H (4.6 mm × 25 cm), 90:10 hexane/IPA, 1 mL/min, 254 nm; t_R = 7.74 min (major enantiomer) and 9.19 min (minor enantiomer).

*N-2-Furoyl-2-aminobutyric acid, 4-tert-Butylbenzyl Thioester (**21**):* Yellow oil (114.0 mg, 80%, 71% ee); $[\alpha]_{546}^{20}$ −22.36 (*c* 1.10, $CHCl_3$); ^1H NMR (400 Hz, $CDCl_3$) δ 0.98 (app t, 3H), 1.29 (s, 9H), 1.73−1.87 (m, 1H), 1.99−2.13 (m, 1H), 4.12 (bs, 2H), 4.81−4.90 (m, 1H), 6.51 (dd, 1H, J_2 = 3.5, 1.6 Hz), 6.78 (d, 1H, J_2 = 8.5 Hz), 7.15 (d, 1H, J_2 = 3.5 Hz), 7.20 (d, 2H, J_2 = 8.2 Hz), 7.31 (d, 2H, J_2 = 8.2 Hz), 7.47 (bs, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 9.6, 26.3, 31.3, 32.9, 34.5 (C), 59.6, 112.3, 115.0, 125.6, 128.5, 133.6 (C), 144.2, 147.3 (C), 150.4 (C), 158.0 (C), 199.6 (C); IR (neat) ν_{max}/cm^{-1} 3282, 2947, 1670, 1650, 1593, 1515, 1475, 1322, 1278, 1180, 1106, 1057, 1004, 917, 882, 833, 751, 695; HRMS (ESI) *m*/*z* calculated for $C_{20}H_{25}NO_3SNa$, $[M + Na]^+$ 382.1453; found, 382.1441. CSP-HPLC analysis: Chiralcel OD-H (4.6 mm × 25 cm), 90:10 hexane/IPA, 1 mL/min, 254 nm, t_R = 9.4 min (major enantiomer) and 11.9 min (minor enantiomer).

*N-2-Furoylvaline, 4-tert-Butylbenzyl Thioester (**22**):* Oily solid (123.0 mg, 82%, 28% ee); $[\alpha]_{546}^{20}$ −15.5 (*c* 0.20, $CHCl_3$); ^1H NMR (400 Hz, $CDCl_3$) δ 0.94 (d, 3H, J_2 = 7.0 Hz), 1.02 (d, 3H, J_2 = 6.9 Hz), 1.29 (s, 9H), 2.35−2.47 (m, 1H), 4.12 (bs, 2H), 4.81−4.89 (m, 1H), 6.52 (dd, 1H, J_2 = 3.5, 1.8 Hz), 6.77 (d, 1H, J_2 = 9.3 Hz), 7.15 (d, 1H, J_2 = 3.5 Hz), 7.20 (d, 2H, J_2 = 8.2 Hz), 7.31 (d, 2H, J_2 = 8.2 Hz), 7.47 (bs, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 16.9, 19.5, 31.3, 31.5, 33.0, 34.5 (C), 63.0, 112.3, 115.1, 125.6, 128.5, 133.6 (C), 144.3, 147.3 (C), 150.4 (C), 158.2 (C), 199.4 (C); IR (neat) ν_{max}/cm^{-1} 3278, 2961, 1682, 1648, 1590, 1517, 1467, 1318, 1286, 1077, 1009, 929, 883, 806, 757, 697; HRMS (ESI) *m*/*z* calculated for $C_{21}H_{27}NO_3SNa$, $[M + Na]^+$ 396.1609; found, 396.1597. CSP-HPLC analysis: Chiralcel OD-H (4.6 mm × 25 cm), 90:10 hexane/IPA, 1 mL/min, 254 nm, t_R = 7.1 min (major enantiomer) and 8.6 min (minor enantiomer).

Determination of the Absolute Configuration. The configuration at the chiral center was assigned by comparison of the sign of the specific rotation determined for enantiomerically pure synthesized *N*-furoyl L-alanine and *N*-furoyl L-phenylalanine (following the general procedure reported for the synthesis of the *N*-2-Furoyl amino acids) and the respective products of the hydrolyzed *N*-furoyl-alanine (**15**) and *N*-furoyl-phenylalanine thioesters (**16**) resulting from the organocatalytic reactions. The hydrolysis was carried out by dissolving the corresponding thioester (0.39 mmol) into a NaOH (0.88 mmol, 2.25 equiv) solution in 1:1 THF/H_2O water (1 mL). The THF was removed in vacuo and the resulting liquid acidified with concentrated HCl until persistent cloudiness appeared (pH ∼ 2). The mixture was transferred to a separating funnel and extracted with $CHCl_3$ (3 × 2 mL). The combined organic layers were evaporated and the resulting solid washed with hexane until the thiol/disulfide was completely removed (monitored by TLC). The resulting solid was thoroughly dried under high vacuum. The optical rotation of enantiomerically pure *N*-furoyl L-alanine was $[\alpha]_{546}^{20}$ +15.2 (*c* 0.25, MeOH) vs $[\alpha]_{546}^{20}$ −7.33 (*c* 0.30, MeOH) obtained for hydrolyzed thioester **15**. The optical rotation of enantiomerically pure *N*-furoyl L-phenylalanine was $[\alpha]_{546}^{20}$ −62 (*c* 0.10, MeOH) vs $[\alpha]_{546}^{20}$ +17.5 (*c* 0.20, MeOH) obtained for hydrolyzed thioester **16**.

■ ASSOCIATED CONTENT

Supporting Information

Selected NMR spectra and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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