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Gold-Catalyzed Oxidative Cyclization of Chiral Homopropargyl Amides: Synthesis of Enantioenriched γ-Lactams

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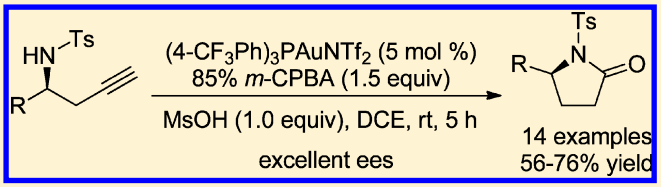
Supporting Information

ABSTRACT: A gold-catalyzed tandem cycloisomerization/oxidation of homopropargyl amides has been developed, which provides ready access to synthetically useful chiral γ-lactams with excellent ee by combining the chiral *tert*-butylsulfinimine chemistry and gold catalysis. The utility of this methodology has also been demonstrated in the synthesis of biologically active compound *S*-MPP and natural product (−)-bgugaine. The use of readily available starting materials, a simple procedure, and mild reaction conditions are other significant features of this method.



INTRODUCTION

Functionalized γ-lactams are widespread among the structures of a large number of biologically active natural (Figure 1) and non-natural products.[1] In addition, they also serve as important intermediates for the synthesis of some complex molecules because of their latent reactivity and highly stereoselective transformation.[2] Therefore, numerous strategies have been developed for their construction,[3] including metal carbene intramolecular C−H insertions,[4] ring expansion of β-lactam derivatives[5] and formal [3 + 2] annulations.[6] However, few examples have been reported about the enantioselective synthesis of γ-lactams, especially those with high efficiency, flexibility, and good modularity.[7]

Homogeneous gold catalysis has proven to be a powerful tool in organic synthesis[8] and is undergoing continual refinement specially as an effective means of preparing heterocycles.[9] Very recently, we have developed an efficient way for the synthesis of γ-lactones from readily available homopropargyl alcohols.[10] Interestingly, mechanistic studies revealed that this reaction presumably went through a tandem Au-catalyzed oxycyclization followed by an acid-accelerated oxidation sequence, which was distinctively different from the related ruthenium-catalyzed reactions where the intermediacy of ruthenium vinylidene was proposed. Moreover, it was found that the conversion of chiral homopropargyl alcohols proceeded well with retention of the stereochemistry, enabling access to chiral γ-lactones.

Inspired by these results, we envisaged that this tandem reaction might also be applied to the preparation of various γ-lactams from the corresponding *N*-homopropargyl amides (Scheme 1). First, 5-endodig cyclization of homopropargyl amide **1** could result in the formation of vinyl gold intermediate **A**. Next, in the presence of acid, intermediate **A** would then be transformed into iminium intermediate **B**, which may finally undergo a *m*-CPBA oxidation to produce the final product **2**. In this context, we describe herein the synthesis of a variety of chiral mutifunctionalized γ-lactams, by successful combination of the aforementioned gold catalysis and the chiral *tert*-butylsulfinimine chemistry. The utility of this strategy was then showcased by the synthesis of biologically active compound *S*-MPP and natural product (−)-bgugaine.

RESULTS AND DISCUSSION

Considering that *N*-homopropargyl carboxamides are not suitable substrates because of the competing gold-catalyzed amide 6-exodig cyclization,[11] the *N*-tosyl amide substrates were chosen for our initial study. First, we synthesized the homopropargylic amide **1a** as the model substrate to examine the reaction. To our delight, the reaction could work well to give the desired product **2a** in 75% ^{1}H NMR yield (Table 1, entry 1) under the previously optimized reaction conditions for the lactone synthesis.[10] Attempts to improve the yield of this reaction by the screening of other gold catalysts and the use of other acids was unsuccessful (Table 1, entries 2−13). Of note, in the presence of 2.5 mol % gold catalyst, γ-lactam **2a** could also be formed in 68% yield (Table 1, entry 14). However, without using any gold catalyst, no desired product **2a** was observed under the acidic reaction conditions, and $PtCl_2$ and $AgNTf_2$ could not catalyze this reaction.

With the optimal reaction conditions, we then decided to synthesize the chiral homopropargyl amide substrates **1** by using Ellman's *tert*-butylsulfinimine chemistry.[12] Delightfully, the *N*-homopropargylsulfonamide **1** could be prepared with excellent enantiomeric excesses upon subsequent removal of *tert*-butylsulfinyl group and tosyl protection (Scheme 2).

With chiral homopropargyl amides in hand, we then probed the reaction scope. As shown in Table 2, all of the reactions

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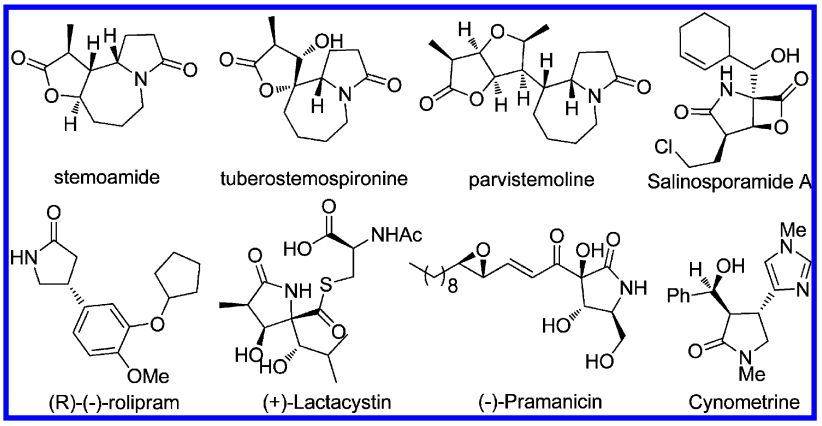


Figure 1. Some examples of natural γ-lactams.

Scheme 1. Formation of γ-Lactams through Gold-Catalyzed Oxidative Cyclization

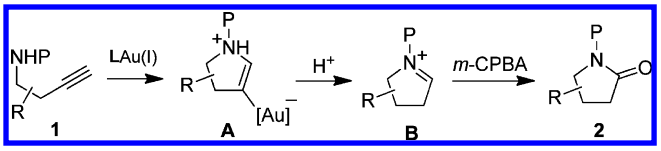
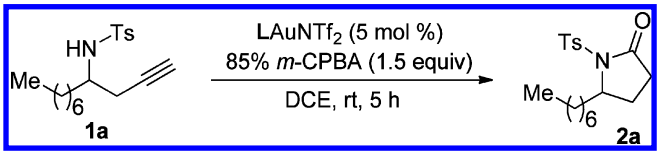


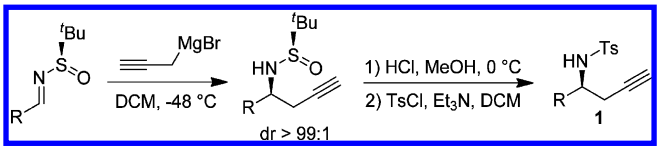
Table 1. Reaction Conditions Optimization[a]



entry	gold catalyst	acid	yield (%)[b]
1	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$	1.0 equiv MsOH	75[c]
2	$(C_6F_5)_3PAuNTf_2$	1.0 equiv MsOH	35
3	$Ph_3PAuNTf_2$	1.0 equiv MsOH	44
4	Cy-JohnPhosAuNTf$_2$	1.0 equiv MsOH	33
5	XPhosAuNTf$_2$	1.0 equiv MsOH	53
6	BrettPhosAuNTf$_2$	1.0 equiv MsOH	32
7	$B_3PAuNTf_2$	1.0 equiv MsOH	37
8	IPrAuNTf$_2$	1.0 equiv MsOH	60
9	Au(III)[d]	1.0 equiv MsOH	56
10	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$	0.5 equiv MsOH	58
11	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$	1.3 equiv MsOH	59
12	$(4\text{-}CF_3C_6H4)_3PAuNTf_2$	1.0 equiv CF_3CO_2H	60
13	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$	1.0 equiv $HNTf_2$	6
14[e]	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$	1.0 equiv MsOH	68

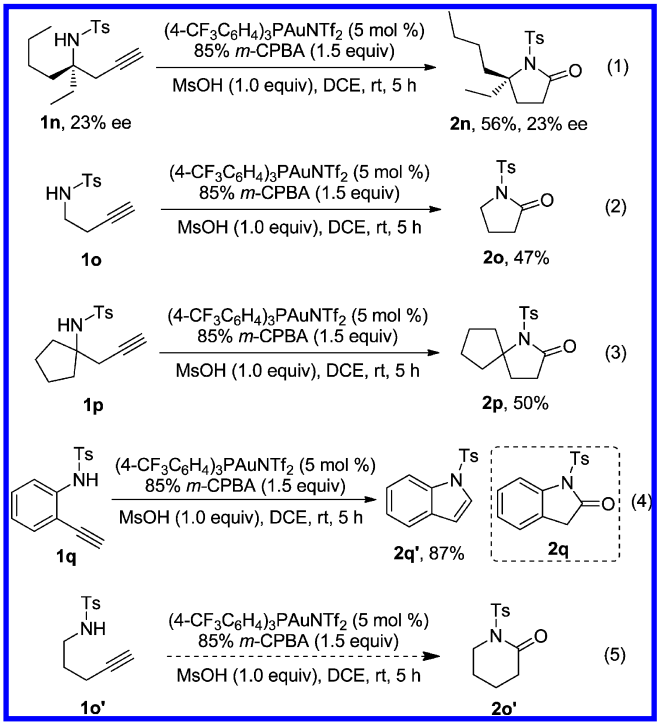
[a]Reaction conditions: [**1a**] = 0.05 M; DCE: 1,2-dichloroethane. [b]Estimated by ^{1}H NMR using dibromomethane as internal reference. [c]Yield of isolated **2a** was 72%. [d]Dichloro(2-picolinato)gold(III). [e]2.5 mol % gold catalyst was used, 10 h.

Scheme 2. Synthesis of Chiral Homopropargyl Amide Substrates 1 Using Ellman's Method



took place smoothly and afforded the corresponding chiral γ-lactams in moderate to good yields. Except for the substrate **2l** (Table 2, entry 12), which only afforded 86% ee, excellent enantioselectivities were achieved in all cases, and essentially no epimerization was observed. This protocol constitutes a good combination of chiral *tert*-butylsulfinimine chemistry with gold catalysis.[13] It is worth noting that the same oxidative cyclization underwent smoothly using (*S*)-(+)-*tert*-butylsulfinamide-derived homopropargyl amide **1a′** instead of (*R*)-(+)-*tert*-butylsulfinamide-derived substrate **1a** to give the opposite enantioselectivity with 99% ee (Table 2, entry 14). Thus, both enantiomers of γ-lactam **2** could be obtained easily just by the choice of the starting chiral source.

The reaction could also be extended to the synthesis of 5,5-disubstituted γ-lactam **2n** in serviceable yield but with low enantioselectivity (23% ee) from the corresponding tertiary homopropargyl amide **1n** (23% ee) prepared according to the Ellman's Method (eq 1).[12c] In addition, substates **1o** and **1p**



were also employed, leading to the corresponding γ-lactams in 47 and 50% yield, respectively (eqs 2 and 3). When aromatic substate **1q** was subjected to this tandem reaction, however, only indole compound **2q′** was observed (eq 4).[14] Attempts to expand this chemistry to the synthesis of 6-membered lactam

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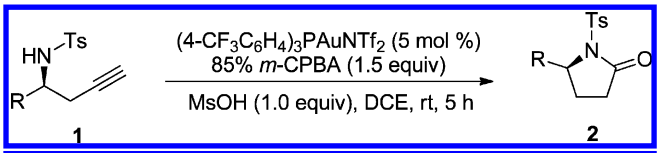
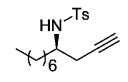
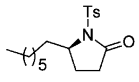
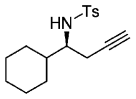
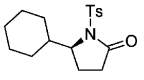
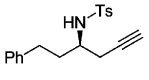
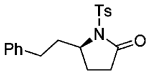
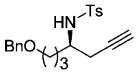
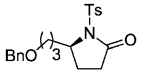
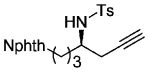
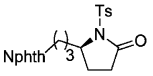
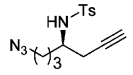
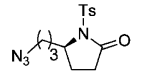
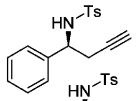
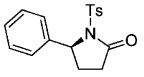
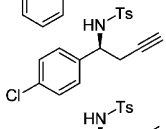
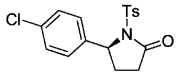
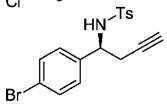
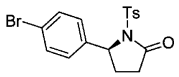
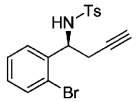
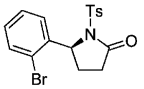
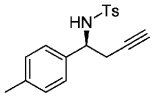
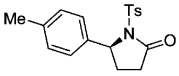
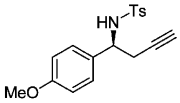
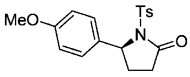
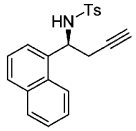
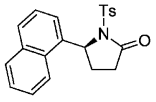
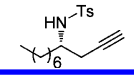
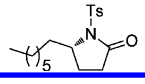
Table 2. Reaction Scope for the Formation of Enantioenriched γ-Lactams[a]



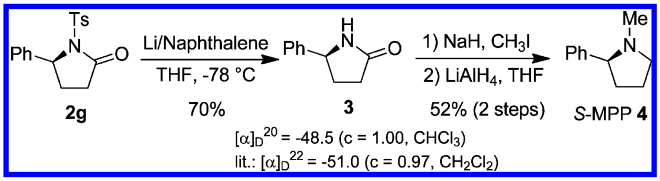
entry	substrate	1	product	2	yield ee
1		1a		2a	75% 99%
2		1b		2b	57% 99%
3		1c		2c	62% 99%
4		1d		2d	60% 98%
5		1e		2e	62% >99%
6		1f		2f	63% 99%
7		1g		2g	73% 99%
8		1h		2h	69% 98%
9		1i		2i	64% 98%
10		1j		2j	76% 98%
11		1k		2k	72% >99%
12		1l		2l	68% 86%
13		1m		2m	68% 99%
14[b]		1a′		2a′	73% 99%

[a]Reactions run in vials; [1] = 0.05 M; isolated yields are reported; ees are determined using HPLC on a chiral stationary phase. [b]Using (*S*)-(+)-*tert*-butylsutfinamide-derived homopropargyl amide **1a′** as the substrate.

were not successful, presumably because of the competing gold-catalyzed 5-exodig cyclization, and further studies in this direction are currently ongoing (eq 5).

Removal of the tosyl group was then examined using **2g** as the model substrate. As illustrated in Scheme 3, lactam

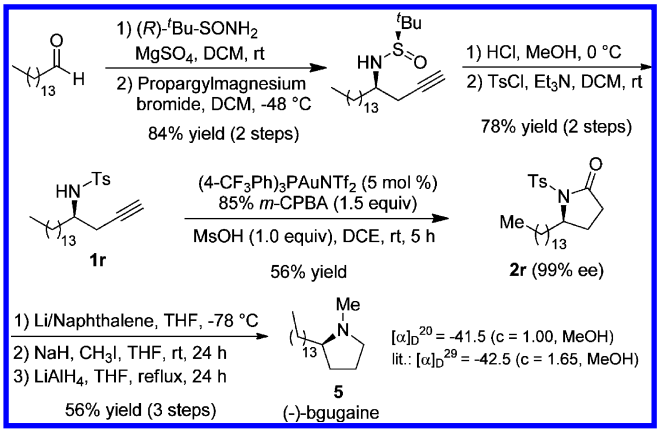
Scheme 3. Synthesis of *S*-MPP 4



compound **3** could be obtained in 70% yield by treating **2g** with Li/Naphthalene, and its specific rotation was almost identical to those reported in the literature,[15] which further confirmed the configuration assumed by Ellman's chemistry.[12] Of note, chiral compound **3** could be easily transformed into biologically active *S*-MPP **4**[16] by *N*-methylation and $LiAlH_4$ reduction in 52% yield (two steps).

With above established sequence, the total synthesis of (−)-bgugaine (**5**)[17] was carried out as outlined in Scheme 4.

Scheme 4. Synthesis of *S*-MPP 4



Starting from commercially available pentadecanal, (−)-bgugaine was synthesized in eight steps in 21% overall yield. Thus, this protocol provides a general and efficient way for the synthesis of versatile optically active *N*-methyl pyrrolidine derivatives.[18]

CONCLUSION

In conclusion, we have developed a gold-catalyzed tandem cycloisomerization/oxidation of homopropargyl amides, leading to the efficient formation of optically active γ-lactams in combination with chiral *tert*-butylsulfinimine chemistry. To the best of our knowledge, this is the first example for γ-lactam synthesis from a readily accessible homopropargyl amide. As was demonstrated in the enantioselective synthesis of biologically active compound *S*-MPP **4** and natural product (−)-bgugaine **5**, we believe this could find great interest in the synthesis of highly functionalized molecules and especially in the synthesis of natural products. Further investigations on this novel tandem gold-catalyzed cycloisomerization/oxidation process are under way.

EXPERIMENTAL SECTION

General Information. Ethyl acetate (ACS grade), hexanes (ACS grade), and anhydrous 1,2-dichloroethane (ACS grade) were obtained commercially and used without further purification. Methylene

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chloride, tetrahydrofuran and diethyl ether were purified according to standard methods unless otherwise noted. Commercially available reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) using silicycle precoated silica gel plates. Flash column chromatography was performed over silica gel (300−400 mesh). High-resolution mass spectra were obtained using electrospray ionization using an ICR analyzer (ESI-MS).

^{1}H NMR spectra were recorded in chloroform-d_3. Chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data is reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, brs = broad singlet, coupling constant(s) in Hz, integration.

^{13}C NMR spectra were recorded in chloroform-d_3. Chemical shifts are reported in ppm with the internal chloroform signal at 77.0 ppm as a standard.

Compounds **1a**−**1n**, **1p** and **1r** were prepared from the corresponding sulfinyl aldimines (5.0 mmol scale) in three steps according to the known procedures.[11a]

(*R*)-4-Methyl-*N*-(undec-1-yn-4-yl)benzenesulfonamide (1a). Pale yellow oil (0.82 g, 51%, 3 steps): $[\alpha]_D^{20}$ = +44.9° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 8.0 Hz), 7.29 (d, 2H, *J* = 8.0 Hz), 4.80 (d, 1H, *J* = 9.0 Hz), 3.36−3.29 (m, 1H), 2.42 (s, 3H), 2.29−2.27 (m, 2H), 1.97 (t, 1H, *J* = 2.5 Hz), 1.57−1.43 (m, 2H), 1.26−1.08 (m, 10H), 0.86 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 138.1, 129.6, 127.0, 79.5, 71.4, 51.7, 34.0, 31.6, 29.0, 25.5, 25.0, 22.6, 21.4, 14.0; IR (neat) 3289(bs), 2926, 2856, 1326, 1159, 1093, 669; MS (ESI, *m*/*z*) 344 (M + Na^+); HRESIMS Calcd for $[C_{18}H_{27}NNaO_2S]^+$ (M + Na^+) 344.1660, found 344.1658.

(*S*)-*N*-(1-Cyclohexylbut-3-yn-1-yl)-4-methylbenzenesulfonamide (1b). White solid (mp 103−105 °C, 0.65 g, 43%, 3 steps): $[\alpha]_D^{20}$ = +46.0° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 8.5 Hz), 7.29 (d, 2H, *J* = 8.5 Hz), 4.88 (d, 1H, *J* = 9.5 Hz), 3.14−3.08 (m, 1H), 2.42 (s, 3H), 2.34−2.28 (m, 1H), 2.21−2.15 (m, 1H), 1.93 (t, 1H, *J* = 2.5 Hz), 1.81 (d, 1H, *J* = 12.5 Hz), 1.69 (d, 2H, *J* = 13.0 Hz), 1.63−1.51 (m, 3H), 1.23−1.02 (m, 3H), 0.96−0.88 (m, 1H), 0.85−0.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 138.1, 129.5, 127.0, 79.6, 71.2, 56.4, 40.1, 29.4, 28.5, 26.1, 25.9, 25.8, 22.1, 21.4; IR (neat) 3289(bs), 2929, 2851, 1448, 1329, 1159, 666; MS (ESI, *m*/*z*) 328 (M + Na^+); HRESIMS Calcd for $[C_{17}H_{23}NNaO_2S]^+$ (M + Na^+) 328.1347, found 328.1345.

(*R*)-4-Methyl-*N*-(1-phenylhex-5-yn-3-yl)benzenesulfonamide (1c). White solid (mp 126−127 °C, 0.80 g, 49%, 3 steps): $[\alpha]_D^{20}$ = +17.0° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, 2H, *J* = 8.5 Hz), 7.28 (d, 2H, *J* = 7.5 Hz), 7.23 (t, 2H, *J* = 7.0 Hz), 7.16 (t, 1H, *J* = 7.5 Hz), 7.04 (d, 2H, *J* = 7.0 Hz), 5.05 (d, 1H, *J* = 9.0 Hz), 3.42−3.35 (m, 1H), 2.63−2.57 (m, 1H), 2.52−2.46 (m, 1H), 2.41 (s, 3H), 2.28 (dd, 2H, *J* = 2.5 Hz, *J* = 5.0 Hz), 1.97 (t, 1H, *J* = 2.5 Hz), 1.90−1.77 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 140.9, 138.0, 129.7, 128.4, 128.3, 127.1, 126.0, 79.1, 71.8, 51.3, 35.7, 31.8, 24.9, 21.5; IR (neat) 3286(bs), 2926, 1326, 1155, 1090, 666; MS (ESI, *m*/*z*) 350 (M + Na^+); HRESIMS Calcd for $[C_{19}H_{21}NNaO_2S]^+$ (M + Na^+) 350.1191, found 350.1189.

(*R*)-*N*-(7-(Benzyloxy)hept-1-yn-4-yl)-4-methylbenzenesulfonamide (1d). White solid (mp 90−92 °C, 0.83 g, 45%, 3 steps): $[\alpha]_D^{20}$ = +28.3° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, 2H, *J* = 8.4 Hz,), 7.37−7.26 (m, 7H), 5.00 (d, 1H, *J* = 8.4 Hz), 4.46 (s, 2H), 3.40−3.30 (m, 3H), 2.41 (s, 3H), 2.34−2.20 (m, 2H), 1.97 (t, 1H, *J* = 2.4 Hz), 1.74−1.61 (m, 2H), 1.58−1.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 138.2, 137.9, 129.6, 128.4, 127.7, 127.6, 127.0, 79.5, 72.9, 71.5, 69.5, 51.7, 30.9, 25.6, 24.9, 21.5; IR (neat) 3283(bs), 2922, 2853, 2118, 1597, 1452, 1325, 1159, 1092, 664; MS (ESI, *m*/*z*) 394 (M + Na^+); HRESIMS Calcd for $[C_{21}H_{25}NNaO_3S]^+$ (M + Na^+) 394.1453, found 394.1453.

(*R*)-*N*-(7-(1,3-Dioxoisoindolin-2-yl)hept-1-yn-4-yl)-4-methylbenzenesulfonamide (1e). This compound was prepared from **1f** (2. 0 mmol scale) in two steps according to the literature procedures.[10] Pale yellow oil (0.29 g, 36%, 2 steps): $[\alpha]_D^{20}$ = +8.0° (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84−7.82 (m, 2H), 7.77−7.71 (m, 4H), 7.27 (d, 2H, *J* = 8.0 Hz), 5.02 (d, 1H, *J* = 12.0 Hz), 3.60 (t, 2H, *J* = 8.0 Hz), 3.50−3.41 (m, 1H), 2.35 (s, 3H), 2.28−2.19 (m, 2H), 1.95 (t, 1H, *J* = 3.0 Hz), 1.75−1.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 143.4, 137.9, 133.9, 131.9, 129.6, 126.9, 123.1, 79.1, 71.7, 51.2, 37.1, 30.9, 25.0, 24.7, 21.4; IR (neat) 3278(bs), 2923, 2852, 2118, 1770, 1708, 1438, 1398, 1330, 1159, 721; MS (ESI, *m*/*z*) 449 (M + K^+); HRESIMS Calcd for $[C_{22}H_{22}KN_2O_4S]^+$ (M + K^+) 449.0937, found 449.0939.

(*R*)-*N*-(7-Azidohept-1-yn-4-yl)-4-methylbenzenesulfonamide (1f). Pale yellow oil (0.58 g, 38%, 3 steps): $[\alpha]_D^{20}$ = +38.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, 2H, *J* = 8.0 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 5.10 (d, 1H, *J* = 12.0 Hz), 3.39−3.32 (m, 1H), 3.20 (t, 2H, *J* = 4.0 Hz), 2.43 (s, 3H), 2.28−2.23 (m, 2H), 2.00 (t, 1H, *J* = 3.0 Hz), 1.65−1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 137.9, 129.8, 126.9, 78.9, 71.9, 51.2, 50.8, 31.2, 30.9, 25.0, 21.5; IR (neat) 3287(bs), 2924, 2853, 1711, 1261, 1159, 750; MS (ESI, *m*/*z*) 329 (M + Na^+); HRESIMS Calcd for $[C_{14}H_{18}N_4NaO_2S]^+$ (M + Na^+) 329.1048, found 329.1046.

(*S*)-4-Methyl-*N*-(1-phenylbut-3-yn-1-yl)benzenesulfonamide (1g). White solid (mp 129−131 °C, 0.52 g, 35%, 3 steps): $[\alpha]_D^{20}$ = −68.2° (*c* = 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, 2H, *J* = 8.5 Hz), 7.22−7.13 (m, 7H), 5.26 (d, 1H, *J* = 7.0 Hz), 4.52−4.48 (m, 1H), 2.64 (dd, 2H, *J* = 3.0 Hz, *J* = 6.0 Hz), 2.38 (s, 3H), 1.97 (t, 1H, *J* = 3.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 139.2, 137.3, 129.4, 128.4, 127.8, 127.2, 126.6, 79.1, 72.1, 55.7, 27.2, 21.4; IR (neat) 3298(bs), 3262, 2920, 1461, 1317, 1165, 663; MS (ESI, *m*/*z*) 322 (M + Na^+); HRESIMS Calcd for $[C_{17}H_{17}NNaO_2S]^+$ (M + Na^+) 322.0878, found 322.0886.

(*S*)-*N*-(1-(4-Chlorophenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (1h). White solid (mp 135−137 °C, 0.68 g, 41%, 3 steps): $[\alpha]_D^{20}$ = −83.0° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.6 (d, 2H, *J* = 8.5 Hz), 7.18−7.14 (m, 4H), 7.08 (d, 2H, *J* = 8.5 Hz), 5.61 (d, 1H, *J* = 7.5 Hz), 4.48 (dd, 1H, *J* = 7.5 Hz, *J* = 13.5 Hz), 2.59 (dd, 2H, *J* = 2.5 Hz, *J* = 5.5 Hz), 2.38 (s, 3H), 1.97 (t, 1H, *J* = 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 137.7, 137.1, 133.6, 129.4, 128.4, 128.0, 127.1, 78.7, 72.3, 55.2, 27.1, 21.4; IR (neat) 3283(bs), 2917, 1596, 1491, 1452, 1324, 1158, 1088, 667; MS (ESI, *m*/*z*) 356 (M + Na^+); HRESIMS Calcd for $[C_{17}H_{16}ClNNaO_2S]^+$ (M + Na^+) 356.0488, found 356.0490.

(*S*)-*N*-(1-(4-Bromophenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (1i). White solid (mp 155−157 °C, 0.60 g, 32%, 3 steps): $[\alpha]_D^{20}$ = −84.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, 2H, *J* = 8.5 Hz), 7.31 (d, 2H, *J* = 8.5 Hz), 7.17 (d, 2H, *J* = 8.0 Hz), 7.02 (d, 2H, *J* = 8.5 Hz), 5.42 (d, 1H, *J* = 7.0 Hz), 4.46 (dd, 1H, *J* = 7.0 Hz, *J* = 13.0 Hz), 2.60−2.58 (m, 2H), 2.40 (s, 3H), 1.99 (t, 1H, *J* = 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 138.2, 137.2, 131.5, 129.5, 128.4, 127.1, 121.8, 78.6, 72.5, 55.2, 27.1, 21.5; IR (neat) 3293(bs), 2923, 1596, 1488, 1432, 1331, 1159, 1093, 718, 663; MS (ESI, *m*/*z*) 400 (M + Na^+), 402 (M + Na^+); HRESIMS Calcd for $[C_{17}H_{16}BrNNaO_2S]^+$ (M + Na^+) 399.9983, found 399.9981.

(*S*)-*N*-(1-(2-Bromophenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (1j). White solid (mp 144−145 °C, 0.55 g, 29%, 3 steps): $[\alpha]_D^{20}$ = −51.3° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, 2H, *J* = 8.5 Hz), 7.42 (dd, 1H, *J* = 1.0 Hz, *J* = 8.0 Hz), 7.29 (dd, 1H, *J* = 1.5 Hz, *J* = 7.5 Hz), 7.17−7.13 (m, 3H), 7.06−7.03 (m, 1H), 5.56 (d, 1H, *J* = 7.5 Hz), 4.95 (dd, 1H, *J* = 6.0 Hz, *J* = 13.5 Hz), 2.71−2.66 (m, 1H), 2.59−2.54 (m, 1H), 2.35 (s, 3H), 1.98 (t, 1H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 138.2, 136.8, 132.8, 129.4, 129.1, 128.6, 127.3, 127.2, 122.2, 78.4, 72.5, 54.6, 26.1, 21.4; IR (neat) 3283(bs), 2917, 1591, 1468, 1438, 1344, 1080, 1018, 947, 746, 770; MS (ESI, *m*/*z*) 400 (M + Na^+), 402 (M + Na^+); HRESIMS Calcd for $[C_{17}H_{16}BrNNaO_2S]^+$ (M + Na^+) 399.9983, found 399.9983.

(*S*)-4-Methyl-*N*-(1-(*p*-tolyl)but-3-yn-1-yl)benzenesulfonamide (1k). White solid (mp 131−132 °C, 0.66 g, 42%, 3 steps): $[\alpha]_D^{20}$ = −77.2° (*c* = 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, 2H, *J* = 8.0 Hz), 7.17 (d, 2H, *J* = 8.0 Hz), 7.01 (dd, 4H, *J* = 5.5 Hz, *J* = 13.5 Hz), 5.35 (d, 1H, *J* = 7.0 Hz), 4.44 (dd, 1H, *J* = 7.0 Hz, *J* = 13.0 Hz), 2.63−2.61 (m, 2H), 2.38 (s, 3H), 2.27 (s, 3H),1.94 (t, 1H, *J* = 3.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 137.5, 137.3, 136.2, 129.4, 129.0, 127.1, 126.5, 79.3, 71.9, 55.6, 27.2, 21.4, 21.0; IR

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(neat) 3286(bs), 3244, 2915, 1514, 1453, 1419, 1318, 1154, 1092, 807, 667; MS (ESI, *m*/*z*) 336 (M + Na^+); HRESIMS Calcd for $[C_{18}H_{19}NNaO_2S]^+$ (M + Na^+) 336.1034, found 336.1036.

(*S*)-*N*-(1-(4-Methoxyphenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (1l). White solid (mp 106−108 °C, 0.59 g, 36%, 3 steps): $[\alpha]_D^{20}$ = −83.6° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, 2H, *J* = 8.5 Hz), 7.18 (d, 2H, *J* = 8.0 Hz), 7.06 (d, 4H, *J* = 8.5 Hz), 6.72 (d, 2H, *J* = 8.5 Hz), 5.26 (d, 1H, *J* = 7.0 Hz), 4.44 (dd, 1H, *J* = 6.5 Hz, *J* = 13.0 Hz), 3.75 (s, 3H), 2.61 (d, 2H, *J* = 9.0 Hz), 2.38 (s, 3H), 1.96 (t, 1H, *J* = 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 143.2, 137.4, 131.3, 129.4, 127.8, 127.2, 113.8, 79.4, 71.9, 55.3, 55.2, 27.2, 21.4; IR (neat) 3285(bs), 2933, 2837, 1611, 1514, 1440, 1159, 830, 666; MS (ESI, *m*/*z*) 352 (M + Na^+); HRESIMS Calcd for $[C_{18}H_{19}NNaO_3S]^+$ (M + Na^+) 352.0983, found 352.0988.

(*S*)-4-Methyl-*N*-(1-(naphthalen-1-yl)but-3-yn-1-yl)benzenesulfonamide (1m). White solid (mp 103−105 °C, 0.52g, 30%, 3 steps): $[\alpha]_D^{20}$ = −29.0° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85−7.79 (m, 2H), 7.69 (d, 1H, *J* = 8.0 Hz), 7.55 (d, 2H, *J* = 8.0 Hz), 7.45−7.43 (m, 3H), 7.30 (t, 1H, *J* = 8.0 Hz), 7.03 (d, 2H, *J* = 8.0 Hz), 5.53 (d, 1H, *J* = 7.5 Hz), 5.35 (dd, 1H, *J* = 6.5 Hz, *J* = 13.0 Hz), 2.88−2.75 (m, 2H), 2.30 (s, 3H), 1.96 (t, 1H, *J* = 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 137.1, 134.5, 133.7, 130.1, 129.2, 128.9, 128.4, 127.1, 126.4, 125.6, 125.0, 124.3, 122.1, 79.2, 72.3, 51.8, 26.7, 21.3; IR (neat) 3290(bs), 2923, 2121, 1598, 1425, 1332, 1159, 1090, 776, 667; MS (ESI, *m*/*z*) 372 (M + Na^+); HRESIMS Calcd for $[C_{21}H_{19}NNaO_2S]^+$ (M + Na^+) 372.1034, found 372.1038.

(*R*)-*N*-(4-Ethyloct-1-yn-4-yl)-4-methylbenzenesulfonamide (1n). Pale yellow oil (0.41 g, 27%, 3 steps): $[\alpha]_D^{20}$ = −1.2° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, 2H, *J* = 8.5 Hz), 7.27 (d, 2H, *J* = 7.5 Hz), 4.64 (s, 1H), 2.42 (s, 3H), 1.97 (t, 1H, *J* = 3.0 Hz), 1.73−1.65 (m, 1H), 1.64−1.57 (m, 2H), 1.54−1.48 (m, 1H), 1.19−1.07 (m, 4H), 0.80 (t, 3H, *J* = 7.0 Hz), 0.77 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 140.2, 129.4, 127.1, 80.0, 71.4, 61.8, 35.5, 29.0, 27.8, 25.2, 22.8, 21.4, 13.8, 7.5; IR (neat) 3282(bs), 2956, 2933, 2871, 1456, 1320, 1158, 1094, 1001, 814, 665; MS (ESI, *m*/*z*) 330 (M + Na^+); HRESIMS Calcd for $[C_{17}H_{25}NNaO_2S]^+$ (M + Na^+) 330.1504, found 330.1512.

***N*-(But-3-yn-1-yl)-4-methylbenzenesulfonamide (1o).** This compound was prepared from but-3-yn-1-ol (2. 0 mmol scale) in two steps according to the literature procedures, and the spectroscopic data match those reported.[19] Pale yellow oil (0.29 g, 65%, 2 steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 8.5 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 5.34 (t, 1H, *J* = 6.5 Hz), 3.09 (dd, 2H, *J* = 6.5 Hz, *J* = 13.5 Hz), 2.42 (s, 3H), 2.35−2.32 (m, 2H), 2.00 (t, 1H, *J* = 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 136.7, 129.6. 126.9. 80.3. 70.6. 41.5. 21.3. 19.6.

4-Methyl-*N*-(1-(prop-2-yn-1-yl)cyclopentyl)benzenesulfonamide (1p). Pale yellow oil (0.69 g, 50%, 3 steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 4.79 (s, 1H), 2.48 (d, 2H, *J* = 8.0 Hz), 2.42 (s, 3H), 2.00 (t, 1H, *J* = 2.5 Hz), 1.93−1.88 (m, 2H), 1.69−1.62 (m, 2H), 1.57−1.53 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 139.8, 129.5, 127.1, 80.8, 70.9, 66.2, 37.2, 29.7, 23.0, 21.5; IR (neat) 3298, 2950, 2123, 1596, 1496, 1455, 1304, 1151, 1095, 1035, 664; MS (ESI, *m*/*z*) 300 (M + Na^+); HRESIMS Calcd for $[C_{15}H_{19}NNaO_2S]^+$ (M + Na^+) 300.1034, found 300.1034.

***N*-(2-Ethynylphenyl)-4-methylbenzenesulfonamide (1q).** This compound was prepared from 2-ethynylaniline (2. 0 mmol scale) according to the literature procedures, and the spectroscopic data match those reported.[20] Pale yellow oil (0.38 g, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, 2H, *J* = 8.5 Hz), 7.59 (d, 1H, *J* = 8.0 Hz), 7.34−7.19 (m, 4H), 7.01 (t, 1H, *J* = 8.0 Hz), 3.37 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 138.4, 135.9, 132.4, 130.1, 129.6, 127.3, 124.1, 119.3, 112.7, 84.4, 78.5, 21.4.

(*R*)-4-Methyl-*N*-(octadec-1-yn-4-yl)benzenesulfonamide (1r). Pale yellow oil (1.51 g, 72%, 3 steps): $[\alpha]_D^{20}$ = +34.9° (*c* = 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 8.0 Hz), 7.30 (d, 2H, *J* = 8.0 Hz), 4.68 (d, 1H, *J* = 9.0 Hz), 3.36−2.30 (m, 1H), 2.43 (s, 3H), 2.28 (d, 2H, *J* = 7.5 Hz), 1.97 (t, 1H, *J* = 2.5 Hz), 1.55−1.44 (m, 2H), 1.32−1.10 (m, 24H), 0.88 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 138.1, 129.6, 127.1, 79.5, 71.4, 51.7, 34.0, 31.9, 29.7, 29.6(4), 29.6(3), 29.6(1), 29.5, 29.3(9), 29.3(8), 29.1, 25.5, 25.0, 22.7, 21.5, 14.1; IR (neat) 3311(bs), 2924, 2853, 2120, 1465, 1429, 1328, 1161, 1094, 814, 666, 551; MS (ESI, *m*/*z*) 442 (M + Na^+); HRESIMS Calcd for $[C_{25}H_{41}NNaO_2S]^+$ (M + Na^+) 442.2756, found 442.2754.

General Procedure of the Gold-Catalyzed Oxidative Cyclization of Chiral Homopropargyl Amides. *m*-CPBA (85%, 91.5 mg, 0.45 mmol), MsOH (3.0 mL, 0.10 M in DCE), and (4-$CF_3Ph)_3PAuNTf_2$ (14.2 mg, 0.015 mmol) were added in this order to a solution of the homopropargyl amide **1** (0.30 mmol) in DCE (3.0 mL) at room temperature. The reaction mixture was stirred at rt, and the progress of the reaction was monitored by TLC. The reaction typically took 5 h. Upon completion, the reaction was diluted with DCM (30 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 15 mL). The resulting solution was extracted again with DCM (30 mL), and the combined organic layers were dried with $MgSO_4$. The mixture was then concentrated, and the residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired products **2**.

(*R*)-5-Heptyl-1-tosylpyrrolidin-2-one (2a). Pale yellow oil (75.9 mg, 75%): $[\alpha]_D^{20}$ = −65.2° (*c* = 0.1, $CHCl_3$); 99% ee (determined by HPLC: Chiralcel AD-H Column, 10/90 *i*-PrOH/hexane, 1.0 mL/min, 200 nm; t_R = 13.29 min (major), 12.46 min (minor)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, 2H, *J* = 8.5 Hz), 7.32 (d, 2H, *J* = 8.5 Hz), 4.41−4.35 (m, 1H), 2.55−2.47 (m, 1H), 2.43 (s, 3H), 2.37−2.30 (m, 1H), 2.21−2.12 (m, 1H), 1.98−1.91 (m, 1H), 1.87−1.82 (m, 1H), 1.68−1.61 (m, 1H), 1.33−1.16 (m, 10H), 0.89 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 144.8, 136.2, 129.4, 128.3, 60.4, 34.6, 31.7, 30.8, 29.3, 29.1, 25.1, 23.6, 22.6, 21.6, 14.0; IR (neat) 2926, 2854, 1737(s), 1361, 1167, 1091, 669; MS (ESI, *m*/*z*) 360 (M + Na^+); HRESIMS Calcd for $[C_{18}H_{27}NNaO_3S]^+$ (M + Na^+) 360.1609, found 360.1611.

(*S*)-5-Heptyl-1-tosylpyrrolidin-2-one (2a′). Pale yellow oil (73.9 mg, 73%): $[\alpha]_D^{20}$ = +63.2° (*c* = 0.1, $CHCl_3$); 99% ee (determined by HPLC: Chiralcel AD-H Column, 10/90 *i*-PrOH/hexane, 0.8 mL/min, 200 nm; t_R = 14.73 min (major), 15.87 min (minor)).

(*S*)-5-Cyclohexyl-1-tosylpyrrolidin-2-one (2b). Pale yellow oil (54.9 mg, 57%): $[\alpha]_D^{20}$ = +5.3° (*c* = 0.5, $CHCl_3$); 99% ee (determined by HPLC: Chiralcel AD-H Column, 10/90 *i*-PrOH/hexane, 1.0 mL/min, 200 nm; t_R = 24.55 min (major), 22.12 min (minor)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, 2H, *J* = 8.5 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 4.35−4.32 (m, 1H), 2.43 (s, 3H), 2.42−2.31 (m, 2H), 2.15−2.02 (m, 2H), 1.96−1.90 (m, 1H), 1.76 (d, 1H, *J* = 13.0 Hz), 1.71−1.63 (m, 3H), 1.37−1.25 (m, 2H), 1.15−1.01 (m, 3H), 0.88−0.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 144.8, 136.0, 129.3, 128.3, 64.7, 41.6, 31.7, 29.5, 26.3, 26.1, 25.8, 25.7, 21.6, 19.7; IR (neat) 2927, 2853, 1732(s), 1358, 1170, 1093, 953; MS (ESI, *m*/*z*) 344 (M + Na^+); HRESIMS Calcd for $[C_{17}H_{23}NNaO_3S]^+$ (M + Na^+) 344.1296, found 344.1298.

(*R*)-5-Phenethyl-1-tosylpyrrolidin-2-one (2c). Pale yellow oil (63.8 mg, 62%): $[\alpha]_D^{20}$ = −27.0° (*c* = 1.0, $CHCl_3$); 99% ee (determined by HPLC: Chiralcel AD-H Column, 10/90 *i*-PrOH/hexane, 1.0 mL/min, 200 nm; t_R = 27.34 min (major), 24.43 min (minor)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, 2H, *J* = 8.0 Hz), 7.30 (t, 4H, *J* = 7.0 Hz), 7.21 (t, 1H, *J* = 7.5 Hz), 7.17 (d, 2H, *J* = 7.0 Hz), 4.45−4.40 (m, 1H), 2.71−2.61 (m, 2H), 2.58−2.51 (m, 1H), 2.42 (s, 3H), 2.40−2.32 (m, 2H), 2.24−2.16 (m, 1H), 2.00−1.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 144.9, 140.4, 136.0, 129.5, 128.5, 128.3, 128.2, 126.2, 59.9, 36.0, 31.4, 30.7, 23.6, 21.6; IR (neat) 2923, 1734(s), 1357, 1165, 668; MS (ESI, *m*/*z*)366 (M + Na^+); HRESIMS Calcd for $[C_{19}H_{21}NNaO_3S]^+$ (M + Na^+) 366.1140, found 366.1140.

(*R*)-5-(3-(Benzyloxy)propyl)-1-tosylpyrrolidin-2-one (2d). Pale yellow oil (69.8 mg, 60%): $[\alpha]_D^{20}$ = +65.0° (*c* = 1.0, $CHCl_3$); 98% ee (determined by HPLC: Chiralcel AD-H Column, 10/90 *i*-PrOH/hexane, 0.8 mL/min, 200 nm; t_R = 36.18 min (major), 33.59 min (minor)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 2H, *J* = 8.4 Hz), 7.38−7.26 (m, 7H), 4.51 (s, 2H), 4.90−4.39 (m, 1H), 3.54−3.46

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(m, 2H), 2.58−2.47 (m, 1H), 2.42 (s, 3H), 2.40−2.29 (m, 1H), 2.22−2.14 (m, 1H), 2.12−2.02 (m, 1H), 1.88− 1.74 (m, 2H), 1.72− 1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 144.8, 138.4, 136.1, 129.5, 128.4, 128.3, 127.7, 127.6, 73.1, 69.7, 60.2, 31.6, 30.7, 25.6, 23.6, 21.6; IR (neat) 2924, 2854, 1730(s), 1596, 1494, 1453, 1355, 1165, 1088, 771, 667; MS (ESI, m/z) 410 (M + Na^+); HRESIMS Calcd for $[C_{21}H_{25}NNaO_4S]^+$ (M + Na^+) 410.1402, found 410.1408.

(*R*)-2-(3-(5-Oxo-1-tosylpyrrolidin-2-yl)propyl)isoindoline-1,3-dione (2e). Pale yellow oil (79.2 mg, 62%): $[\alpha]_D^{20}$ = −32.0° (c = 0.5, $CHCl_3$); >99% ee (determined by HPLC: Chiralcel OD-H Column, 10/90 *i*-PrOH/hexane, 0.6 mL/min, 200 nm; t_R =181.16 min (major), 168.94 min (minor)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 2H), 7.87−7.83 (m, 2H), 7.75−7.70 (m, 2H), 7.32 (d, J = 8.0 Hz, 2H), 4.42 (t, J = 8.0 Hz, 1H), 3.72 (t, J = 7.2 Hz, 2H), 2.55−2.48 (m, 1H), 2.44 (s, 3H), 2.40−2.30 (m, 1H), 2.24−2.16 (m, 1H), 2.09−1.99 (m, 1H), 1.86−1.80 (m, 1H), 1.73−1.67 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 168.3, 144.9, 135.9, 134.0, 132.0, 129.5, 128.4, 123.3, 59.7, 37.5, 31.9, 30.6, 24.4, 23.6, 21.7; IR (neat) 2924, 2853, 1710(s), 1357, 1219, 1088, 772; MS (ESI, m/z) 449 (M + Na^+); HRESIMS Calcd for $[C_{22}H_{22}N_2NaO_5S]^+$ (M + Na^+) 449.1147, found 449.1149.

(*R*)-5-(3-Azidopropyl)-1-tosylpyrrolidin-2-one (2f). Pale yellow oil (60.8 mg, 63%): $[\alpha]_D^{20}$ = −51.5° (c = 0.5, $CHCl_3$); 99% ee (determined by HPLC: Chiralcel AD-H Column, 10/90 *i*-PrOH/hexane, 1.0 mL/min, 200 nm; t_R = 32.81 min (major), 35.61 min (minor)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 4.41 (t, J = 8.4 Hz, 1H), 3.40−3.29 (m, 2H), 2.59−2.48 (m, 1H), 2.44 (s, 3H), 2.40−2.32 (m, 1H), 2.67−2.16 (m, 1H), 2.08−2.00 (m, 1H), 1.87−1.72 (m, 2H), 1.68−1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 145.1, 135.9, 129.5, 128.3, 59.7, 51.0, 32.1, 30.6, 24.8, 23.8, 21.6; IR (neat) 2958, 2924, 2093, 1729(s), 1596, 1461, 1356, 1260, 1086, 812, 665; MS (ESI, m/z) 345 (M + Na^+); HRESIMS Calcd for $[C_{14}H_{18}N_4NaO_3S]^+$ (M + Na^+) 345.0997, found 345.0999.

(*S*)-5-Phenyl-1-tosylpyrrolidin-2-one (2g). White solid (mp 129−130 °C, 69.0 mg, 73%): $[\alpha]_D^{20}$ = −53.4° (c = 1.0, $CHCl_3$); 99% ee (determined by HPLC: Chiralpak IB Column, 10/90 *i*-PrOH/hexane, 0.8 mL/min, 200 nm; t_R = 22.16 min (major), 24.67 min (minor)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, 2H, J = 10.5 Hz), 7.31−7.25 (m, 3H), 7.18−7.11 (m, 4H), 5.45 (dd, 1H, J = 2.0 Hz, J = 8.4 Hz), 2.75−2.51 (m, 3H), 2.39 (s, 3H), 2.01−1.94 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 144.8, 140.6, 135.4, 129.1, 128.7, 128.5, 128.0, 126.0, 62.9, 30.6, 28.3, 21.6; IR (neat) 2923, 1738(s), 1451, 1360, 1168, 1088, 668; MS (ESI, m/z) 338 (M + Na^+); HRESIMS Calcd for $[C_{17}H_{17}NNaO_3S]^+$ (M + Na^+) 338.0827, found 338.0827.

(*S*)-5-(4-Chlorophenyl)-1-tosylpyrrolidin-2-one (2h). White solid (mp 143−145 °C, 72.4 mg, 69%): $[\alpha]_D^{20}$ = −31.8° (c = 0.5, $CHCl_3$); 98% ee (determined by HPLC: Chiralpak IB Column, 10/90 *i*-PrOH/hexane, 0.8 mL/min, 200 nm; t_R = 24.74 min (major), 27.64 min (minor)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, 2H, J = 10.0 Hz), 7.30 (d, 2H, J = 5.0 Hz), 7.20 (d, 2H, J = 10.0 Hz), 7.10 (d, 2H, J = 10.0 Hz), 5.4 (dd, 1H, J = 2.0 Hz, J = 7.5 Hz), 2.69−2.47 (m, 3H), 2.41 (s, 3H), 1.95−1.90 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 145.1, 139.4, 135.5, 134.0, 129.2, 129.0, 128.5, 127.4, 62.3, 30.5, 28.3, 21.6; IR (neat) 2923, 1738(s), 1492, 1359, 1168, 1089, 665; MS (ESI, m/z) 372 (M + Na^+); HRESIMS Calcd for $[C_{17}H_{16}ClNNaO_3S]^+$ (M + Na^+) 372.0437, found 372.0435.

(*S*)-5-(4-Bromophenyl)-1-tosylpyrrolidin-2-one (2i). White solid (mp 132−134 °C, 75.7 mg, 64%): $[\alpha]_D^{20}$ = −16.0° (c = 0.5, $CHCl_3$); 98% ee (determined by HPLC: Chiralpak IB Column, 10/90 *i*-PrOH/hexane, 0.8 mL/min, 200 nm; t_R = 27.73 min (major), 31.21 min (minor)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, 2H, J = 8.5 Hz), 7.42 (d, 2H, J = 8.5 Hz), 7.21 (d, 2H, J = 8.5 Hz), 7.02 (d, 2H, J = 8.5 Hz), 5.39 (dd, 1H, J = 6.0 Hz, J = 8.0 Hz), 2.68−2.47 (m, 3H), 2.42 (s, 3H), 1.95−1.90 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 145.1, 139.9, 135.4, 131.9, 129.3, 128.5, 127.8, 122.0, 62.4, 30.5, 28.2, 21.6; IR (neat) 2923, 1736(s), 1612, 1514, 1359, 1169, 1088, 669, 607; MS (ESI, m/z) 416 (M + Na^+), 418 (M + Na^+); HRESIMS Calcd for $[C_{17}H_{16}BrNNaO_3S]^+$ (M + Na^+) 415.9932, found 415.9940.

(*S*)-5-(2-Bromophenyl)-1-tosylpyrrolidin-2-one (2j). White solid (mp 163−164 °C, 89.8 mg, 76%): $[\alpha]_D^{20}$ = −114.2° (c = 0.5, $CHCl_3$); 98% ee (determined by HPLC: Chiralcel AD-H Column, 10/90 *i*-PrOH/hexane, 1.0 mL/min, 200 nm; t_R = 23.01 min (major), 32.61 min (minor)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, 2H, J = 8.5 Hz), 7.59 (d, 1H, J = 9.0 Hz), 7.28 (d, 2H, J = 8.0 Hz), 7.24−7.16 (m, 2H), 7.10 (d, 1H, J = 9.5 Hz), 5.77 (d, 1H, J = 8.0 Hz), 2.61−2.52 (m, 2H), 2.44 (s, 3H), 2.42−2.37 (m, 1H), 2.01−1.93 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 145.2, 139.4, 135.4, 133.5, 129.4, 128.7, 127.6, 121.7, 62.4, 30.0, 27.3, 21.6; IR (neat) 2924, 1742(s), 1595, 1468, 1442, 1360, 1320, 1280, 1169, 1112, 952, 814, 665; MS (ESI, m/z) 416 (M + Na^+), 418 (M + Na^+); HRESIMS Calcd for $[C_{17}H_{16}BrNNaO_3S]^+$ (M + Na^+) 415.9932, found 415.9938.

(*S*)-5-(*p*-Tolyl)-1-tosylpyrrolidin-2-one (2k). Pale yellow oil (71.2 mg, 72%): $[\alpha]_D^{20}$ = −42.1° (c = 0.5, $CHCl_3$); >99% ee (determined by HPLC: Chiralcel AD-H Column, 10/90*i*-PrOH/hexane, 0.8 mL/min, 254 nm; t_R = 37.31 min (major), 29.11 min (minor)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, 2H, J = 8.5 Hz), 7.17 (d, 2H, J = 8.0 Hz), 7.09 (d, 2H, J = 8.0 Hz), 7.01 (d, 2H, J = 8.0 Hz), 5.41 (dd, 1H, J = 6.5 Hz, J = 8.5 Hz), 2.71−2.64 (m, 1H), 2.60−2.45 (m, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 1.98−1.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 144.8, 137.8, 137.7, 135.6, 129.4, 129.1, 128.5, 126.0, 62.9, 30.6, 28.5, 21.6, 21.1; IR (neat) 2923, 2854, 1738(s), 1596, 1515, 1360, 1324, 1169, 953, 814, 669; MS (ESI, m/z) 352 (M + Na^+); HRESIMS Calcd for $[C_{18}H_{19}NNaO_3S]^+$ (M + Na^+) 352.0983, found 352.0988.

(*S*)-5-(4-Methoxyphenyl)-1-tosylpyrrolidin-2-one (2l). Pale yellow oil (70.5 mg, 68%): $[\alpha]_D^{20}$ = −20.3° (c = 0.3, $CHCl_3$); 86% ee (determined by HPLC: Chiralcel AD-H Column, 10/90 *i*-PrOH/hexane, 1.0 mL/min, 200 nm; t_R = 39.82 min (major), 31.29 min (minor)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, 2H, J = 8.5 Hz), 7.17 (d, 2H, J = 8.0 Hz), 7.05 (d, 2H, J = 8.5 Hz), 6.80 (d, 2H, J = 8.5 Hz), 5.40 (dd, 1H, J = 6.5 Hz, J = 8.5 Hz), 3.81 (s, 3H), 2.72−2.65 (m, 1H), 2.60−2.47 (m, 2H), 2.39 (s, 3H), 1.98−1.93 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 159.4, 144.7, 135.6, 132.8, 129.1, 128.5, 127.4, 114.1, 62.6, 55.3, 30.7, 28.3, 21.6; IR (neat) 2923, 2852, 1739(s), 1490, 1410, 1359, 1168, 1104, 1009, 953, 667; MS (ESI, m/z) 368 (M + Na^+); HRESIMS Calcd for $[C_{18}H_{19}NNaO_4S]^+$ (M + Na^+) 368.0932, found 368.0930.

(*S*)-5-(Naphthalen-1-yl)-1-tosylpyrrolidin-2-one (2m). White solid (mp 189−191 °C, 74.4 mg, 68%): $[\alpha]_D^{20}$ = −166.0° (c = 0.5, $CHCl_3$); 99% ee (determined by HPLC: Chiralcel AD-H Column, 10/90 *i*-PrOH/hexane, 1.0 mL/min, 200 nm; t_R = 30.69 min (major), 40.12 min (minor)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94−7.78 (m, 5H), 7.59−7.52 (m, 2H), 7.29−7.25 (m, 3H), 7.13 (d, J = 7.0 Hz, 1H), 6.29 (d, J = 8.5 Hz, 1H), 2.73−2.55 (m, 2H), 2.46−2.41 (m, 4H), 2.07−2.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 145.1, 135.5, 135.4, 134.1, 129.6, 129.3, 129.1, 128.8, 128.5, 126.7, 126.0, 124.9, 122.4, 60.1, 30.5, 28.0, 21.6; IR (neat) 2924, 2854, 1736(s), 1597, 1360, 1260, 1168, 1089, 773, 667; MS (ESI, m/z) 388 (M + Na^+); HRESIMS Calcd for $[C_{21}H_{19}NNaO_3S]^+$ (M + Na^+) 388.0983, found 388.0985.

(*R*)-5-Butyl-5-ethyl-1-tosylpyrrolidin-2-one (2n). Pale yellow oil (54.4 mg, 56%): $[\alpha]_D^{20}$ = −2.7° (c = 0.3, $CHCl_3$); 23% ee (determined by HPLC: Chiralcel AD-H Column, 5/95 *i*-PrOH/hexane, 1.0 mL/min, 200 nm; t_R = 21.63 min (major), 17.55 min (minor)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, 2H, J = 8.5 Hz), 7.32 (d, 2H, J = 8.0 Hz), 2.45 (s, 3H), 2.40−2.36 (m, 2H), 2.29−2.22 (m, 1H), 2.21−2.15 (m, 1H), 2.00−1.94 (m, 2H), 1.90−1.78 (m, 2H), 1.42−1.24 (m, 4H), 0.97 (t, 3H, J = 7.5 Hz), 0.92 (t, 3H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 144.7, 136.5, 129.2, 129.0, 74.2, 40.0, 33.0, 30.3, 28.2, 26.3, 23.0, 21.6, 14.0, 8.5; IR (neat) 2928, 1732(s), 1597, 1466, 1358, 1172, 1158, 1087, 814, 672, 562; MS (ESI, m/z) 346 (M + Na^+); HRESIMS Calcd for $[C_{17}H_{25}NNaO_3S]^+$ (M + Na^+) 346.1453, found 346.1452.

1-Tosylpyrrolidin-2-one (2o). Pale yellow oil (33.7 mg, 47%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, 2H, J = 8.5 Hz), 7.33 (d, 2H, J = 8.0 Hz), 3.90 (t, 2H, J = 7.0 Hz), 2.44 (s, 3H), 2.43 (t, 2H, J = 8.0 Hz), 2.12−2.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 145.1, 135.2, 129.6, 128.1, 47.2, 32.2, 21.6, 18.2; IR (neat) 2918, 1728(s),

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1594, 1351, 1298, 1197, 1170, 1117, 961; MS (ESI, *m*/*z*) 262 (M + Na^+); HRESIMS Calcd for $[C_{11}H_{13}NNaO_3S]^+$ (M + Na^+) 262.0514, found 262.0514.

1-Tosyl-1-azaspiro[4.4]nonan-2-one (2p). Pale yellow oil (44.2 mg, 50%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, 2H, *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 2.66−2.60 (m, 2H), 2.43 (s, 3H), 2.38 (t, 2H, *J* = 8.0 Hz), 1.96 (t, 4H, *J* = 7.5 Hz), 1.78−1.72 (m, 2H), 1.67−1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 144.6, 136.8, 129.3, 128.5, 75.4, 37.6, 36.2, 30.3, 24.0, 21.6; IR (neat) 3359, 2923, 1732, 1597, 1452, 1345, 1289, 1164, 1087, 665; MS (ESI, *m*/*z*) 316 (M + Na^+); HRESIMS Calcd for $[C_{15}H_{19}NNaO_3S]^+$ (M + Na^+) 316.0983, found 316.0986.

1-Tosyl-1*H*-indole (2q′). This compound is known, and the spectroscopic data match those reported.[21] Pale yellow oil (70.6 mg, 87%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, 1H, *J* = 8.5 Hz), 7.75 (d, 2H, *J* = 8.5 Hz), 7.56 (d, 1H, *J* = 4.0 Hz), 7.53 (d, 1H, *J* = 8.5 Hz), 7.32−7.28 (m, 1H), 7.23−7.20 (m, 3H), 6.65 (dd, 1H, *J* = 0.5 Hz, *J* = 3.5 Hz), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 135.5, 134.9, 130.8, 129.8, 126.8, 126.3, 124.5, 123.2, 121.3, 113.6, 109.0, 21.5.

(*R*)-5-Tetradecyl-1-tosylpyrrolidin-2-one (2r). Pale yellow oil (73.1 mg, 56%): $[\alpha]_D^{20}$ = −44.2° (*c* = 0.6, $CHCl_3$); 99% ee (determined by HPLC: Chiralcel AS-H Column, 10/90 *i*-PrOH/hexane, 0.6 mL/min, 200 nm; t_R = 12.79 min (major), 9.50 min (minor)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, 2H, *J* = 8.5 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 4.41−4.36 (m, 1H), 2.55−2.46 (m, 1H), 2.43 (s, 3H), 2.36−2.30 (m, 1H), 2.21−2.12 (m, 1H), 1.98−1.92 (m, 1H), 1.87−1.82 (m, 1H), 1.68−1.63 (m, 1H), 1.33−1.15 (m, 24H), 0.88 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 144.8, 136.2, 129.4, 128.3, 60.4, 34.6, 31.9, 30.8, 29.7, 29.6(6), 29.6(5), 29.6(3), 29.6(1), 29.5, 29.4, 29.3, 25.1, 23.6, 22.7, 21.6, 14.1; IR (neat) 2914, 2850, 1725(s), 1471, 1359, 1198, 1171, 1087, 954, 671; MS (ESI, *m*/*z*) 458 (M + Na^+); HRESIMS Calcd for $[C_{25}H_{41}NNaO_3S]^+$ (M + Na^+) 458.2705, found 458.2710.

(*S*)-5-Phenylpyrrolidin-2-one (3). Naphthalene (1.80 g, 14.0 mmol) was dissolved in previously degassed THF (30 mL). Lithium (0.10 g, 14.0 mmol) was added, and the mixture was sonicated for 30 min and then stirred at room temperature for 2 h in order to obtain a 0.5 M dark green Li-naphthalenide solution. *N*-Tosyl lactam **2g** (0.45 g, 1.43 mmol) was dissolved in THF (10 mL), and the resulting solution was cooled to −78 °C. The Li-naphthalenide was then added dropwise until the reaction mixture stayed permanently dark green (ca. 10 mL). The mixture was stirred at −78 °C for 30 min and at room temperature for 30 min before quenching with 1.0 M $NaHCO_3$ (ca. 10 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography afforded **3** (0.16 g, 70% yield as a yellow oil). This compound is known, and the spectroscopic data match those reported:[15] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.34 (m, 2H), 7.31−7.28 (m, 3H), 6.56 (s, 1H), 4.75 (t, 1H, *J* = 7.0 Hz), 2.60−2.53 (m, 1H), 2.50−2.36 (m, 2H), 2.00−1.93 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 142.5, 128.9, 127.8, 125.6, 58.0, 31.3, 30.2; $[\alpha]_D^{20}$ = −48.5° (*c* = 1.0, $CHCl_3$) {lit.[15] $[\alpha]_D^{20}$ = −51.0° (*c* = 0.97, CH_2Cl_2)}.

(*S*)-1-Methyl-2-phenylpyrrolidine (4). **3** (3 mmol, 0.48 g) was added to a suspension of sodium hydride (3.3 mmol, 0.079 g) in THF (50 mL). Iodomethane (15 mmol, 2.13 g) was added, and the reaction was left at room temperature for 48 h. The solvent was removed, and the residue was resuspended in ethyl acetate (20 mL), washed with water (2 × 10 mL), and dried ($MgSO_4$). The organic layer was concentrated, and the residue was purified by column chromatography to afford (*S*)-1-methyl-5-phenylpyrrolidin-2-one (0.30 g, 57% yield as a yellow oil). $LiAlH_4$ (118 mg, 3.1 mmol) was added to a solution of above (*S*)-1-methyl-5-phenylpyrrolidin-2-one (109 mg, 0.62 mmol) in THF (12 mL), and the mixture was stirred at 70 °C for 24 h. Then, the mixture was carefully poured into 2 N aqueous NaOH and extracted with EtOAc. The organic phase was washed with 2 N aqueous HCl, and the aqueous phase was then basified to pH = 14 with 4 N aqueous NaOH, extracted with EtOAc, and dried ($MgSO_4$). The organic layer was concentrated, and the residue was purified by column chromatography (hexane/EtOAc/20% aq. ammonia: 90/10/0.5) to afford **4** (91 mg, 91% yield as a yellow oil). This compound is known, and the spectroscopic data match those reported:[22] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.29 (m, 4H), 7.26−7.22 (m, 1H), 3.26−3.22 (m, 1H), 3.03 (t, 1H, *J* = 8.5 Hz), 2.28 (dd, 1H, *J* = 9.0 Hz, *J* = 17.5 Hz), 2.21−2.13 (m, 4H), 2.02−1.91 (m, 1H), 1.83−1.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 128.4, 127.5, 127.0, 71.7, 57.1, 40.5, 35.1, 22.5; $[\alpha]_D^{20}$ = −34.6° (*c* = 0.2, $CHCl_3$) {lit.[22] $[\alpha]_D^{20}$ = −73.2° (*c* = 1.0, CH_2Cl_2)}.

(*R*)-1-Methyl-2-tetradecylpyrrolidine (5).[17] Compound **5** (1.0 mmol scale) was prepared according to the same procedures as described for the synthesis of compound **4**. Pale yellow oil (157 mg, 56%, 3 steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.07−3.03 (m, 1H), 2.29 (s, 3H), 2.11 (dd, 1H, *J* = 18.0 Hz, *J* = 8.5 Hz), 1.97−1.88 (m, 2H), 1.80−1.71 (m, 1H), 1.69−1.62 (m, 2H), 1.46−1.38 (m, 1H), 1.33−1.17 (m, 25H), 0.88 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 66.5, 57.4, 40.5, 33.9, 31.9, 30.8, 30.0, 29.7, 29.6(9), 29.6(8), 29.6(7), 29.6(6), 29.6(5), 29.6(2), 29.3, 26.7, 22.7, 21.8, 14.1; $[\alpha]_D^{20}$ = −41.5° (*c* = 1.0, MeOH) {lit.[17c] $[\alpha]_D^{29}$ = −42.5° (*c* = 1.65, MeOH)}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra and HPLC chromatograms for all described compounds. 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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