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Gold Catalysis |*Hot Paper*|

Gold-Catalyzed Tandem Cycloisomerization–Halogenation of Chiral Homopropargyl Sulfonamides

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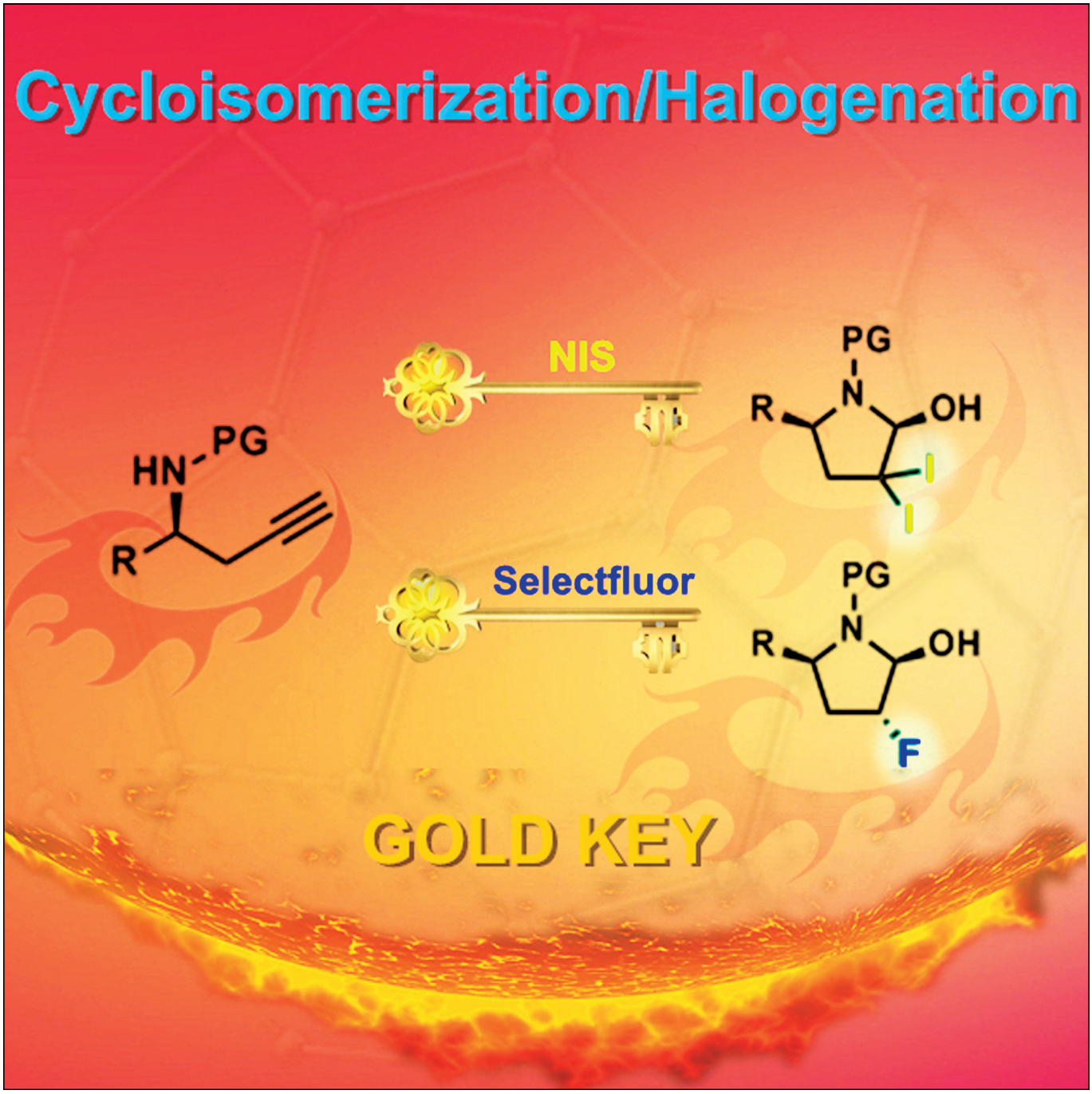
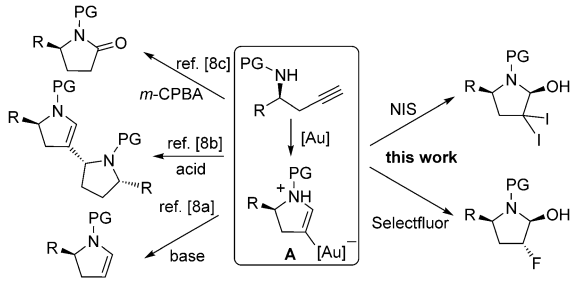


Abstract: Two new gold-catalyzed tandem cycloisomerization–halogenation reactions of chiral homopropargyl sulfonamides have been developed. Various enantioenriched 3,3-diiodopyrrolidin-2-ols and 3-fluoropyrrolidin-2-ols were obtained in moderate-to-good yields with excellent enantio- and diastereoselectivity.

Introduction

Organic halides are highly useful and valuable compounds that can be found in a large number of biologically active natural products and pharmaceutical agents.[1] In addition, they can also serve as versatile substrates for various synthetic transformations.[2] As a result, a range of halogenation reactions have been developed to prepare these compounds, mainly by treating substrates with elemental halogen species or by adding reagents such as *N*-iodo- (NIS), *N*-bromo- (NBS), or *N*-chlorosuccinimide (NCS).[3] However, these reactions suffer from limited substrate scope, harsh reaction conditions, competitive side reactions, and low yields. In particular, there is a lack of efficient synthetic methods for the enantioselective synthesis of halogenated products.[4] Therefore, the exploration of novel approaches to halogenation that have high enantioselectivity, flexibility, and good modularity is highly desirable.

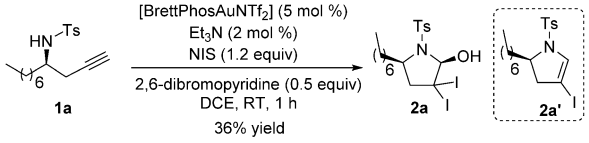
Homogeneous gold catalysis has received extensive attention over the past decade, and it has enabled facile synthesis of an incredible variety of complicated skeletons from readily available starting materials under relatively mild reaction conditions.[5,6] Our interest in this field is focused on the exploration of gold-catalyzed tandem reactions and their applications in diversity-based organic synthesis.[7] In our recent study on gold-catalyzed cycloisomerization-initiated tandem reactions,[8] we reported the facile and practical construction of a series of heterocycle skeletons from readily available chiral homopropargyl sulfonamides by combining chiral *tert*-butylsulfinimine chemistry and gold catalysis (Scheme 1).[8a–c] Herein, we describe two novel gold-catalyzed tandem 5-*endo-dig* cycloisomerization–halogenation reactions of chiral homopropargyl sulfonamides that use either NIS or 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) as the halogen source and the efficient formation of various enantioenriched 3,3-diiodopyrrolidin-2-ols **2** and 3-fluoropyrrolidin-2-ols **3**. Importantly, excellent diastereocontrol was achieved in both transformations.



Scheme 1. Gold-catalyzed 5-*endo-dig* cycloisomerization-initiated tandem reactions based on chiral homopropargyl sulfonamides. PG = protecting group; *m*-CPBA = *meta*-chloroperbenzoic acid.

Results and Discussion

Very recently, we demonstrated an efficient gold-catalyzed *anti*-Markovnikov hydroamination of chiral homopropargyl sulfonamides that led to enantioenriched 2,3-dihydropyrroles in excellent yields.[8a] Inspired by this result, we envisioned that vinyl-gold intermediate **A** might be further trapped by electrophilic NIS to afford the corresponding 4-iodo-2,3-dihydropyrrole.[9] Surprisingly, when substrate **1a** was treated with NIS (1.2 equiv) under the previously optimized reaction conditions 3,3-diiodopyrrolidin-2-ol **2a** was isolated in 36% yield, instead of the anticipated product **2a'** (Scheme 2).[10,11] Notably, excellent *cis* diastereoselectivity was achieved in this transformation.



Scheme 2. Ts = *para*-toluenesulfonyl, Tf = trifluoromethanesulfonyl, DCE = 1,2-dichloroethane.

We then set out to screen different conditions for this reaction by using homopropargyl sulfonamide **1a** as a model substrate. Considering that two iodine atoms were introduced during this process, we used NIS (2.1 equiv) to optimize the reaction conditions. The influence of different gold catalysts with a range of electronic and steric characteristics was investigated first (Table 1, entries 1–7). [BrettPhosAuNTf$_2$] showed the best catalytic activity: the desired 3,3-diiodopyrrolidin-2-ol **2a** was obtained in 52% yield, albeit with a small amount of pyrrolidine byproduct **2aa**, which was formed by gold-catalyzed tandem cycloisomerization–dimerization of **1a** (Table 1, entry 6).[8b] Notably, in the absence of any gold catalyst none

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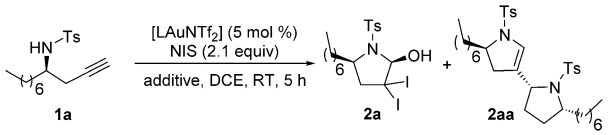
Table 1. Optimization of the reaction conditions.[a]



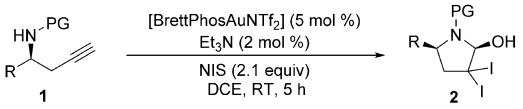
Entry	Metal catalyst	Additive [mol%]	Yield [%][b] 2a	2aa
1	$[Me_3PAuNTf_2]$	–	14	3
2[c]	$[IPrAuNTf_2]$	–	<5	<1
3[c]	$[Ph_3PAuNTf_2]$	–	<5	<1
4	$[(ArO)_3PAuNTf_2]$[d]	–	12	7
5	$[XPhosAuNTf_2]$	–	16	8
6	$[BrettPhosAuNTf_2]$	–	52	6
7[c]	$[(4\text{-}CF_3C_6H_4)_3PAuNTf_2]$	–	<5	<1
8[c]	$AgNTf_2$	–	<1	<1
9[e]	–	–	<1	<1
10	$[BrettPhosAuNTf_2]$	Et_3N (2)	69	<1
11	$[BrettPhosAuNTf_2]$	Et_3N (5)	30	<1
12[f]	$[BrettPhosAuNTf_2]$	Et_3N (2)	68	<1

[a] Reactions run in vials without exclusion of air or moisture; [**1a**] = 0.05 M. [b] Estimated by ^1H NMR spectroscopy by using diethyl phthalate as internal reference. [c] Compound **2a** was consumed but the reaction gave a complicated mixture of products. [d] Ar = 2,4-di-*tert*-butylphenyl. [e] 90% of **1a** remained unreacted. [f] The reaction was performed in a flame-dried vial with dry DCE as the solvent and H_2O (2 equiv) as an additive.

of the desired product **2a** was formed (Table 1, entry 9). $AgNTf_2$ did not catalyze this transformation (Table 1, entry 8). To our delight, the use of Et_3N (2 mol%) minimized the formation of pyrrolidine **3a** and led to the formation of **2a** in 69% yield (Table 1, entry 10); a similar result was obtained in the presence of water (2 equiv) (Table 1, entry 12).[12] However, the yield of **2a** decreased significantly with an increased loading of Et_3N (Table 1, entry 11).

With the optimized reaction conditions in hand, the scope of this tandem reaction was explored (Table 2). A series of

Table 2. Reaction scope for the formation of 3,3-diiodopyrrolidin-2-ols **2**.[a]



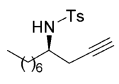
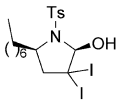
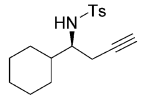
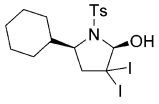
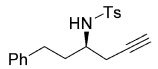
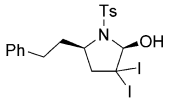
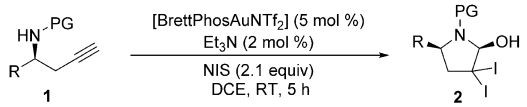
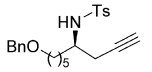
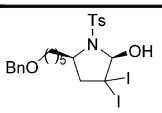
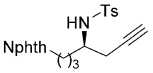
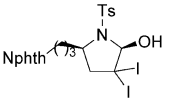
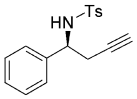
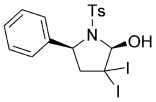
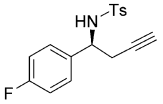
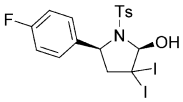
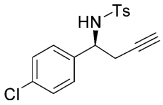
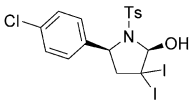
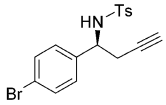
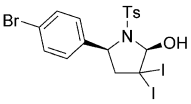
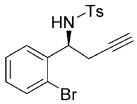
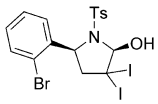
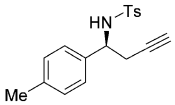
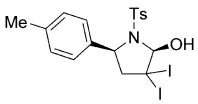
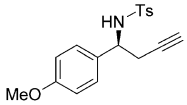
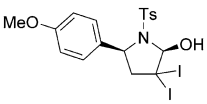
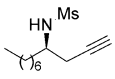
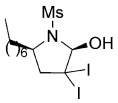
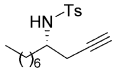
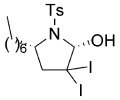
Entry	Substrate	1	Product	2	Yield [%]
1[b]		**1a**		**2a**	63
2		**1b**		**2b**	66
3		**1c**		**2c**	68

Table 2. (Continued)



Entry	Substrate	1	Product	2	Yield [%]
4		**1d**		**2d**	66
5		**1e**		**2e**	75
6		**1f**		**2f**	64
7		**1g**		**2g**	69
8		**1h**		**2h**	65
9		**1i**		**2i**	72
10		**1j**		**2j**	70
11		**1k**		**2k**	73
12		**1l**		**2l**	72
13		**1m**		**2m**	60
14		**1n**		**2n**	64

[a] Reactions run in vials without exclusion of air or moisture; [**1**] = 0.05 M; isolated yields are reported. [b] 99% *ee*, determined by HPLC on a chiral stationary phase.

chiral homopropargyl amides **1** (easily prepared by using Ellman's *tert*-butylsulfinimine chemistry)[13] were suitable substrates for this transformation, and the corresponding 3,3-diiodopyrrolidin-2-ols **2** were obtained in moderate-to-good yields. A range of functional groups were also well tolerated, including phenyl (Table 2, entry 3), protected hydroxy (Table 2, entry 4), and *N*-phthaloyl groups (Table 2, entry 5). Aromatic substrates bearing *para*-substituted electron-donating or elec-

tron-withdrawing substituents (e.g., F, Cl, Br, Me, and OMe) on the phenyl ring also worked well in the reaction to smoothly yield the desired products (Table 2, entries 6–9, 11, and 12). Moreover, even the sterically hindered substrate **1j** was compatible with this transformation (Table 2, entry 10). Changing the N-protecting group from *N*-tosyl (Ts) to *N*-mesyl (Ms) had a slight effect on the reaction: **2m** was formed in 60% yield (Table 2, entry 13). Notably, with (*S*)-(+)-*tert*-butylsulfinimide-derived homopropargyl amide **1n** instead of (*R*)-(+)-*tert*-butylsulfinimide-derived **1a** as the substrate, the reaction proceeded smoothly to afford the desired product **2n** in 64% yield with the opposite enantioselectivity to **2a** (Table 2, entry 14). In these transformations, the enantiomeric excess (*ee*) was well maintained; we determined the *ee* of **2a** as a representative example (Table 2, entry 1). Importantly, excellent *cis* diastereoselectivity (diastereomeric ratio (d.r.) > 50:1, determined by crude ^{1}H NMR spectroscopy) was achieved in all cases. The molecular structure of **2g** was further confirmed by X-ray crystallography (Figure 1).[14] Thus, this protocol provides a highly efficient and practical route to prepare both enantiomers of 3,3-diiodopyrrolidin-2-ols **2** by simply adjusting the starting chiral source. Our attempts to extend the reaction to *tert*-butylsulfonylamide **1o**, *tert*-butylsulfinylamide **1p**, 5-amino-1-yne **1q**, and internal alkyne **1r**[15] only resulted in the formation of inseparable mixtures.

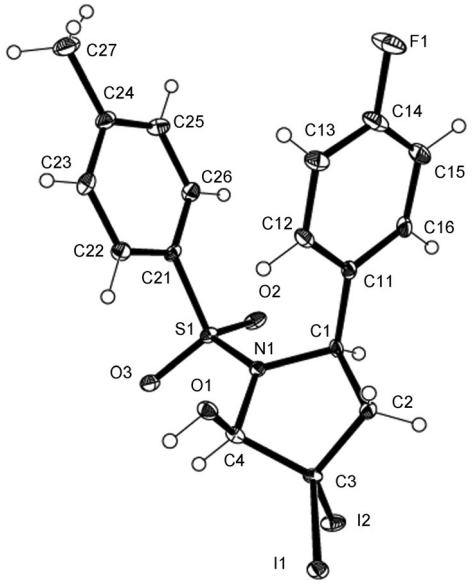
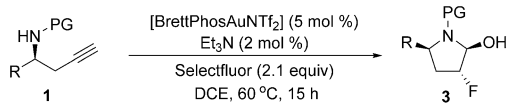
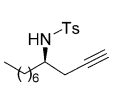
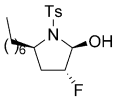
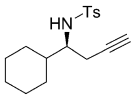
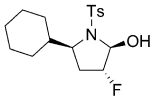
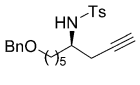
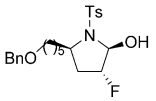
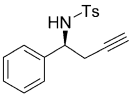
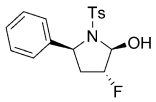
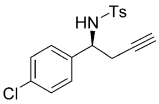
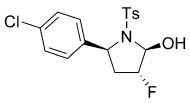
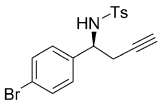
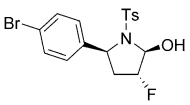
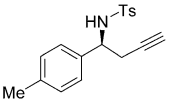
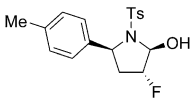
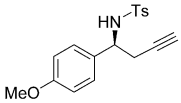
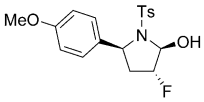


Figure 1. X-ray structure of **2g**.

Attempts to expand this chemistry to a tandem cycloisomerization–bromination sequence have been unsuccessful as yet. However, interestingly, the reaction gave the corresponding monofluorinated pyrrolidin-2-ols **3** by using Selectfluor as the fluorination reagent. As shown in Table 3, treatment of chiral homopropargyl amides **1** with Selectfluor (2.1 equiv) in the presence of [BrettPhosAuNTf$_2$] (5 mol%) and Et$_3$N (2 mol%) produced 3-fluoropyrrolidin-2-ols **3a**–**3h** in 54–71% yield with excellent diastereoselectivities (d.r. > 10:1, determined by crude ^{1}H NMR spectroscopy). Compound **3d** was further characterized by X-ray crystallography (Figure 2).[14]

Table 3. Reaction scope for the formation of 3-fluoropyrrolidin-2-ols **3**.[a]



Entry	Substrate	1	Product	3	Yield [%]
1		**1a**		**3a**	61
2		**1b**		**3b**	54
3		**1d**		**3c**	61
4[b]		**1f**		**3d**	55
5		**1h**		**3e**	56
6		**1i**		**3f**	60
7		**1k**		**3g**	71
8		**1l**		**3h**	62

[a] Reactions run in vials without exclusion of air and moisture; [**1**] = 0.05 M; isolated yields are reported. [b] 99% *ee*, determined by HPLC on a chiral stationary phase.

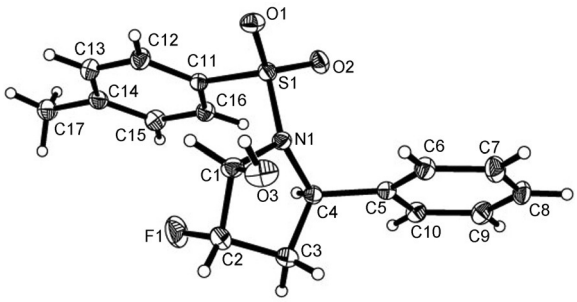
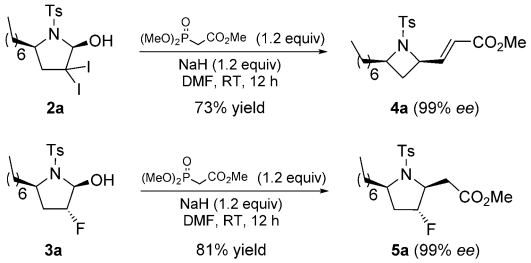


Figure 2. X-ray structure of **3d**.

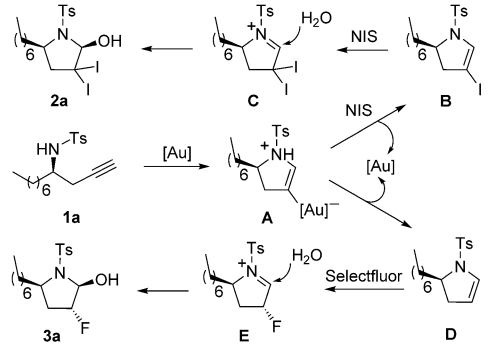
Pyrrolidin-2-ols **3** are potentially useful in organic synthesis and are valuable precursors for the preparation of important enantioenriched heterocycles. For example, 3,3-diiodopyrroli-

din-2-ol **2a** was diastereoselectively transformed into the corresponding azetidine **4a** (73%, d.r. > 10:1) without detriment to the *ee*. The reaction was initiated by a Horner–Wadsworth–Emmons olefination, which was followed by a formal N–H insertion into a carbene derived from the diiodo moiety (Scheme 3). Furthermore, enantioenriched pyrrolidine **5a** was readily synthesized with high diastereoselectivity (d.r. > 10:1) by a Horner–Wadsworth–Emmons olefination of **3a** and a subsequent aza-Michael reaction (Scheme 3).[16]



Scheme 3. Synthetic applications.

A plausible reaction pathway to rationalize the formation of **2a** and **3a** was proposed (Scheme 4).[17] The reaction starts with formation of the vinyl gold intermediate **A** by alkyne π coordination and concomitant *5-endo-dig* cyclization.[18] Intermediate **A** reacts with NIS to provide vinyl iodide **B**, which is further converted into the iminium intermediate **C** in the presence of another molecule of NIS. Finally, trace water in the reaction system attacks intermediate **C** to afford the target product **2a**. However, in the presence of Selectfluor the reaction presumably proceeded by the reaction of 2,3-dihydropyrrole **D** with Selectfluor; the formation of **D** was clearly observed by ^{1}H NMR spectroscopy of the reaction mixture.[19] Notably, the observed *cis* stereochemistry may be the result of thermodynamic control, which is also supported by the fact that X-ray structures of **2g** and **3d** are consistent with the *cis* product being sterically less congested than the alternative *trans* product.



Scheme 4. Plausible mechanism for the formation of **2a** and **3a**.

Conclusion

We have developed an unexpected gold-catalyzed tandem cycloisomerization–diiodination of chiral homopropargyl sulfonamides, which allows the efficient synthesis of highly functionalized enantioenriched 3,3-diiodopyrrolidin-2-ols, and thus makes it possible to realize an alkyne tetrafunctionalization with high diastereoselectivity. Moreover, gold-catalyzed tandem cycloisomerization–fluorination was also been achieved with moderate-to-good yields and excellent enantio- and diastereo-control. The use of readily available substrates, a simple procedure, and mild reaction conditions (in particular, no requirement to exclude moisture or air) render this method potentially useful in organic synthesis. Further investigations into synthetic applications of the current protocol are in progress in our laboratory.

Experimental Section

All melting points were determined without correction. ^{1}H NMR spectra were obtained at 400 or 500 MHz, and ^{13}C NMR spectra were obtained at 100 or 125 MHz. Spectra were recorded for samples in solution in $CDCl_3$ or [D_6]DMSO, and the residual protonated solvent signal was used as an internal standard. Coupling constants (*J*) are given in Hz.

General procedure for the preparation of 3,3-diiodopyrrolidin-2-ols 2

NIS (141.7 mg, 0.63 mmol), Et_3N (2.0 mL, 0.003 mmol mL^{-1} in DCE) and [BrettPhosAuNTf$_2$] (15.3 mg, 0.015 mmol) were added, in this order, to a solution of homopropargyl amide **1** (0.30 mmol) in DCE (4.0 mL) at RT. The reaction mixture was stirred at RT, and the reaction progress was monitored by TLC; the reaction typically took 5 h. On completion, the mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate) to afford the desired product **2**.

Compound 2a: Oil (111.7 mg, 63%); $[\alpha]_D^{20} = -80.0^\circ$ ($c = 1.0$ in $CHCl_3$); 99% *ee* (HPLC: Chiralpak ASH column; 10:90 *i*PrOH/hexane; flow rate = 0.6 mL min^{-1}; $\lambda = 200$ nm; retention time (t_R) = 38.96 (major), 32.82 min (minor)); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.83$ (d, $J = 6.4$ Hz, 2H), 7.33 (d, $J = 6.4$ Hz, 2H), 5.73 (d, $J = 2.4$ Hz, 1H), 3.91–3.85 (m, 1H), 3.42 (d, $J = 2.4$ Hz, 1H), 2.94–2.84 (m, 2H), 2.43 (s, 3H), 2.08–1.98 (m, 1H), 1.69–1.61 (m, 1H), 1.32–1.99 (m, 10H), 0.90 ppm (t, $J = 1.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 143.9$, 135.9, 129.6, 127.7, 92.9, 61.5, 54.9, 33.8, 31.7, 29.4, 29.1, 25.2, 22.6, 21.6, 14.0, −4.1 ppm; IR (neat): $\tilde{\nu} = 3458$ (br), 2951, 2926, 2853, 1597, 1468, 1342, 1162, 1028, 814, 680, 582, 548 cm^{-1}; MS (ESI): *m/z*: 614 [$M + Na^+$]; HRMS: *m/z* calcd for $C_{18}H_{27}I_2NNaO_3S^+$: 613.9699 [$M + Na^+$]; found: 613.9693.

Compound 2b: Oil (113.9 mg, 66%); $[\alpha]_D^{20} = -38.0^\circ$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, [D_6]DMSO): $\delta = 7.76$ (d, $J = 8.4$ Hz, 2H), 7.42 (d, $J = 5.6$ Hz, 1H), 7.39 (d, $J = 8.0$ Hz, 2H), 5.67 (d, $J = 6.0$ Hz, 1H), 3.83–3.77 (m, 1H), 2.66–2.60 (m, 1H), 2.55–2.49 (m, 1H), 2.38 (s, 3H), 1.68–1.62 (m, 2H), 1.52–1.46 (m, 2H), 1.40–1.34 (m, 1H), 1.16–1.02 (m, 2H), 1.01–0.87 (m, 1H), 0.78–0.50 ppm (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 142.9$, 137.8, 129.2, 126.8, 92.4, 64.8, 48.4, 37.2, 29.2, 26.1, 25.8, 25.5, 25.1, 20.9, 3.4 ppm; IR (neat): $\tilde{\nu} =$ 3470 (br), 2926, 2853, 1594, 1448, 1344, 1162, 1092, 814, 669, 579,

545 cm^{-1}; MS (ESI): *m/z*: 598 [$M+Na^+$]; HRMS: *m/z* calcd for $C_{17}H_{23}I_2NNaO_3S^+$: 597.9386 [$M+Na^+$]; found: 597.9415.

Compound 2c: Oil (121.8 mg, 68%); $[\alpha]_D^{20}=-30.5^\circ$ ($c=1.0$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.71$ (d, $J=8.3$ Hz, 2H), 7.30–7.16 (m, 5H), 7.12 (d, $J=7.0$ Hz, 2H), 5.71 (s, 1H), 3.89–3.79 (m, 2H), 2.99 (dd, $J=14.0$, 9.4 Hz, 1H), 2.87 (dd, $J=14.0$, 6.0 Hz, 1H), 2.71–2.57 (m, 1H), 2.52–2.42 (m, 1H), 2.42–2.32 (m, 4H), 2.10–1.98 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=143.9$, 140.7, 135.0, 129.6, 128.4, 128.3, 127.8, 126.0, 92.9, 60.7, 54.7, 34.9, 31.3, 21.5, −4.6 ppm; IR (neat): $\tilde{\nu}=3467$ (br), 3024, 2923, 2853, 1597, 1496, 1454, 1339, 1159, 1092, 1025, 812, 753, 671, 579, 548 cm^{-1}; MS (ESI): *m/z*: 620 [$M+Na^+$]; HRMS: *m/z* calcd for $C_{19}H_{21}I_2NNaO_3S^+$: 619.9229 [$M+Na^+$]; found: 620.9258.

Compound 2d: Oil (132.5 mg, 66%); $[\alpha]_D^{20}=-65.5^\circ$ ($c=0.5$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.80$ (d, $J=8.2$ Hz, 2H), 7.40–7.27 (m, 7H), 5.69 (s, 1H), 4.49 (s, 2H), 3.91–3.79 (m, 1H), 3.65 (d, $J=7.8$ Hz, 1H), 3.43 (t, $J=6.5$ Hz, 2H), 2.95–2.75 (m, 2H), 2.39 (s, 3H), 2.06–1.96 (m, 1H), 1.70–1.62 (m, 1H), 1.61–1.53 (m, 2H), 1.38–1.26 (m, 2H), 1.24–1.14 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=143.9$, 138.6, 135.8, 129.6, 128.3, 127.7, 127.6, 127.5, 92.9, 72.8, 70.1, 61.4, 54.8, 33.8, 29.5, 26.0, 24.9, 21.6, −4.1 ppm; IR (neat): $\tilde{\nu}=3461$ (br), 2926, 2854, 1597, 1451, 1348, 1163, 1093, 1026, 816, 673, 586, 550 cm^{-1}; MS (ESI): *m/z*: 692 [$M+Na^+$]; HRMS: *m/z* calcd for $C_{23}H_{29}I_2NNaO_4S^+$: 691.9804 [$M+Na^+$]; found: 691.9793.

Compound 2e: Oil (153.0 mg, 75%); $[\alpha]_D^{20}=-64.5^\circ$ ($c=1.0$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.87$–7.82 (m, 2H), 7.80 (d, $J=8.3$ Hz, 2H), 7.74–7.69 (m, 2H), 7.30 (d, $J=8.1$ Hz, 2H), 5.69 (s, 1H), 3.95–3.87 (m, 2H), 3.72–3.56 (m, 2H), 2.91 (dd, $J=14.1$, 9.5 Hz, 1H), 2.80 (dd, $J=14.1$, 6.0 Hz, 1H), 2.41 (s, 3H), 2.08–1.97 (m, 1H), 1.84–1.74 (m, 1H), 1.71–1.55 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=168.3$, 144.0, 135.5, 133.9, 131.9, 129.7, 127.8, 123.2, 92.9, 60.7, 54.3, 37.6, 30.5, 24.1, 21.6, −4.6 ppm; IR (neat): $\tilde{\nu}=3458$ (br), 2923, 2856, 1773, 1706 (s), 1440, 1403, 1344, 1159, 1050, 719, 674, 585 cm^{-1}; MS (ESI): *m/z*: 703 [$M+Na^+$]; HRMS: *m/z* calcd for $C_{22}H_{22}I_2N_2NaO_5S^+$: 702.9236 [$M+Na^+$]; found: 702.9225.

Compound 2f: Oil (109.3 mg, 64%); $[\alpha]_D^{20}=-31.0^\circ$ ($c=1.0$ in $CHCl_3$); ^1H NMR (500 MHz, [D$_6$]DMSO): $\delta=7.73$ (s, 1H), 7.27 (d, $J=8.3$ Hz, 2H), 7.20–7.07 (m, 7H), 5.77 (s, 1H), 4.79 (dd, $J=9.6$, 6.3 Hz, 1H), 3.09 (dd, $J=14.0$, 6.3 Hz, 1H), 2.77 (dd, $J=14.1$, 9.6 Hz, 1H), 2.29 ppm (s, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): $\delta=143.1$, 138.1, 137.6, 129.3, 128.4, 128.3, 127.8, 127.2, 93.2, 64.3, 58.3, 21.4, 2.3 ppm; IR (neat): $\tilde{\nu}=3460$ (br), 2950, 2927, 2852, 1710, 1605, 1487, 1308, 1216, 1159, 1058, 830, 646, 585, 553 cm^{-1}; MS (ESI): *m/z*: 592 [$M+Na^+$]; HRMS: *m/z* calcd for $C_{17}H_{17}I_2NNaO_3S^+$: 591.8916 [$M+Na^+$]; found: 591.8918.

Compound 2g: White solid (112.7 mg, 69%); m.p. 156–158 °C; $[\alpha]_D^{20}=-26.5^\circ$ ($c=2.0$ in $CHCl_3$); ^1H NMR (500 MHz, [D$_6$]DMSO): $\delta=7.77$ (d, $J=6.2$ Hz, 1H), 7.29 (d, $J=8.3$ Hz, 2H), 7.20 (dd, $J=8.7$, 5.5 Hz, 2H), 7.14 (d, $J=8.0$ Hz, 2H), 6.90 (t, $J=8.9$ Hz, 2H), 5.76 (d, $J=6.1$ Hz, 1H), 4.80 (dd, $J=9.5$, 6.3 Hz, 1H), 3.10 (dd, $J=14.1$, 6.3 Hz, 1H), 2.75 (dd, $J=14.5$, 9.9 Hz, 1H), 2.30 ppm (s, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): $\delta=161.9$ (d, $J=243.7$ Hz), 143.2, 137.6, 134.3, 130.3 (d, $J=8.3$ Hz), 129.3, 127.2, 115.1 (d, $J=21.4$ Hz), 93.2, 63.5, 58.2, 21.4, 1.9 ppm; IR (neat): $\tilde{\nu}=3458$ (br), 2959, 2928, 2852, 1708, 1605, 1509, 1338, 1226, 1159, 1038, 836, 676, 587, 545 cm^{-1}; MS (ESI): *m/z*: 610 [$M+Na^+$]; HRMS calcd for $C_{17}H_{16}FI_2NNaO_3S^+$: 609.8822 [$M+Na^+$]; found: 609.8851.

Compound 2h: Oil (117.7 mg, 65%); $[\alpha]_D^{20}=-64.5^\circ$ ($c=0.5$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.42$ (d, $J=8.2$ Hz, 2H), 7.17 (d, $J=8.4$ Hz, 2H), 7.12–7.06 (m, 4H), 6.04 (s, 1H), 4.89 (dd, $J=8.9$, 6.8 Hz, 1H), 3.85 (s, 1H), 3.20–2.92 (m, 2H), 2.37 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=143.7$, 136.3, 135.7, 133.9, 129.3, 129.2, 128.5, 127.5, 92.8, 64.0, 58.6, 21.5, −3.5 ppm; IR (neat): $\tilde{\nu}=3470$ (br), 2957, 2917, 2853, 1371, 1661, 1600, 1487, 1347, 1159, 1092, 1036, 814, 671, 585, 545 cm^{-1}; MS (ESI): *m/z*: 626 [$M+Na^+$]; HRMS: *m/z* calcd for $C_{17}H_{16}ClI_2NNaO_3S^+$: 625.8526 [$M+Na^+$]; found: 625.8548.

Compound 2i: White solid (140.0 mg, 72%); m.p. 163–165 °C; $[\alpha]_D^{20}=-38.5^\circ$ ($c=1.0$ in $CHCl_3$); ^1H NMR (400 MHz, [D$_6$]DMSO): $\delta=7.81$ (d, $J=6.0$ Hz, 1H), 7.31 (d, $J=8.2$ Hz, 2H), 7.26 (d, $J=8.4$ Hz, 2H), 7.15 (d, $J=8.4$ Hz, 2H), 7.12 (d, $J=8.5$ Hz, 2H), 5.75 (d, $J=5.7$ Hz, 1H), 4.75 (dd, $J=9.4$, 6.3 Hz, 1H), 3.11 (dd, $J=14.1$, 6.3 Hz, 1H), 2.74 (dd, $J=14.1$, 9.6 Hz, 1H), 2.32 ppm (s, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): $\delta=143.3$, 137.6, 137.3, 131.2, 130.5, 129.4, 127.3, 121.1, 93.2, 63.5, 57.9, 21.4, 1.6 ppm; IR (neat): $\tilde{\nu}=3438$ (br), 2956, 2923, 2850, 1593, 1487, 1411, 1344, 1324, 1159, 1041, 1007, 946, 808, 657, 583, 543 cm^{-1}; MS (ESI): *m/z*: 670 [$M+Na^+$]; HRMS: *m/z* calcd for $C_{17}H_{16}BrI_2NNaO_3S^+$: 669.8021 [$M+Na^+$]; found: 669.8048.

Compound 2j: White solid (136.1 mg, 70%); m.p. 160–162 °C; $[\alpha]_D^{20}=-60.0^\circ$ ($c=0.4$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.67$ (d, $J=8.2$ Hz, 2H), 7.55 (dd, $J=7.8$, 1.6 Hz, 1H), 7.48 (dd, $J=7.9$, 1.0 Hz, 1H), 7.25 (d, $J=9.2$ Hz, 2H), 7.18 (t, $J=7.5$ Hz, 1H), 7.09 (td, $J=7.7$, 1.7 Hz, 1H), 5.90 (s, 1H), 5.38 (dd, $J=9.4$, 6.2 Hz, 1H), 3.73 (s, 1H), 3.22 (dd, $J=14.2$, 6.2 Hz, 1H), 2.93 (dd, $J=14.2$, 9.6 Hz, 1H), 2.39 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=144.2$, 137.4, 134.6, 132.4, 129.6, 129.4, 129.2, 128.2, 127.9, 122.3, 93.2, 63.9, 57.8, 21.6, −5.5 ppm; IR (neat): $\tilde{\nu}=3455$ (br), 2956, 2923, 2853, 1714, 1596, 1470, 1440, 1348, 1160, 1112, 1036, 812, 758, 671, 588, 540 cm^{-1}; MS (ESI): *m/z*: 670 [$M+Na^+$]; HRMS: *m/z* calcd for $C_{17}H_{16}BrI_2NNaO_3S^+$: 669.8021 [$M+Na^+$]; found: 669.8023.

Compound 2k: White solid (127.7 mg, 73%); m.p. 157–159 °C; $[\alpha]_D^{20}=-40.0^\circ$ ($c=1.0$ in $CHCl_3$); ^1H NMR (400 MHz, [D$_6$]DMSO): $\delta=7.72$ (d, $J=6.1$ Hz, 1H), 7.26 (d, $J=8.3$ Hz, 2H), 7.11 (d, $J=8.1$ Hz, 2H), 7.03 (d, $J=8.1$ Hz, 2H), 6.88 (d, $J=7.9$ Hz, 2H), 5.75 (d, $J=5.6$ Hz, 1H), 4.72 (dd, $J=9.6$, 6.2 Hz, 1H), 3.05 (dd, $J=14.1$, 6.2 Hz, 1H), 2.75 (dd, $J=14.1$, 9.6 Hz, 1H), 2.30 (s, 3H), 2.21 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta=143.0$, 137.6, 137.2, 134.9, 129.3, 128.9, 128.3, 127.3, 93.2, 64.1, 58.2, 21.4, 21.1, 2.5 ppm; IR (neat): $\tilde{\nu}=3428$ (br), 2959, 2917, 2850, 1614, 1515, 1442, 1330, 1257, 1154, 1128, 1106, 1042, 828, 674, 588, 546 cm^{-1}; MS (ESI): *m/z*: 606 [$M+Na^+$]; HRMS: *m/z* calcd for $C_{18}H_{19}I_2NNaO_3S^+$: 605.9073 [$M+Na^+$]; found: 605.9066.

Compound 2l: White solid (129.4 mg, 72%); m.p. 166–168 °C; $[\alpha]_D^{20}=-35.0^\circ$ ($c=1.0$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.41$ (d, $J=8.3$ Hz, 2H), 7.15 (d, $J=8.7$ Hz, 2H), 7.07 (d, $J=8.1$ Hz, 2H), 6.66 (d, $J=8.7$ Hz, 2H), 6.03 (d, $J=1.6$ Hz, 1H), 4.90 (dd, $J=8.5$, 7.3 Hz, 1H), 3.83–3.78 (m, 1H), 3.76 (s, 3H), 3.06 (dd, $J=7.9$, 1.6 Hz, 2H), 2.34 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=159.4$, 143.1, 136.7, 129.3, 129.0, 128.9, 127.5, 113.7, 92.7, 64.3, 58.7, 55.3, 21.4, −2.5 ppm; IR (neat): $\tilde{\nu}=3419$ (br), 2962, 2920, 2847, 1611, 15110, 1442, 1328, 1252, 1154, 1106, 1033, 826, 671, 579, 550 cm^{-1}; MS (ESI): *m/z*: 622 [$M+Na^+$]; HRMS: *m/z* calcd for $C_{18}H_{19}I_2NNaO_4S^+$: 621.9022 [$M+Na^+$]; found: 621.9045.

Compound 2m: Oil (92.7 mg, 60%); $[\alpha]_D^{20}=-51.0^\circ$ ($c=1.0$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta=5.74$ (s, 1H), 4.09–4.00 (m, 1H), 3.84–3.67 (m, 1H), 3.09 (s, 3H), 2.98 (dd, $J=14.0$, 6.0 Hz, 1H), 2.87 (dd, $J=14.0$, 9.3 Hz, 1H), 2.18–2.08 (m, 1H), 1.70–1.59 (m, 1H), 1.37–1.18 (m, 10H), 0.88 ppm (t, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=92.8$, 61.3, 54.7, 42.3, 34.1, 31.7, 29.4, 29.1, 25.4, 22.5, 14.0, −2.2 ppm; IR (neat): $\tilde{\nu}=3461$ (br), 2956, 2925, 2852, 1658, 1459, 1338, 1156, 1035, 971, 769, 660, 553 cm^{-1}; MS (ESI): *m/z*: 538 [$M+Na^+$]; HRMS: *m/z* calcd for $C_{18}H_{19}I_2NNaO_4S^+$: 537.9386 [$M+Na^+$]; found: 537.9372.

General procedure for the preparation of 3-fluoropyrrolidin-2-ols 3

Selectfluor (223.2 mg, 0.63 mmol), Et_3N (2.0 mL, 0.003 mmol mL^{-1} in DCE) and [BrettPhosAuNTf$_2$] (15.3 mg, 0.015 mmol) were added, in this order, to a solution of homopropargyl amide **1** (0.30 mmol) in DCE (4.0 mL) at RT. The reaction mixture was stirred at 60 °C, and the progress of the reaction was monitored by TLC; the reaction typically took 15 h. On completion, the reaction mixture was concentrated and the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate) to afford the desired product **3**.

Compound 3 a: Oil (65.5 mg, 61%); $[\alpha]_D^{20} = -120.0^\circ$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.72$ (d, $J = 8.3$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 5.48 (dd, $J = 12.3$, 2.0 Hz, 1H), 4.80 (dd, $J = 50.7$, 3.2 Hz, 1H), 3.59 (dtt, $J = 12.3$, 6.0, 3.0 Hz, 1H), 3.27 (s, 1H), 2.42 (s, 3H), 2.26–1.93 (m, 3H), 1.69–1.57 (m, 1H), 1.37–1.20 (m, 10H), 0.89 ppm (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 143.8$, 135.3, 129.6, 127.4, 93.9 (d, $J = 176.4$ Hz), 88.3 (d, $J = 33.6$ Hz), 59.7, 36.4, 35.9 (d, $J = 20.5$ Hz), 31.8, 29.4, 29.2, 25.3, 22.6, 21.5, 14.0 ppm; IR (neat): $\tilde{\nu} = 3460$ (br), 2924, 2853, 1598, 1464, 1341, 1162, 1093, 1026, 814, 739, 665, 598 cm^{-1}; MS (ESI): *m/z*: 380 [M+Na$^+$]; HRMS: *m/z* calcd for $C_{18}H_{28}FNNaO_3S^+$: 380.1666 [M+Na$^+$]: found: 380.1669.

Compound 3 b: White solid (55.3 mg, 54%); m.p. 126–128 °C; $[\alpha]_D^{20} = -73.5^\circ$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.72$ (d, $J = 8.2$ Hz, 2H), 7.30 (d, $J = 8.1$ Hz, 2H), 5.47 (d, $J = 12.7$ Hz, 1H), 4.76 (dd, $J = 50.9$, 3.1 Hz, 1H), 3.66–3.56 (m, 1H), 3.05–2.97 (m, 1H), 2.42 (s, 3H), 2.21–2.01 (m, 2H), 1.98–1.83 (m, 2H), 1.83–1.66 (m, 3H), 1.58 (d, $J = 12.4$ Hz, 1H), 1.37–1.19 (m, 2H), 1.17–1.04 (m, 1H), 1.00–0.80 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 143.8$, 135.2, 129.6, 127.4, 93.9 (d, $J = 176.4$ Hz), 88.2 (d, $J = 33.6$ Hz), 64.1, 39.8, 30.7 (d, $J = 20.6$ Hz), 30.4, 26.6, 26.5, 25.8, 25.2, 21.5 ppm; IR (neat): $\tilde{\nu} = 3468$ (br), 2925, 2852, 1598, 1449, 1341, 1161, 1093, 1029, 814, 667, 598, 548 cm^{-1}; MS (ESI): *m/z*: 364 [M+Na$^+$]; HRMS: *m/z* calcd for $C_{17}H_{24}FNNaO_3S^+$: 364.1353 [M+Na$^+$]; found: 364.1357.

Compound 3 c: Oil (81.7 mg, 61%); $[\alpha]_D^{20} = -93.5^\circ$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.71$ (d, $J = 8.3$ Hz, 2H), 7.46–7.29 (m, 5H), 7.28 (d, $J = 7.9$ Hz, 2H), 5.47 (d, $J = 12.1$ Hz, 1H), 4.77 (dd, $J = 50.7$, 3.1 Hz, 1H), 4.50 (s, 2H), 3.63–3.51 (m, 2H), 3.47 (t, $J = 6.5$ Hz, 2H), 2.40 (s, 3H), 2.22–1.87 (m, 3H), 1.70–1.56 (m, 3H), 1.45–1.23 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 143.7$, 138.5, 135.1, 129.5, 128.3, 127.6 127.4, 127.3, 93.8 (d, $J = 176.9$ Hz), 88.1 (d, $J = 33.1$ Hz), 72.7, 70.1, 59.4, 36.2, 35.7 (d, $J = 20.5$ Hz), 29.5, 26.0, 25.0, 21.5 ppm; IR (neat): $\tilde{\nu} = 3471$ (br), 2934, 2859, 1598, 1495, 1453, 1344, 1162, 1094, 1027, 815, 738, 699, 665, 597, 550 cm^{-1}; MS (ESI): *m/z*: 458 [M+Na$^+$]; HRMS: *m/z* calcd for $C_{23}H_{30}FNNaO_4S^+$: 458.1772 [M+Na$^+$]; found: 458.1772.

Compound 3 d: White solid (55.3 mg, 55%); m.p. 145–147 °C; $[\alpha]_D^{20} = -120.0^\circ$ ($c = 0.5$ in $CHCl_3$); 99% *ee* (HPLC: Chiralcel IB column; 10:90 *i*PrOH/hexane; flow rate = 0.6 mL min^{-1}; $\lambda = 200$ nm; $t_R = 11.27$ (major), 12.53 min (minor)); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.61 (d, $J = 8.1$ Hz, 2H), 7.34 (d, $J = 6.8$ Hz, 2H), 7.31–7.19 (m, 5H), 5.73 (d, $J = 12.4$ Hz, 1H), 4.90 (dd, $J = 50.6$, 2.7 Hz, 1H), 4.65 (dd, $J =$ 9.8, 6.8 Hz, 1H), 3.73 (s, 1H), 2.56–2.16 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 143.7$, 140.7, 135.3, 129.5, 128.5, 127.7, 127.5, 126.9, 94.0 (d, $J = 177.6$ Hz), 88.0 (d, $J = 33.5$ Hz), 63.2, 41.0 (d, $J =$ 20.3 Hz), 21.5 ppm; IR (neat): $\tilde{\nu} = 3473$ (br), 2983, 2926, 1598, 1494, 1456, 1339, 1160, 1094, 814, 736, 597 cm^{-1}; MS (ESI): *m/z*: 358 [M+Na$^+$]; HRMS: *m/z* calcd for $C_{17}H_{18}FNNaO_3S^+$: 358.0884 [M+Na$^+$]; found: 358.0885.

Compound 3 e: White solid (62.1 mg, 56%); m.p. 157–159 °C; $[\alpha]_D^{20} = -128.0^\circ$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.60$ (d, $J = 8.3$ Hz, 2H), 7.29–7.19 (m, 6H), 5.74 (d, $J = 12.2$ Hz, 1H), 4.89 (dd, $J = 50.6$, 3.0 Hz, 1H), 4.62 (dd, $J = 9.8$, 6.7 Hz, 1H), 3.91 (s, 1H), 2.55–2.32 (m, 1H), 2.41 (s, 3H), 2.32–2.11 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 144.0$, 139.4, 135.2, 133.5, 129.5, 128.6, 128.4, 127.5, 93.9 (d, $J = 178.0$ Hz), 87.9 (d, $J = 33.2$ Hz), 62.4, 40.9 (d, $J =$ 20.3 Hz), 21.5 ppm; IR (neat): $\tilde{\nu} = 3480$ (br), 2919, 2849, 1492, 1339, 1160, 1090, 1038, 1013, 817, 675, 598 cm^{-1}; MS (ESI): *m/z*: 392 [M+Na$^+$]; HRMS: *m/z* calcd for $C_{17}H_{17}ClFNNaO_3S^+$: 392.0494 [M+Na$^+$]; found: 392.0502.

Compound 3 f: Oil (74.5 mg, 60%); $[\alpha]_D^{20} = -185.0^\circ$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.59$ (d, $J = 8.2$ Hz, 2H), 7.37 (d, $J = 8.3$ Hz, 2H), 7.27–7.17 (m, 4H), 5.74 (d, $J = 12.2$ Hz, 1H), 4.89 (dd, $J = 50.5$, 2.6 Hz, 1H), 4.61 (dd, $J = 9.8$, 6.8 Hz, 1H), 4.04–3.92 (m, 2H), 2.56–2.41 (m, 1H), 2.42 (s, 3H), 2.31–2.10 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 144.0$, 139.8, 135.2 131.6, 129.5, 128.7, 127.5 121.6, 93.8 (d, $J = 178.1$ Hz), 87.8 (d, $J = 33.3$ Hz), 62.5, 40.9 (d, $J = 20.4$ Hz), 21.5 ppm; IR (neat): $\tilde{\nu} = 3472$ (br), 2924, 2851, 1597, 1488, 1341, 1160, 1094, 1039, 1010, 816, 670, 598 cm^{-1}; MS (ESI): *m/z*: 435 [M+Na$^+$]; HRMS: *m/z* calcd for $C_{17}H_{17}BrFNNaO_3S^+$: 435.9989 [M+Na$^+$]; found: 435.9998.

Compound 3 g: White solid (74.4 mg, 71%); m.p. 138–140 °C; $[\alpha]_D^{20} = -110.0^\circ$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.60$ (d, $J = 8.2$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 4H), 7.08 (d, $J = 7.8$ Hz, 2H), 5.70 (d, $J = 12.6$ Hz, 1H), 4.89 (dd, $J = 50.6$, 2.8 Hz, 1H), 4.60 (dd, $J =$ 9.8, 6.7 Hz, 1H), 3.74 (s, 1H), 2.40 (s, 3H), 2.53–2.15 (m, 2H), 2.32 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 143.7$, 137.7, 137.4, 135.2, 129.4, 129.2 127.5, 126.8, 94.0 (d, $J = 177.6$ Hz), 87.9 (d, $J =$ 33.5 Hz), 62.9, 40.9 (d, $J = 20.2$ Hz), 21.5, 21.1 ppm; IR (neat): $\tilde{\nu} =$ 3469 (br), 2923, 2853, 1597, 1515, 1340, 1159, 1094, 1039, 813, 664, 598 cm^{-1}; MS (ESI): *m/z*: 372 [M+Na$^+$]; HRMS: *m/z* calcd for $C_{18}H_{20}FNNaO_3S^+$: 372.1040 [M+Na$^+$]; found: 372.1044.

Compound 3 h: White solid (68.0 mg, 62%); m.p. 144–146 °C; $[\alpha]_D^{20} = -135.0^\circ$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.60$ (d, $J = 8.3$ Hz, 2H), 7.28–7.22 (m, 4H), 6.80 (d, $J = 8.7$ Hz, 2H), 5.72 (d, $J = 12.5$ Hz, 1H), 4.90 (dd, $J = 50.6$, 2.9 Hz, 1H), 4.60 (dd, $J = 9.9$, 6.6 Hz, 1H), 3.88–3.79 (m, 1H), 3.78 (s, 3H), 2.52–2.41 (m, 1H), 2.40 (s, 3H), 2.36–2.16 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 159.1, 143.6, 135.3, 132.6, 129.4, 128.2, 127.5, 113.8, 93.9 (d, $J =$ 177.5 Hz), 87.8 (d, $J = 33.5$ Hz), 62.7, 55.2, 40.9 (d, $J = 20.3$ Hz), 21.5 ppm; IR (neat): $\tilde{\nu} = 3478$ (br), 2926, 2852, 1613, 1598, 1514, 1463, 1340, 1247, 1160, 1094, 1034, 829, 674, 597 cm^{-1}; MS (ESI): *m/z*: 388 [M+Na$^+$]; HRMS: *m/z* calcd for $C_{18}H_{20}FNNaO_4S^+$: 388.0989 [M+Na$^+$]; found: 388.0922.

Procedure for the preparation of 4 a

Anhydrous DMF (4 mL) was added to a flame-dried flask, and the flask was purged with N_2. Sodium hydride (14.4 mg, 0.36 mmol, 1.2 equiv, 60% in mineral oil) was added followed by trimethylphosphoroacetate (65.5 mg, 0.36 mmol, 1.2 equiv). The mixture was stirred for 1 h at RT then hemiaminal **2 a** (177.3 mg, 0.3 mmol) in a solution of DMF (2 mL) was added. The reaction mixture was stirred for 12 h at RT then quenched with a saturated aqueous solution of NH_4Cl (30 mL). The resulting solution was extracted with EtOAc (2×30 mL) and washed with brine (2×30 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Compound **4 a** was obtained as a clear oil (86.2 mg, 73%) after column chromatography on silica gel.[20] $[\alpha]_D^{20} = +72.0^\circ$ ($c = 0.5$ in $CHCl_3$); 99% *ee* (HPLC: Chiralcel IC column; 10:90 *i*PrOH/hexane; flow rate = 0.8 mL min^{-1}; $\lambda = 200$ nm; $t_R = 66.21$ (major), 63.85 min (minor)); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.69$ (d, $J = 8.5$ Hz, 2H), 7.36 (d, $J = 8.5$ Hz, 2H), 6.91 (dd, $J =$ 15.6, 5.4 Hz, 1H), 6.09 (dd, $J = 15.6$, 1.3 Hz, 1H), 4.30 (dd, $J = 13.2$,

7.7 Hz, 1H), 3.86–3.77 (m, 1H), 3.74 (s, 3H), 2.46 (s, 3H), 2.48–2.39 (m, 1H), 2.34–2.24 (m, 1H), 1.87–1.77 (m, 1H), 1.74–1.65 (m, 1H), 1.31–1.16 (m, 10H), 0.88 ppm (t, $J=6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=166.6$, 146.3, 144.3, 132.7, 129.7, 128.4, 121.9, 60.7, 58.8, 51.6, 36.2, 31.7, 29.4, 29.3, 29.1, 24.1, 22.6, 21.6, 14.1 ppm; IR (neat): $\tilde{\nu}=2926$, 2855, 1726 (s), 1662, 1597, 1541, 1436, 1347, 1162, 1038, 987, 816, 665, 605 cm^{-1}; MS (ESI): *m/z*: 416 [$M+Na^+$]; HRMS: *m/z* calcd for $C_{21}H_{31}NNaO_4S^+$: 416.1866 [$M+Na^+$]; found: 416.1869.

Procedure for the preparation of 5a

Compound **5a** was prepared according to the procedure described above for **4a**. Clear oil; 100.5 mg, 81%; $[\alpha]_D^{20}=+50.0^\circ$ ($c=0.2$ in $CHCl_3$); 99% *ee* (HPLC: Chiralcel IC column; 10:90 *i*PrOH/hexane; flow rate = 0.6 mL min^{-1}; $\lambda=200$ nm; $t_R=32.80$ (major), 26.29 min (minor)); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.73$ (d, $J=8.3$ Hz, 2H), 7.31 (d, $J=8.0$ Hz, 2H), 4.83 (dd, $J=50.8$, 3.0 Hz, 1H), 4.29–4.18 (m, 1H), 3.72 (s, 3H), 3.59–3.50 (m, 1H), 2.95 (ddd, $J=16.3$, 4.4, 2.7 Hz, 1H), 2.42 (s, 3H), 2.37 (ddd, $J=16.3$, 10.8, 1.2 Hz, 1H), 2.23–2.11 (m, 2H), 1.87–1.50 (m, 2H), 1.35–1.21 (m, 10H), 0.89 ppm (t, $J=6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=170.5$, 143.7, 133.7, 129.5, 127.8, 94.1 (d, $J=179.4$ Hz), 64.2 (d, $J=23.9$ Hz), 59.6, 51.9, 39.4 (d, $J=10.1$ Hz), 36.6, 36.5 (d, $J=21.2$ Hz), 31.8, 29.4, 29.2, 25.4, 22.6, 21.5, 14.1 ppm; IR (neat): $\tilde{\nu}=2955$, 2925, 2854, 1739 (s), 1599, 1494, 1463, 1348, 1311, 1162, 1093, 1026, 978, 815, 740, 663 cm^{-1}; MS (ESI): *m/z*: 436 [$M+Na^+$]; HRMS: *m/z* calcd for $C_{21}H_{32}FNNaO_4S^+$: 436.1928 [$M+Na^+$]; found: 436.1928.

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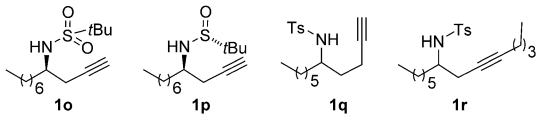
[15] For the structures of compounds **1 o–r,** see below:



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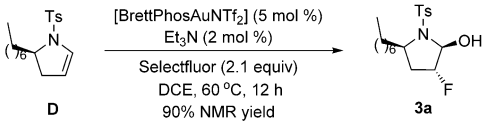

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