Tetrahedron 68 (2012) 4320–4327

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Influence of chiral thiols on the diastereoselective synthesis of γ-lactams from cyclic anhydrides

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ARTICLE INFO

Article history:
Received 21 January 2012
Received in revised form 5 March 2012
Accepted 8 March 2012
Available online 28 March 2012

Keywords:
Thiol
Chiral auxiliary
Lactam
Multi-component reaction

ABSTRACT

The synthesis of γ-lactams from both four-component and imine-anhydride reactions is reported. The synthesis of 2-phenylcyclohexanethiol is described and this compound was evaluated along with an additional seven chiral thiols. A range of selectivity and yields was observed and comparisons to established reactions are made in order to account for the observed reactivity.

1. Introduction

The control of absolute configuration in multi-component reactions (MCRs) is often challenging, especially in the case of four-component reactions (4CRs) with broad substrate reactivity, i.e., where all of the components can be independently varied. For example, commonly used MCRs, such as the Ugi, Hantzsch, and Biginelli reactions have been employed successfully with only a small number of chiral substrates.[1,2] Studies in our laboratory are aimed at controlling the absolute configuration of γ-lactams formed by our labs recently disclosed 4CR (Fig. 1A)[3] or by the formal cycloaddition of imines with cyclic anhydrides.[4] Although both reactions exhibit superb diastereoselectivity for the formation of two or three stereogenic centers on the lactam center, there is currently no method to prepare enantiomerically enriched products by either route.

2. Results and discussion

2.1. Thiols as chiral auxiliaries

We elected to start our search for control of absolute stereoinduction in these two lactam-forming reactions with chiral thiols. Chiral auxiliaries have frequently been used as a means of synthesizing enantiomerically enriched compounds,[5] however, the use of chiral thiols in this capacity is rare. The only reported chiral thiol auxiliaries are ones derived from norephedrine[6] and camphor.[7] In both of these cases, the scaffolds have been previously utilized in the form of chiral alcohol auxiliaries by Abiko[8a,b] and Helmchen,[9a,b] respectively. As a result, known chiral thiols represent a small number of structural motifs based on the analogous chiral alcohols. One of the most important chiral alcohols, 2-phenylcyclohexanol, was first reported by Whitesell.[10] The superb selectivity of this substrate in many different reactions suggested that the sulfur analog might be similarly useful.[11] Herein we report the first synthesis of 2-phenyl-cyclohexane thiol and the assessment of this compound along with seven other chiral thiols in stereoselective γ-lactam syntheses (Fig. 1B).

2.2. Why chiral thiols?

Because the thio-substituted enolate intermediate (**5**) immediately precedes the formation of both the lactam stereocenters, we envisioned a chiral thiol auxiliary as the best strategy for asymmetric induction. This thiol auxiliary-based strategy was also viable due to both the ease with which the sulfur moiety can be removed from the γ-lactam products as well as the potential to access both the *syn* and *anti* isomers of lactam product after removal of the auxiliary. We sought to use the 'thio-Whitesell' specifically due to high diastereoselectivity observed at the same temperature (>100 °C) required for our 4CR using the Whitesell in an azomethine-ylide cycloaddition.[12]

In selecting additional potential structural motifs for chiral thiol auxiliaries, we wanted a diverse array of scaffolds that were also synthetically accessible. To accomplish this, we started with chiral

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doi:10.1016/j.tet.2012.03.027

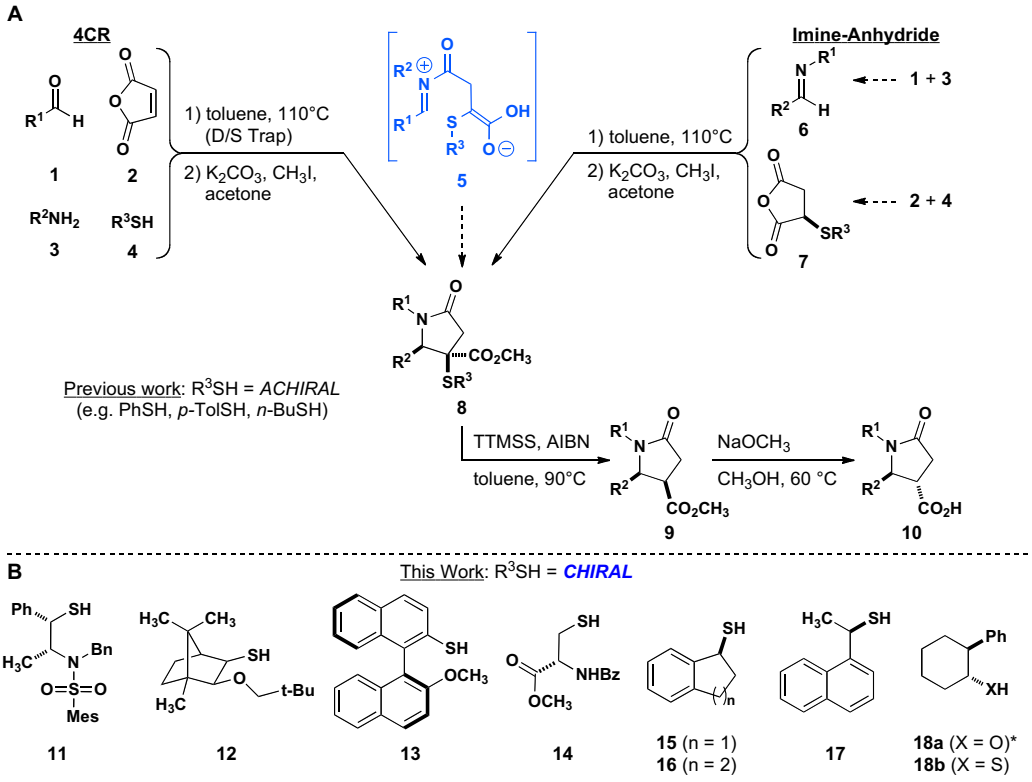
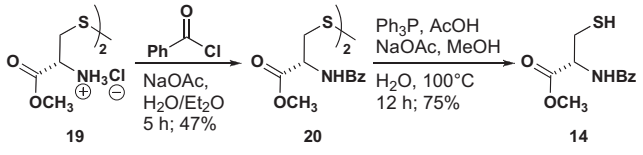


Fig. 1. (A) Four component reaction (4CR) and imine-anhydride reaction leading to γ-lactam product **8** followed by de-sulfurization and epimerization. (B) Chiral thiol auxiliaries (Mes=2,4,6-trimethylphenyl, Bz=benzoyl, *Whitesell auxiliary shown for comparison).

thiols that have been previously synthesized and, if possible, already used in asymmetric synthesis.

2.3. Thiols derived from the chiral pool

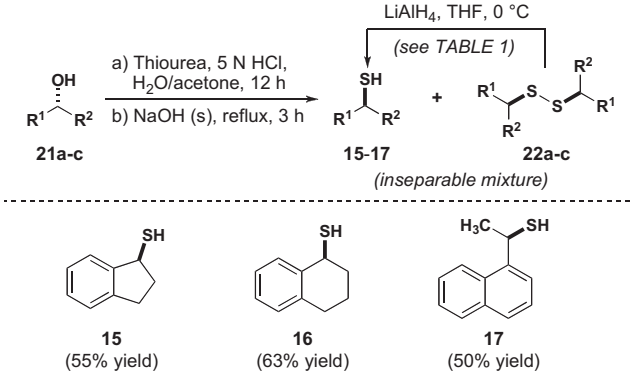
Thiol **11** has been utilized as an auxiliary in the formation of *anti*-aldol products and was obtained via a reported six-step sequence[6] from (1*S*,2*R*)-(+)-norephedrine. Thiol **12** has been utilized as an auxiliary in the reduction of α-sulfinyl ketones[13a] and the alkylation of sulfinimines[13b] and was obtained via a reported four-step sequence[7] from (+)-camphor. The synthesis of binaphthyl thiol **13** has been reported,[14] but to this point has never been used for asymmetric synthesis. However, the binaphthyl structural motif has been used in a wide variety of auxiliaries and ligands for catalysis.[15] Thiol **13** was obtained via the reported four-step sequence from (*S*)-BINOL. The last of our chiral pool derived thiols (**14**) was derived from L-cystine (**19**, the disulfide dimer of L-cysteine) in a two-step synthesis (Scheme 1). L-Cystine dimethyl ester dihydrochloride (**19**) was benzoylated[16] under biphasic conditions to give the corresponding *N*,*N*′-dibenzoyl product (**20**), which was subjected to disulfide cleavage conditions[17] to give *N*-Benzoyl-L-cysteine methyl ester (**14**).



Scheme 1. Synthesis of thiol **14**.

2.4. Thiols derived from commercially available alcohols

In addition to our chiral pool derived thiols, we targeted a set of chiral thiols that could be easily derived from commercially available alcohols. Thiols **15**–**17** were prepared via identical two-step synthetic sequences from 1-indanol (**21a**), 1,2,3,4-tetrahydro-1-naphthol (**21b**), and 1-(1-naphthyl)ethanol (**21c**), respectively, (Scheme 2). The alcohols were each treated with thiourea[18] under acidic conditions to give the corresponding isothiouronium salts. Hydrolysis of these salts using sodium hydroxide[19] gave inseparable mixtures of the target thiols (**15**–**17**) and their corresponding disulfides[20] (**22a**–**c**). In order to convert these mixtures to the target thiols, a variety of disulfide cleavage conditions[17,21a–f] were attempted (Table 1) on a small sample of disulfide **22b**.



Scheme 2. Synthesis of thiols **15**–**17**.

Ultimately, $LiAlH_4$ in THF was found to effect complete conversion of **22b** to the target thiol **16**, and so was used for conversion of the other disulfide mixtures to their respective thiols. The harsh conditions necessary for these substrates when compared to **14** probably originate from the steric congestion of bulky secondary carbons at the point of sulfur attachment. Although thiols **15**–**17** were prepared in racemic form, assessment of diastereoselectivity

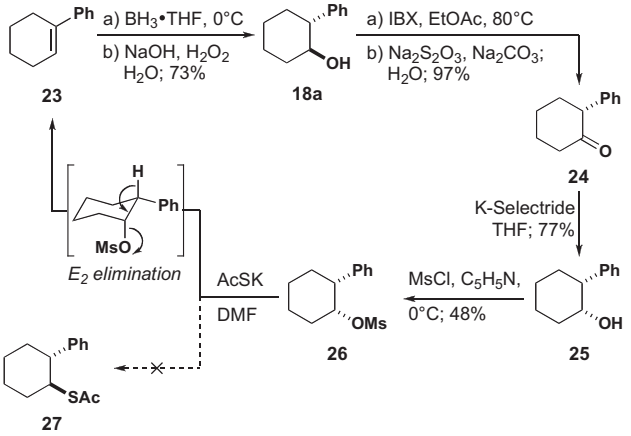
Table 1
Attempted disulfide cleavage conditions of **22b** to thiol **16**

Entry	Conditions	Conversion
1	Ph_3P, NaOAc, AcOH, H_2O/CH_3OH, reflux, 12 h	<5%
2	$LiBH_4$, THF, 0 °C to rt, 12 h	<5%
3	$NaBH_4$, THF, 0 °C to rt, 12 h	<5%
4	$NaBH_4$, THF, reflux, 12 h	<5%
5	Mg^0, CH_3OH/benzene, rt, 12 h	<5%
6	In^0, NH_4Cl, EtOH, reflux, 12 h	<5%
7	$LiAlH_4$, Et_2O, 0 °C to rt, 12 h	~50%
8	$LiAlH_4$, THF, 0 °C to rt, 12 h	>95%

is still possible and each can be prepared as a single enantiomer if needed.

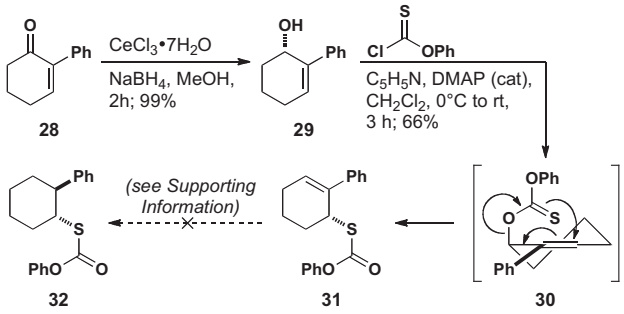
2.5. Synthesis of 2-phenyl-cyclohexane thiol (18b)

We initially sought to synthesize **18b** by a simple sulfur nucleophile displacement route (Scheme 3). Starting from the commercially available alkene **23**, hydroboration/oxidation[22] to **18a**, oxidation to **24**, and diastereoselective reduction[23] provided cis alcohol **25** in high yield for the three steps. Although formation of the corresponding mesylate[24] **26** was uneventful, attempted displacement with KSAc to produce **27** resulted in complete elimination to yield starting alkene **23**. This result is consistent with facile E2 elimination from *anti*-periplanar arrangement of the axial mesylate and benzylic hydrogen at the β-position. Although the ease with which elimination occurred was surprising with such a week base, divergent reactivity of similarly substituted *cis*- and *trans*-cyclohexyl tosylates has been reported for attempted displacement reactions with KOAc.[25]



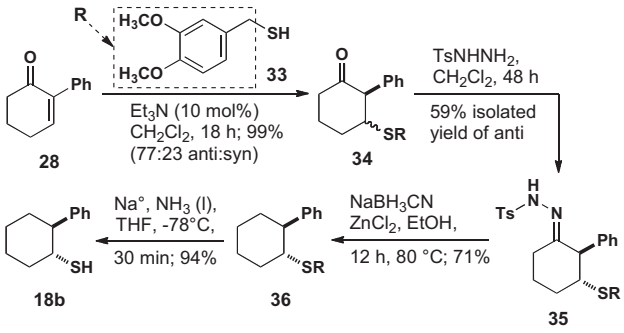
Scheme 3. Attempted route to thiol **18b** via nucleophilic displacement.

In order to avoid elimination, we envisioned a route to **18b** in which we attach sulfur to the cyclohexyl scaffold by a 3,3-sigmatropic rearrangement,[26] which affects a similar swap of oxygen for sulfur (Scheme 4). Reduction of α-phenyl enone[27] **28** under Luche conditions[28] to yield allylic alcohol **29** was achieved in quantitative yield. Acylation with *O*-phenyl chlorothionoformate gave allylic *O*-thiocarbonate intermediate **30**, which upon warming to room temperature underwent a 3,3-sigmatropic rearrangement to *S*-thiocarbonate **31**, which was isolated in good yield. Unfortunately, all attempts at hydrogenation of **31** were unsuccessful, even under forcing conditions, such as increased pressure of H_2, elevated temperature, and an excess of catalyst in a flow reactor at pressures that exceeded 100 bar.[29] This lack of reactivity is most likely due to the high steric demand of the trisubstituted olefin with allylic substitution.



Scheme 4. Attempted route to thiol **18b** via 3,3-sigmatropic rearrangement.

The successful synthesis of **18b** was achieved by introducing sulfur to the cyclohexyl scaffold by conjugate addition of benzyl mercaptan to a cyclohexenone (Scheme 5). Although the reaction was successful with benzyl mercaptan, the extreme stench of this reagent prompted us to employ odorless[30,31] benzyl thiol **33**, which underwent conjugation addition to α-phenyl enone **28** in nearly quantitative yield. Thiol **33** was synthesized in four steps from veratraldehyde.[30] NMR analysis of the crude conjugate addition product showed only the *anti* isomer formed under reaction conditions, but epimerization at the α-stereocenter occurred during column chromatography. The ratio of the inseparable *syn* and *anti* isomers of **34** after chromatography was slightly variable and hovered around 75:25 in favor of *anti*-**34**. Upon reaction with tosyl hydrazide the desired *anti*-**35** could be isolated as a single isomer at both the carbon stereogenic centers and with respect to hydrazone geomerty.[32] Reduction of **35** using sodium-cyanoborohydride yielded cyclohexyl compound **36**, which after de-protection by dissolving metal reduction gave target thiol **18b**.



Scheme 5. Completed synthesis of thiol **18b**.

2.6. Evaluation of thiols as chiral auxiliaries

Chiral thiols **11**–**17** and **18b** were examined in both lactam-forming reactions and exhibited a range of yield and diastereoselectivity. Although high *syn*/*anti* selectivity was still observed for the formation of the two γ-lactam stereogenic centers, the products were isolated in universally low yield and with modest stereoselectivity with respect to the thiol chirality (Table 2). For compounds **40a**–**e**, the same diastereomeric ratio was observed regardless of whether they were obtained by the 4CR or imine-anhydride reaction. These results are most likely due to both reactions proceeding through the same thio-substituted enolate intermediates in the proposed penultimate step of each reaction (Fig. 2).

The general lack of reactivity observed for branched alkyl thiols seems to be consistent, which is a deviation from the high yields previously observed for aryl thiols, such as thiocresol.[3] That said, no attempt was made to optimize the yields of these reactions on

Table 2
Thiols as chiral auxiliaries in 4CR and imine-anhydride reaction

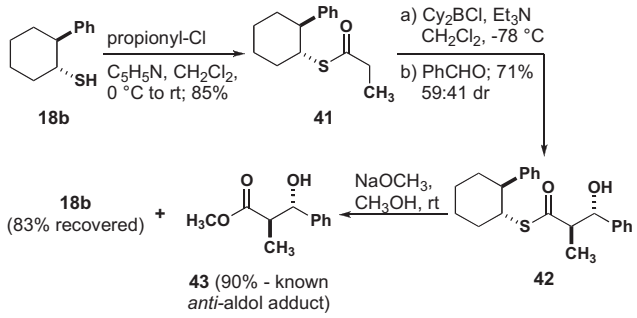
Entry	R_3SH	Product	4CR yield	Imine-anhydride yield	dr[a]
1	**12**	**40a**	21%	31%	62:38
2	**13**	—[b]	—[b]	—[b]	—[b]
3	**14**	**40b**	41%	41%	54:46
4	**15**	**40c**	44%	42%	51:49
5	**16**	**40d**	23%	20%	64:36
6	**17**	**40e**	17%	38%	64:36
7	**18b**	—[b]	—[b]	—[b]	—[b]

[a] Relative to chiral thiol auxiliary (>95:5 *syn*/*anti* selectivity observed for the stereocenters of the lactam).
[b] No discernable products in the reaction mixture.

a substrate-by-substrate basis and we have previously observed lower yields with benzyl mercaptan when compared to thiophenols. In the cases for the most sterically demanding thiols (**13** and **18b**), no discernable products were observed in both the 4CR and imine-anhydride reaction. In the case of norephedrine-derived thiol **11**, no product was observed in the γ-lactam forming 4CR and the imine-anhydride reaction gave irreproducible results and low mass recovery.[33] Based on low yields seen with the other alkyl thiols as well as the high molecular weight of this thiol relative to the others, we chose not to pursue this thiol further.

Thiol **16** is notable in that the major isomer formed by this reaction crystallized from the mixture of the two isomers initially isolated. The structure was determined by X-ray diffraction and it is clear that the long C–S bonds result in a significant distance between the stereogenic center of the thioether the newly formed centers of the γ-lactam. Given the ease with which this compound can be prepared in enantiomerically pure[34] form and the propensity for the major isomer to separate by crystallization, it is possible that this route could eventually be optimized for the production of useful quantities of enantiomerically pure γ-lactams.

In addition to evaluating thiol **18b** in the 4CR and imine-anhydride reaction, we wanted to ascertain its effectiveness in reactions reported with other chiral thiol auxiliaries. Since norephedrine-derived thiol **11** has been used previously in an *anti*-aldol reaction with high diastereoselectivity, we wanted a direct comparison to the 'thio-Whitesell' auxiliary **18b** in the same reaction (Scheme 6). Acylation of thiol **18b** with propionyl chloride yielded thio-ester **41** in high yield. *E*-selective enolization (Cy_2BCl/Et_3N)[35] at −78 °C followed by addition of benzaldehyde yielded the *anti*-aldol product (**42**) as a 59:41 mixture of diastereomers in 71% yield. *trans*-Esterification of aldol adduct **42** was readily achieved by treatment with sodium methoxide, affording methyl ester **43** in 90% yield with an 83% recovery of auxiliary **18b**. As a point of comparison, norephedrine-derived thiol **11** was reported to give a 93:7 diastereomeric mixture in the same reaction. It is clear that the stereo-differentiating environment provide by **18b** when attached to a pro-stereogenic enolate center is slight.



Scheme 6. Aldol addition using thiol-Whitesell analog **18b**.

The lack of reactivity of this thiol in the 4CR paired with the lack of selectivity of less sterically demanding substrates suggests that the structural requirements for a thiol to exhibit high selectivity and reactivity is exceedingly narrow. Alkyl thiols exhibit markedly lower reactivity in this 4CR even when they are unbranched, so it is unlikely that the right balance will be found with a branched chiral thiol. On the other hand, the BINOL-derived chiral thiophenol **13** also exhibited low reactivity, presumably solely from the increased steric demand. The long C–S bond lengths add a layer of difficulty by increasing the distance between the resident stereogenic center of the thiol and the nascent center during enolate attack on the iminium ion. The ideal chiral controller for this reaction would maintain the high reactivity of aromatic thiols and still provide a chiral environment that dictates the facial selectivity of the enolate, which may not be possible with the thiol component. These studies have helped focus our future efforts on using chiral amines, developing chiral catalysts and on new and chemically distinct MCRs.

3. Conclusion

In summary, we have synthesized a series of structurally diverse chiral thiols and examined their utility as auxiliaries in our lab's recently disclosed 4CR and in a related imine-anhydride reaction. These studies required a diastereoselective route to the sulfur

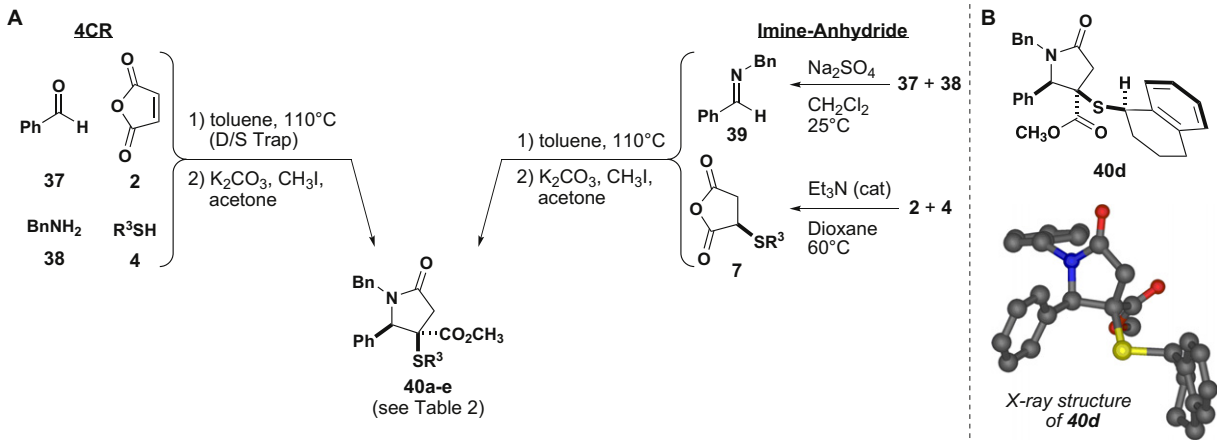


Fig. 2. (A) Chiral thiols in 4CR and imine-anhydride reactions. (B) X-ray crystal structure of the major isomer of lactam **40d**.

analog of Whitesell's auxiliary (**18**), which was achieved after significant effort on three potential routes. This thiol exhibited poor reactivity in our lactam syntheses and poor diastereo-control in a boron-mediated aldol reaction that was executed in order to draw direct comparison to the influence of another thiol-based auxiliary. Although a viable reagent for controlling the absolute stereochemistry of γ-lactam synthesis by the imine anhydride reaction or 4CR is still lacking, we have gained valuable information about the synthesis and reactivity of chiral thiols. With the synthetic routes established by this study, the stage is set the exploration of chiral thiols as chiral controllers for other useful transformations and, potentially, for their incorporation into novel ligands for transition metal catalysts.

4. Experimental section

4.1. Materials and instrumentation

Unless otherwise specified, all commercially available reagents were used as received. All reactions using dried solvents were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Dry solvent was dispensed from a solvent purification system that passes solvent through two columns of dry neutral alumina. Silica gel chromatographic purifications were performed by flash chromatography with silica gel (sigma, grade 62, 60–200 mesh) packed in glass columns; the eluting solvent for each purification was determined by thin layer chromatography (TLC). Analytical TLC was performed on glass plates coated with 0.25 mm silica gel using UV for visualization.

^{1}H NMR spectra were obtained on a Varian UNITY INOVA spectrometer (300 MHz) or Varian UNITY INOVA spectrometer (600 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent ($CHCl_3$, s, δ 7.26). Multiplicities are given as: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet). Proton-decoupled ^{13}C NMR spectra were obtained on a Varian UNITY INOVA 400 spectrometer (100 MHz) or Varian UNITY INOVA 600 spectrometer (150 MHz). ^{13}C chemical shifts are reported relative to $CDCl_3$ (δ 77.2 ppm). IR frequencies are given in cm^{-1} and spectra were obtained on a Bruker Tensor 27 FT-IR spectrometer equipped with a DTGS detector and Smart Orbit single bounce diamond ATR accessory. High-resolution mass spectra were obtained on a Thermo Fisher LTQ Orbitrap spectrometer.

4.2. General procedure for thiol formation from alcohols

To a solution of benzylic alcohol (7.90 mmol) and thiourea (1.20 g, 15.80 mmol) in a 1:1 mixture of acetone/H_2O (8.0/8.0 mL, 0.5 M) was added 5 N hydrochloric acid dropwise (2.4 mL, 12.00 mmol), and the solution was stirred at room temperature for 12 h. The mixture was basified with NaOH (0.96 g, 24.00 mmol) and the solution was refluxed for 3 h. The reaction was cooled to room temperature, acidified with 10% hydrochloric acid, and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (hexane) afforded an inseparable mixture of the target thiol (**15**–**17**) and the corresponding disulfide (**22a**–**c**; diastereomeric mixture) by ^{1}H and ^{13}C NMR.

To a cooled (0 °C) solution of thiol/disulfide in THF (40.0 mL, 0.2 M) was added lithium aluminum hydride (0.35 g, 9.10 mmol). After 18 h, 10% hydrochloric acid was added dropwise until a gray amorphous solid formed. The mixture was then filtered, and the filtrate was dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes) afforded the thiol product as a colorless oil.

*4.2.1. Indanol derived thiol (**15**).* Yield (55% over two steps) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51–7.48 (m, 1H), 7.36–7.29 (m, 3H), 4.48 (dd, J=7.1, 13.5 Hz, 1H), 3.21–3.15 (m, 1H), 3.00–2.93 (m, 1H), 2.75–2.68 (m, 1H), 2.17–2.10 (m, 1H), 1.97 (d, J=7.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.3, 142.9, 127.8, 127.2, 124.9, 124.7, 43.3, 38.4, 31.2. IR (neat) 2557, 635 cm^{-1}. HRMS (ESI) m/z calcd for C_9H_9S $(M-H)^-$ 149.0430, found 149.0440.

*4.2.2. Tetrahydro-naphthol derived thiol (**16**).* Yield (63% over two steps) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, J=6.8 Hz, 1H), 7.14–7.06 (m, 2H), 7.03 (d, J=6.8 Hz, 1H), 4.33 (s, 1H), 2.85–2.79 (m, 1H), 2.76–2.69 (m, 1H), 2.18–2.10 (m, 2H), 1.95 (d, J=6.3 Hz, 2H), 1.81–1.75 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 136.2, 129.9, 129.3, 126.8, 126.0, 38.2, 33.7, 29.1, 18.9. IR (neat) 2567, 648 cm^{-1}. HRMS (ESI) m/z calcd for $C_{10}H_{11}S$ $(M-H)^-$ 163.0587, found 163.0584.

4.3. Preparation of 2-phenyl-cyclohexane thiol

*4.3.1. Allylic thio-carbonate (**31**).* To a cooled (0 °C) solution of allylic alcohol **30** (85 mg, 0.49 mmol), C_5H_5N (0.24 mL, 2.93 mmol), and DMAP (6 mg, 0.05 mmol) in CH_2Cl_2 (2.5 mL) was added *O*-phenyl chlorothionoformate (0.20 mL, 1.47 mmol) as a solution in CH_2Cl_2 (2.5 mL). After 2 h, the ice bath was removed, and after stirring for 1 h at room temperature, the reaction was quenched with H_2O. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, concentrated in vacuo, and the crude product was purified by flash chromatography (10:90 to 15:85 CH_2Cl_2/hexanes) to afford the thiocarbonate as a clear oil (103 mg, 66%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42–7.39 (m, 2H), 7.36–7.32 (m, 4H), 7.29–7.26 (m, 1H), 7.22–7.19 (m, 1H), 7.12–7.09 (m, 2H), 6.22 (dd, J=3.0, 4.8 Hz, 1H), 4.75 (s, 1H), 2.33–2.19 (m, 3H), 2.15–2.08 (m, 1H), 1.91–1.79 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 151.3, 140.2, 135.0, 131.1, 129.6, 128.6, 127.6, 126.2, 126.1, 121.5, 44.4, 30.7, 25.9, 18.0. IR (neat) 1719 cm^{-1}. HRMS (ESI) m/z calcd for $C_{19}H_{19}O_2S$ $(M+H)^+$ 311.1100, found 311.1100.

*4.3.2. Conjugate addition product (**34**).* To a solution of 2-phenyl-2-cyclohexene-1-one (102 mg, 0.59 mmol) and odor-free[30] benzyl thiol **33** (171 mg, 0.93 mmol) in CH_2Cl_2 was added triethylamine (8.0 μL, 0.06 mmol). The solution was stirred for 18 h, the solvent was removed in vacuo and the crude product was purified by flash chromatography (50:50 CH_2Cl_2/hexanes to CH_2Cl_2 to 20:80 EtOAc/CH_2Cl_2) to afford the conjugate addition product as a clear oil (211 mg, 99%, 77:23 *anti*/*syn*; inseparable diastereomeric mixture). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01–6.96 (m, 2H), 6.70 (d, J=7.9 Hz, 1H), 6.63–6.58 (m, 2H), 3.84 (d, J=3.7 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.54 (d, J=11.3 Hz, 1H), 3.35 (d, J=13.4 Hz, 1H), 3.27 (d, J=13.4 Hz, 1H), 2.95 (td, J=3.7, 11.3 Hz, 1H), 2.44–2.38 (m, 1H), 2.33–2.27 (m, 1H), 2.12–2.07 (m, 1H), 1.92–1.81 (m, 1H), 1.74–1.61 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 149.0, 148.1, 136.66, 130.4, 130.1, 129.4, 128.2, 128.00, 127.27, 120.9, 111.7, 110.6, 63.5, 55.91, 55.78, 48.4, 41.2, 35.4, 32.9, 25.0. *Visible Peaks for Minor Diastereomer*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.39 (m, 2H), 7.34–7.32 (m, 1H), 7.25–7.22 (m, 1H), 6.80–6.74 (m, 2H), 6.67 (d, J=8.2 Hz, 1H), 6.53–6.49 (m, 1H), 3.92 (d, J=4.4 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.25–3.20 (m, 1H), 3.12 (d, J=13.3 Hz, 1H), 2.55–2.47 (m, 2H), 2.38–2.33 (m, 1H), 2.23–2.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 148.9, 136.2, 129.9, 127.26, 121.1, 112.1, 110.7, 60.7, 55.88, 49.5, 40.8, 36.1, 31.6, 23.0. IR (neat) 1713 cm^{-1}. HRMS (ESI) m/z calcd for $C_{21}H_{24}NaO_3S$ $(M+Na)^+$ 379.1344, found 379.1343.

*4.3.3. Anti-hydrazone (**35**).* To a solution of **34** (70 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL, 0.1 M) was added tosyl hydrazide (44 mg, 0.24 mmol) and the reaction was stirred for 48 h. The mixture was

concentrated in vacuo and the crude product was purified by column chromatography (15:85 to 30:70 EtOAc/hexanes) to afford the *anti*-hydrazone product as a colorless solid (62 mg, 59%). Mp 118–126 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.38 (d, J=8.0 Hz, 2H), 7.30–7.25 (m, 3H), 7.06 (d, J=8.0 Hz, 2H), 6.98–6.94 (m, 2H), 6.74–6.65 (m, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 3.44 (d, J=9.6 Hz, 1H), 3.40 (d, J=9.6 Hz, 1H), 3.05 (td, J=3.8, 9.2, 1H), 2.52–2.46 (m, 1H), 2.36 (s, 3H), 2.15 (s, 1H), 2.14–2.11 (m, 1H), 2.05–1.97 (m, 1H), 1.93–1.86 (m, 1H), 1.69–1.60 (m, 1H), 1.54–1.45 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.6, 149.2, 148.2, 143.7, 138.9, 135.0, 130.5, 130.0, 129.8, 129.6, 129.5, 129.3, 128.4, 128.12, 128.08, 128.0, 127.5, 126.8, 121.1, 112.0, 110.9, 56.10, 56.09, 56.0, 46.8, 35.4, 31.5, 31.2, 29.5, 26.1, 23.5, 21.8. IR (neat) 3196, 1736 cm^{-1}. HRMS (ESI) m/z calcd for $C_{28}H_{33}N_2O_4S_2$ $(M+H)^+$ 525.1876, found 525.1874.

*4.3.4. Tosylhydrazone reduction (**36**).* To a solution of hydrazone **35** (197 mg, 0.38 mmol) in EtOH (15.0 mL, 0.025 M) was added $NaBH_3CN$ (99 mg, 1.50 mmol) and a 1 N solution of $ZnCl_2$ (0.38 mL, 0.38 mmol) in Et_2O. The resulting suspension was refluxed for 12 h. The reaction was quenched with 1 N NaOH solution and NaCl, then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography to afford the reduced product as a clear oil (91 mg, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23–7.20 (m, 1H), 7.13–7.08 (m, 2H), 6.74 (d, J=8.1 Hz, 1H), 6.67 (d, J=2.0 Hz, 1H), 6.64 (dd, J=2.0, 8.1 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.34 (d, J=13.4 Hz, 1H), 3.27 (d, J=13.4 Hz, 1H), 2.58 (td, J=3.8, 11.5 Hz, 1H), 2.50 (td, J=3.6, 11.5 Hz, 1H), 2.24–2.18 (m, 1H), 1.90–1.85 (m, 1H), 1.85–1.80 (m, 1H), 1.80–1.74 (m, 1H), 1.52–1.42 (m, 2H), 1.40–1.29 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.1, 148.0, 145.5, 131.2, 128.4, 127.9, 126.5, 121.1, 112.1, 110.1, 56.1, 56.0, 51.4, 48.0, 36.3, 35.04, 34.96, 27.0, 26.4. IR (neat) 655 cm^{-1}. HRMS (ESI) m/z calcd for $C_{21}H_{26}NaO_2S$ $(M+Na)^+$ 365.1551, found 365.1542.

*4.3.5. 2-Phenyl-cyclohexane thiol (**18b**).* A solution of thioether **36** (107 mg, 0.31 mmol) in THF (3.1 mL, 0.1 M) was added drop-wise to a well-stirred solution of sodium metal (36 mg, 1.56 mmol) in liquid ammonia (~3 mL) at −78 °C. After 1 h at −78 °C, 5 mL of CH_3OH was added followed by 5 mL of satd NH_4Cl. After warming to room temperature, the mixture was partitioned between H_2O and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and the crude product was purified by flash chromatography (0:100 to 3:97 EtOAc/hexanes) to afford the free thiol as a colorless oil (56 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.28 (m, 2H), 7.25–7.16 (m, 3H), 3.11–3.02 (m, 1H), 2.46 (td, J=3.6, 11.3 Hz, 1H), 2.22–2.15 (m, 1H), 1.94–1.79 (m, 3H), 1.55–1.40 (m, 4H), 1.34 (d, J=4.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 128.7, 127.8, 126.8, 54.5, 44.0, 37.1, 36.0, 27.2, 26.6. IR (neat) 2573, 623 cm^{-1}. HRMS (ESI) m/z calcd for $C_{12}H_{15}S$ $(M-H)^-$ 191.0900, found 191.0896.

4.4. General procedure for forming γ-lactams

Method A (*4CR*). A solution of thiol (1.00 mmol), maleic anhydride (98 mg, 1.0 mmol), benzyl amine (0.11 mL, 1.0 mmol), and benzaldehyde (0.10 mL, 1.0 mmol) in toluene (10.0 mL, 0.1 M) was refluxed with a Dean–Stark trap for 18 h. After cooling to room temperature, the solvent was removed in vacuo. The residue was then re-dissolved in acetone (10 mL, 0.1 M), followed by addition of anhydrous K_2CO_3 (0.55 g, 4.0 mmol) and CH_3I (0.25 mL, 4.0 mmol). This mixture was stirred for 12 h, and then the solvent was removed in vacuo. The residue was partitioned between H_2O and EtOAc, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and the crude product was purified by flash chromatography (0:100 to 60:40 EtOAc/hexanes) to afford the γ-lactam.

Method B (*Imine-Anhydride*). To a solution of maleic anhydride (98 mg, 1.0 mmol) and triethylamine (1.5 μL, 0.01 mmol) in benzene (1.0 mL) was added thiol (1.0 mmol) as a solution in benzene (1.5 mL). The solution was heated to 60 °C for 30 min then cooled to room temperature. Concentration in vacuo afforded the thio-substituted succinic anydride product, which was used without further purification.

To a solution of benzaldehyde (0.10 mL, 1.0 mmol), and Na_2SO_4 (0.43 g, 3.0 mmol) in CH_2Cl_2 (10.0 mL, 0.1 M) was added benzyl amine (0.11 mL, 1.0 mmol). After stirring for 3 h, the reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo to afford the imine product. The imine was re-dissolved in toluene (10.0 mL, 0.1 M) and was added to the thio-substituted succinic anhydride. This mixture was refluxed for 18 h. After cooling to room temperature, the solvent was removed in vacuo. The residue was methylated and purified in the same manner as in method A.

*4.4.1. Lactam from camphor derived thiol (**40a**).* Yield (21% by method A, 31% by method B, 62:38 dr, inseparable mixture, yellow oil). Major diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.27 (m, 3H), 7.17 (m, 2H), 7.02 (m, 3H), 5.14 (d, J=15.1 Hz, 1H), 4.92 (s, 1H), 3.63 (s, 3H), 3.57 (d, J=16.6 Hz, 1H), 3.45 (d, J=15.1 Hz, 1H), 3.07 (d, J=7.6 Hz, 1H), 3.03 (d, J=7.7 Hz, 1H), 2.81 (d, J=7.7 Hz, 1H), 2.70 (d, J=7.6 Hz, 1H), 1.61 (m, 2H), 1.38 (d, J=4.0 Hz, 1H), 1.27 (d, J=4.0 Hz, 1H), 0.93 (s, 1H), 0.91 (m, 1H), 0.89 (s, 3H), 0.84 (s, 3H), 0.78 (s, 3H), 0.65 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.4, 172.1, 135.94, 135.5, 134.4, 129.04, 128.95, 128.71, 128.25, 127.82, 89.3, 83.6, 67.3, 55.3, 53.4, 53.1, 52.95, 50.3, 47.1, 44.8, 40.8, 33.4, 32.7, 28.5, 26.9, 21.17, 21.15, 11.9. *Visible peaks for minor diastereomer*: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39–7.36 (m, 3H), 7.29–7.27 (m, 3H), 7.17–7.15 (m, 2H), 5.11 (d, J=9.8 Hz, 1H), 3.66 (s, 3H), 3.43–3.39 (m, 2H), 2.49 (d, J=7.6 Hz, 1H), 2.42 (d, J=7.7 Hz, 1H), 0.75 (s, 3H), 0.70 (s, 9H), 0.68 (s, 3H), 0.66 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 171.8, 135.90, 128.68, 128.31, 127.80, 88.8, 83.1, 67.0, 54.9, 53.3, 53.03, 52.9, 50.1, 47.3, 45.1, 41.1, 33.2, 32.6, 28.4, 27.0, 21.5, 21.16, 11.8. IR (neat) 1727, 1699 cm^{-1}. HRMS (ESI) m/z calcd for $C_{34}H_{46}NO_4S$ $(M+H)^+$ 564.3142, found 564.3144.

*4.4.2. Lactam from cystine derived thiol (**40b**).* Yield (41% by method A, 41% by method B, 54:46 dr; inseparable mixture, yellow oil). *NMR Peaks for major & minor isomers are nearly indistinguishable*: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (t, J=7.5 Hz, 3H), 7.52 (s, 2H), 7.46–7.40 (m, 4H), 7.40–7.37 (m, 3H), 7.34 (s, 4H), 7.27 (s, 2H), 7.26 (s, 1H), 7.21–7.15 (m, 4H), 7.02–6.98 (m, 3H), 6.62 (d, J=7.4 Hz, 2H), 5.14 (d, J=14.8 Hz, 2H), 4.93 (s, 1H), 4.92 (s, 1H), 4.80–4.73 (m, 2H), 3.81 (d, J=27.1 Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.63 (s, 3H), 3.60 (s, 3H), 3.44 (d, J=14.8 Hz, 2H), 3.37 (d, J=17.5 Hz, 1H), 3.17 (d, J=7.1 Hz, 1H), 2.87–2.84 (m, 1H), 2.81 (d, J=7.1 Hz, 1H), 2.78 (d, J=6.8 Hz, 1H), 2.66 (dd, J=6.2, 12.9 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.84, 171.83, 171.3, 171.2, 170.7, 170.6, 167.1, 167.0, 135.6, 134.4, 134.2, 133.6, 132.13, 132.11, 129.43, 129.41, 129.0, 128.9, 128.82, 128.81, 128.78, 128.77, 128.76, 128.73, 128.5, 128.4, 128.0, 127.33, 127.32, 66.82, 66.78, 55.5, 55.3, 53.59, 53.56, 53.02, 52.97, 51.9, 51.6, 45.0, 40.73, 40.69, 32.56, 32.54. IR (neat) 3321, 1729, 1685, 1681 cm^{-1}. HRMS (ESI) m/z calcd for $C_{30}H_{31}N_2O_6S$ $(M+H)^+$ 547.1898, found 547.1896.

*4.4.3. Lactam from indanol derived thiol (**40c**).* Yield (21% by method A, 31% by method B, 51:49 dr; inseparable mixture, yellow oil). *NMR Peaks for major & minor isomers are nearly indistinguishable*: ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.42–7.38 (m, 6H), 7.32–7.27 (m, 6H), 7.24–7.21 (m, 4H), 7.12–6.98 (m, 12H), 5.20 (d, J=14.8 Hz, 1H), 5.17 (d, J=14.8 Hz, 1H), 5.13 (s, 1H), 4.95 (s, 1H), 4.09 (s, 2H), 3.98 (s, 1H), 3.95 (s, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.67 (d, J=17.1 Hz, 1H), 3.52 (d, J=17.1 Hz, 1H), 3.46 (dd, J=4.3, 14.5 Hz, 2H), 2.97 (d,

J=17.0 Hz, 1H), 2.92–2.83 (m, 4H), 2.77–2.68 (m, 3H), 2.44–2.40 (m, 1H), 2.30–2.26 (m, 1H), 1.92–1.87 (m, 1H), 1.80–1.76 (m, 1H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 173.0, 172.6, 172.0, 171.7, 143.46, 143.43, 142.3, 141.7, 135.83, 135.78, 134.77, 134.2, 129.33, 129.26, 129.0, 128.82, 128.80, 128.4, 128.3, 127.97, 127.95, 127.90, 127.88, 126.7, 126.6, 125.3, 124.63, 124.57, 67.4, 67.2, 56.4, 55.8, 53.6, 53.5, 48.61, 48.59, 45.0, 44.8, 41.5, 41.4, 35.7, 35.2, 31.1, 31.0. IR (neat) 1726, 1699 cm^{-1}. HRMS (ESI) m/z calcd for $C_{28}H_{28}NO_3S$ $(M+H)^+$ 458.1785, found 458.1784.

*4.4.4. Lactam from tetrahydro-naphthol derived thiol (**40d**).* Yield (23% by method A, 20% by method B, 64:36 dr). A small sample of the major diastereomer was isolated by crystallization from semi-pure mixture in CH_3OH for characterization (colorless crystalline solid): mp 153–156 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.34 (m, 3H), 7.31–7.27 (m, 3H), 7.20–7.17 (m, 2H), 7.06–7.00 (m, 5H), 6.95–6.91 (m, 1H), 5.17 (d, J=14.8 Hz, 1H), 4.93 (s, 1H), 3.99–3.96 (m, 1H), 3.71 (d, J=16.7 Hz, 1H), 3.66 (s, 3H), 3.44 (d, J=14.8 Hz, 1H), 3.04 (d, J=16.7 Hz, 1H), 2.68–2.55 (m, 2H), 1.86–1.74 (m, 2H), 1.71–1.60 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.8, 171.8, 137.6, 135.9, 135.8, 134.3, 130.7, 129.24, 129.21, 128.8, 128.4, 127.9, 127.1, 126.0, 67.6, 56.1, 53.3, 44.8, 44.4, 41.7, 30.5, 28.8, 19.0. IR (neat) 1724, 1698 cm^{-1}. HRMS (ESI) m/z calcd for $C_{29}H_{30}NO_3S$ $(M+H)^+$ 472.1941, found 472.1941.

*4.4.5. Lactam from 1-(1-naphthyl)ethanol derived thiol (**40e**).* Yield (21% by method A, 38% by method B, 64:36 dr, colorless oil). A small sample of the major diastereomer was isolated by HPLC for characterization: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, J=8.0 Hz, 2H), 7.67 (d, J=8.0 Hz, 1H), 7.49–7.41 (m, 6H), 7.35 (t, J=7.6 Hz, 2H), 7.24–7.18 (m, 4H), 6.98–6.92 (m, 2H), 5.09 (d, J=14.8 Hz, 1H), 4.95 (s, 1H), 4.41 (br s, 1H), 3.42 (d, J=14.8 Hz, 1H), 3.06 (s, 3H), 2.97 (d, J=17.3 Hz, 1H), 2.55 (d, J=17.3 Hz, 1H), 1.27 (d, J=6.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 171.7, 139.5, 135.7, 134.6, 133.9, 130.3, 129.2, 129.1, 128.6, 128.2, 128.1, 127.8, 126.1, 125.7, 125.4, 67.2, 55.7, 52.7, 44.7, 40.8, 24.1. IR (neat) 1730, 1700 cm^{-1}. HRMS (ESI) m/z calcd for $C_{31}H_{30}NO_3S$ $(M+H)^+$ 496.1941, found 496.1941.

4.5. Other applications of 2-phenyl-cyclohexane thiol

*4.5.1. Propionylated thiol (**41**).* To a solution of thiol **18b** (81 mg, 0.42 mmol) in CH_2Cl_2 (2.1 mL, 0.2 M) was added pyridine (46 μL, 0.57 mmol) followed by propionyl chloride (66 μL, 0.76 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was diluted with Et_2O and was washed with H_2O and brine. The organics were dried ($MgSO_4$) and concentrated in vacuo to give the crude product, which was purified by flash chromatography (5:95 EtOAc/hexanes) to afford the thio-ester as a colorless oil (89 mg, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (t, J=7.7 Hz, 2H), 7.20–7.17 (m, 1H), 7.15 (d, J=7.7 Hz, 2H), 3.74–3.67 (m, 1H), 2.56 (td, J=3.6, 12.0 Hz, 1H), 2.38–2.29 (m, 2H), 2.22–2.17 (m, 1H), 2.00–1.93 (m, 1H), 1.85–1.80 (m, 2H), 1.60–1.50 (m, 3H), 1.45–1.36 (m, 1H), 1.00–0.96 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.8, 144.5, 128.2, 127.4, 126.4, 49.3, 47.0, 37.4, 36.5, 35.2, 26.7, 26.2, 9.7. IR (neat) 1686 cm^{-1}. HRMS (ESI) m/z calcd for $C_{15}H_{21}OS$ $(M+H)^+$ 249.1308, found 249.1305.

*4.5.2. Thio-Whitesell aldol adduct (**42**).* To a solution of thio-ester **41** (25 mg, 0.10 mmol), in CH_2Cl_2 (5.0 mL, 0.02 M) at −78 °C was added dicyclohexylboron chloride (0.20 mL, 1.0 M in hexane, 0.20 mmol), then Et_3N (56 μL, 0.40 mmol). The reaction mixture was stirred for 2 h, then freshly distilled benzaldehyde (43 μL, 0.40 mmol) was added. The reaction mixture was stirred at −78 °C for 4 h, followed by the addition of pH 7 buffer (1 mL), CH_3OH (3 mL), and the careful addition of 30% H_2O_2 (1 mL). The reaction mixture was stirred vigorously for 14 h, and then partitioned between H_2O and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (15:85 EtOAc/hexanes) to yield the aldol adduct as a colorless oil (25 mg, 71%, 59:41 dr, inseparable mixture). ^{1}H NMR (600 MHz, $CDCl_3$; *distinguishable peaks for minor diastereomer italicized*) δ 7.32–7.29 (m, 2H), 7.27 (m, 3H), 7.26–7.22 (m, 6H), 7.21–7.18 (m, 3H), 7.17–7.14 (m, 3H), 4.61 (d, J=8.3 Hz, 1H), *4.51* (*d*, *J=8.6 Hz*, *1H*), *3.83–3.77* (*m*, *1H*), 3.79–3.74 (m, 1H), 2.76–2.70 (m, 2H), *2.60* (*td*, *3.9*, *12.2 Hz*, *1H*), 2.55 (td, J=3.9 Hz, 12.2, 1H), 2.21–2.14 (m, 2H), 2.02–1.93 (m, 2H), 1.89–1.80 (m, 3H), 1.66–1.49 (m, 5H), 1.45–1.33 (m, 2H), *0.82* (*d*, *J=7.1*, *3H*), 0.63 (d, J=7.1 Hz, 3H). 13C NMR (150 MHz, $CDCl_3$; *distinguishable peaks for minor diastereomer italicized*) δ *202.90*, 202.88, *144.5*, 144.4, *141.7*, 141.2, *133.9*, 130.4, *129.4*, 128.7, 128.6, *128.5*, *128.4*, 128.3, 128.2, *128.1*, *127.85*, 127.82, 126.87, *126.81*, 126.71, *126.67*, 76.72, *76.69*, *55.95*, 55.71, 50.24, *50.03*, *47.33*, 47.09, *36.38*, 36.29, 34.99, *34.88*, 26.95, *26.93*, 26.33, *26.32*, 15.45, *15.43*. IR (neat) 3459, 1692 cm^{-1}. HRMS (ESI) m/z calcd for $C_{22}H_{27}O_2S$ $(M+H)^+$ 355.1726, found 355.1726.

Acknowledgements

This research was supported by startup funds from UC Davis and the NSF in the form of a CAREER award to J.T.S.

Supplementary data

^{1}H and ^{13}C NMR for novel compounds, experimental procedures for compounds **17**, **29**, and **43**, and X-ray crystallographic data for compounds **35** and **40d**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.03.027.

References and notes

1. See, for example: (a) Banfi, L.; Basso, A.; Cerulli, V.; Rocca, V.; Riva, R. *Beilstein J. Org. Chem.* **2011**, *7*, 976 and references cited therein; (b) For previous work on the Ugi 4CR, including chiral substrates, see Doemling, A. *Chem. Rev.* **2006**, *106*, 17.
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