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Asymmetric α-Alkynylation of Piperidine *via N*-Sulfinyliminium Salts

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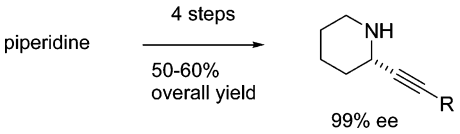


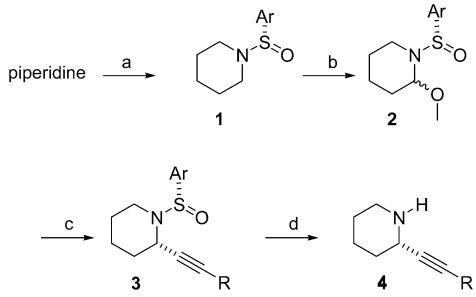
Piperidine was stereoselectively α-alkynylated in a four-step sequence made up of transformation to a chiral nonracemic *N*-sulfinylpiperidine, anodic oxidation to *N*-sulfinyliminium ion equivalent, alkynylation through addition of a mixed organoaluminum derivative, and final acidic deprotection of the sulfoxide. Overall yields are around 50%, and the diastereoselectivity of the nucleophilc addition was between 92 and 99% de, allowing isolation of the final product with 99% enantiomeric purity.

Introduction

Asymmetric substitution α to the nitrogen of amines is still a challenging synthetic problem particularly in cyclic series. Though several successes were reported,[1] there is no general method available allowing functionalization of pyrrolidine, piperidine, morpholine, etc. For example, while the carbanion of *N*-Boc-pyrrolidine is stereoselectively alkylated in the presence of sparteine, the reaction is much more problematic with piperidine.[2] It thus seems important to further develop methods for the asymmetric α-substitution of amines in general and piperidine in particular. In this context, we recently reported on the preparation of α-methoxy-*N*-sulfinylpiperidines **2** (Scheme 1) which are synthetic equivalent of *N*-sulfinyliminium ions[3] and therefore could add nucleophiles.

They were synthesized from piperidine in two steps and 50−70% overall yield *via* the anodic oxidation[4] of *N*-sulfinylpiperidine as the key step. We also already reported the addition of silyl enol ether onto methoxy derivatives **2** which furnished interesting α-functionalized piperidines with a good diastereoselectivity.[3] While interesting, the method was somewhat hampered by the formation of byproducts corresponding to the addition at the sulfur atom[5] and to the deprotonation of the iminium to enamine. In the course of this study we further investigated various nucleophiles and want to present herein

SCHEME 1. Complete Sequence of Alkynylation of Piperidine[a]



[a] Conditions and reagents: (a) MeMgBr, THF, 0 °C, then ArSOMenthyl; (b) MeOH, anodic oxidation; (c) CH_2Cl_2, TMSOTf, R-CC-$AlMe_2$, −78 °C; (d) 3 M HCl/MeOH.

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(1) See for example, (a) Wilkinson, T.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155−158. (b) Ashweek, N. J.; Brandt, P.; Coldman, I.; Gawley, R. E.; Haeffner, F.; Klein, R.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2005**, *127*, 449−457. (c) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4497−4499 and in nonasymmetric series. (d) Murahashi, S.-I.; Komiya, N.; Terai, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 6931−6933. (e) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220−14221. (f) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810−11811.

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the addition of acetylenic alanes which occurred cleanly without byproducts and with an excellent diastereoselectivity.

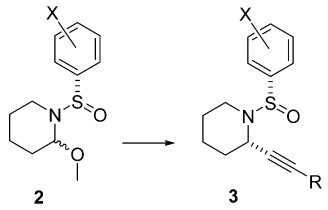
The addition of acetylides to imines is a classical method described for the preparation of enantioenriched propargyl amines and has received a great deal of attention during recent years.[5,6] The chirality can be brought through different methods including the use of chiral auxiliaries or asymmetric catalyst. The use of more electrophilic species such as iminium or *N*-acyliminium salts (or nitrones) is more scarcely represented.[7] The addition of acetylides to chiral *N*-sulfinyl imines has also been reported.[8] It is noteworthy that only *N*-*tert*-butylsulfinyl imines were studied and that the diastereoselectivity of the reaction was dependent upon the choice of the metal of the organometallic species as well as the nature of the Lewis acid.

We then envisaged the alkynylation of the α-methoxy-*N*-sulfinyl **2** as iminium equivalent species. Thanks to the easy acidic cleavage of the N−S bond, the overall sequence would provide an efficient asymmetric synthesis of α-alkynylpiperidines from piperidine (Scheme 1).

The choice of the metal of the acetylide was first addressed. Zinc acetylides have been largely used in several studies of imine alkynylation and could be prepared *in situ* according to the procedure described by Carreira.[8a,10] In our hands, the reaction of *N*-*p*-tolylsulfinylpiperidine **2a** with phenylacetylene and $Zn(OTf)_2$ showed an important formation of enamine (about 30%), together with about 30% of attempted alkynylpiperidine[11] in a modest diastereoselectivity. It was thus preferred to further investigate other organometallic species.

We turned our attention to aluminum derivatives. Alkynylalanes received much less attention[12] than the corresponding magnesium, lithium, zinc, etc., derivatives. Nevertheless, it can be anticipated that aluminum derivatives would react onto the potential iminium with high regioselectivity since it has been reported that they are prone to give 1,4-addition product[13] and hopefully without any deprotonation. With the aim to avoid the formation of enamine from α-methoxy-*N*-sulfinylpiperidines, we choose to prepare the alkynylalanes under the conditions developed by L. Micouin[14] using only catalytic amount of base (Et_3N). First experiments were done from *N*-*p*-tolylsulfinyl derivatives with phenylacetylene dimethylalane.

TABLE 1. Addition of Dimethylalkynylaluminium to α-Methoxy-*N*-sulfinyl Piperidines



2 **3**

X	R	alkynylated compound	yield,[a] %	de,[b] %
p-CH_3	Ph	**3a**	92	30
	Ph	**3a**	30[c]	30[c]
	$Cl(CH_2)_3$	**3b**	96	34
p-CF_3	$Cl(CH_2)_3$	**3c**	50	30
o-CH_3	Ph	**3d**	76	82
	$CH_3(CH_2)_2$	**3e**	74	88
o-CF_3	Ph	**3f**	93	94
	$Cl(CH_2)_3$	**3g**	71	99
	$CH_3(CH_2)_2$	**3h**	92	92
	$(CH_3)_2CH(CH_2)_2$	**3i**	86	97
	H	**3j**	82	96
	$CH_2{=}C(CH_3)$	**3k**	90	96
	1-cyclohexenyl	**3l**	91	93

[a] Isolated yields. [b] Determined by NMR and HPLC on crude reaction mixtures. [c] Using the Zn acetylide according to ref 10.

The iminium salt was generated by addition of 1.2 equiv of TMSOTf to the methoxy derivative **2a** in CH_2Cl_2 at −78 °C, prior to the addition of the dimethylalkynylaluminum compound (about 1.5 M in heptane; 2 equiv). After 30 min at low temperature, a clean and complete reaction has occurred and alkynylated piperidine was isolated in very high yield. There is no addition onto the sulfur atom, and only trace amounts of enamine was detected in a few cases. With this method in hands, we then investigated the diastereoselectivity of the reaction which, we thought, may be dependent upon the structure of the aryl group borne at the sulfur atom.

The results are reported in the Table. It can be seen that the diastereoselectivity was quite low with a *p*-tolylsulfinyl group (compounds **3a**,**b**) as well as with an electron-withdrawing group at the para position of the aromatic group (X = *p*-CF_3, compound **3c**).

It thus clearly appears from the table that the methyl or trifluoromethyl groups should be at the ortho position to have a significant effect on the diastereoselectivity. Then, in all cases, (compounds **3d**−**l**) a very high diastereoselectivity was observed, particularly if X = *o*-CF_3 since de values higher than

(5) This side reaction was known in the *N*-sulfinylimine series and was generally circumvented by the use of t-Bu- instead of *p*-tolylsulfinylimine. See (a) Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396−3397. (b) Davis, F. A.; Qu, J.; Srirajan, V.; Joseph, R.; Titus, D. D. *Heterocycles* **2002**, *58*, 251−258.

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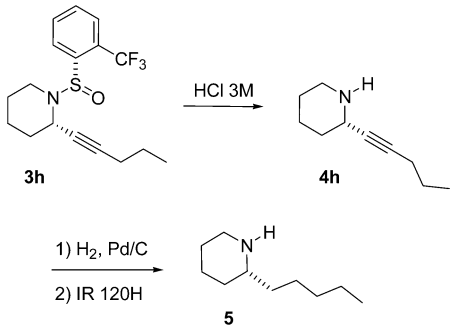
SCHEME 2. Absolute Configuration Determination



92% were observed. Several acetylenic groups could be introduced on the piperidine skeleton, and the presence of double bond or primary halide was also compatible with this simple and efficient procedure. The major isomer could be easily isolated after simple flash chromatography as a single isomer furnishing enantiopure piperidine derivatives (as proved by chiral HPLC on compounds **3d** and **3f**).

The configuration of the newly created center was determined by chemical correlation. We choose to start from piperidine derivative **3h** obtained in 92% de, and the major diastereoisomer was isolated as a pure isomer and submitted to a brief 3 M HCl/MeOH treatment to give quantitatively the deprotected piperidine **4h** (Scheme 2). Hydrogenation of the triple bond led to 2-pentylpiperidine (**5**) which optical rotation ($[\alpha]_D$ −10.4 ($CHCl_3$, *c* 0.7) indicated that the 2*R* configuration was attained (lit.[15] $[\alpha]_D$ +10.0 ($CHCl_3$, *c* 0.52) for the *S* isomer).

We eventually verified that the alkynyl group was introduced on the same face of the iminium of both *o*-tolyl- and *o*-trifluoromethylphenylsulfinyl derivatives since compound **4h** obtained from **3e** or **3h** exhibited the same sign of optical rotation ($[\alpha]_D$ −14 and −16 (MeOH, *c* 0.5), respectively). The better diastereoselectivity is probably due to the larger steric demand of the *o*-CF_3 group.

Experimental Section

General Experimental Procedure for the Synthesis of Compounds 3d−l. To a solution of methoxy-*N*-sulfinylpiperidine **2**[3] (0.2 mmol) in anhydrous dichloromethane (2 mL) was added at −78 °C trimethylsilyl trifluoromethanesulfonate 99% (0.24 mmol). After 45 min at the same temperature, the alkynylalane[14b,c] (0.4 mmol) was added and the reaction was monitored by HPLC (Exsil CN; 100 Å; 5 μm; 250 × 4.6 mm; wavelength 254 nm; flow rate 2 mL/min; in *n*-heptane/ethyl acetate or TLC in diethyl ether/*n*-heptane 7/3 and quenched by addition of 2 mL of a 2 M Rochelle's salt solution after 30 min at −78 °C. The product was extracted with dichloromethane and the organic layer washed successively with water and brine. After drying (Na_2SO_4), the organic layer was evaporated under reduced pressure and the oily residue purified by column chromatography on silica gel neutralized with triethylamine. The major diastereomer was isolated and characterized.

(*S*)-2-Phenylethynyl-1-((*S*)-toluene-2-sulfinyl)piperidine (3d). Colorless oil (0.152 mmol, 0.05 g, 76%). $[\alpha]^{22}_D$ +24.2 (*c* 1.45, MeOH). R_f = 0.43 (diethyl ether/*n*-heptane 7/3). HPLC analysis was carried out using Exsil CN (4.6 × 250 mm); 100 Å; 5 μm; *n*-heptane/ethyl acetate = 9/1; wavelength, 254 nm; flow rate 2.0 mL/min; t_r = 10.6 min. Chiralpak AD (4.6 × 250 mm); *n*-hexane/*i*-PrOH 9/ 1; 0.8 mL/min; t_r = 11.2 min; (*rac*, t_r = 11.2 min, , t_r = 12.2 min). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.43 (m, 1H); 1.67 (m, 2H); 1.90 (m, 3H); 2.42 (s, 3H); 3.13 (m, 1H); 3.38 (ddd, *J* = 12.6, 3.0, 3.0 Hz, 1H); 4.62 (t, *J* = 3.9 Hz, 1H); 7.22 (m, 1H); 7.31 (m, 3H); 7.42 (m, 4H); 7.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 18.7; 20.2; 25.9; 32.4; 41.8; 48.7; 85.7; 86.8; 122.9; 125.5; 126.2; 128.20; 128.21; 130.8; 131.1; 131.7; 136.3; 141.2. IR (neat) 3055, 2937, 2847, 2219, 1598, 1447, 1365, 1325, 1268, 1088, 1034, 916, 880. MS: *m*/*z* 346 (M + Na). Elemental Analysis: calcd. C 74.30%, H 6.50%, N 4.33%; found: C 74.81%, H 6.71%, N 4.43%.

(*S*)-2-Pent-1-ynyl-1-((*S*)-toluene-2-sulfinyl)piperidine (3e). Colorless oil (0.148 mmol, 0.043 g, 74%). $[\alpha]^{22}_D$ +57.3 (*c* 1.2, MeOH). R_f = 0.28 (diethyl ether/*n*-heptane 7/3). HPLC analysis was carried out using Exsil CN (4.6 × 250 mm); 100 Å; 5 μm; *n*-heptane: ethyl acetate = 9:1; wavelength, 254 nm; flow rate 2.0 mL/min; t_r = 7.9 min ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.99 (t, *J* = 7.2 Hz, 3H); 1.35 (m, 1H); 1.53 (m, *J* = 7.2 Hz, 2H); 1.62 (m, 3H); 1.8 (m, 2H); 2.18 (ddd, *J* = 7.2, 2.1, 2.1 Hz, 2H); 2.38 (s, 3H); 3.0 (m, 1H); 3.28 (ddd, *J* = 12.6, 2.7, 2.7 Hz, 1H); 4.4 (m, 1H); 7.22 (m, 1H); 7.39 (m, 2H); 7.95 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 13.5; 18.7; 20.1; 20.7; 22.2; 25.9; 32.7; 40.9; 48.9; 77.5; 86.2; 125.5; 126.0; 130.7; 131.0; 136.3; 141.3. IR (neat): 3048, 2930, 2237, 1716, 1451, 1332, 1275, 1095, 902. MS: *m*/*z* 312 (M + Na). Elemental Analysis: calcd. C 70.58%, H 7.96%, N 4.84%; found: C 70.42%, H 7.64%, N 4.84%.

(*S*)-2-Phenylethynyl-1-((*S*)-2-trifluoromethylbenzenesulfinyl)piperidine (3f). Colorless oil (0.186 mmol, 0.07 g, 93%). $[\alpha]^{22}_D$ +29.1 (*c* 1.1, MeOH). R_f = 0.33 (diethyl ether/*n*-heptane 6/4). HPLC analysis was carried out using Exsil CN (4.6 × 250 mm); 100 Å; 5 μm; *n*-heptane:ethyl acetate = 9:1; wavelength, 254 nm; flow rate 2.0 mL/min; t_r = 8.4 min. Chiralpak AD (4.6 × 250 mm); *n*-hexane/EtOH 95/5; 0.8 mL/min; t_r = 12.3 min; (*rac*, t_r = 11.7 min, t_r = 12.3 min). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.38 (m, 1H); 1.63 (m, 2H); 1.90 (m, 3H); 2.90 (m, 1H); 3.26 (ddd, *J* = 12.6, 2.4, 2.4 Hz, 1H); 4.72 (t, *J* = 3.6 Hz, 1H); 7.30 (m, 3H); 7.42 (m, 2H); 7.61 (m, 1H); 7.77 (m, 2H); 8.27 (d, *J* = 7.5 Hz, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 19.9, 25.3, 31.7, 40.3, 49.4, 85.9, 86.6, 121.9, 122.8, 126.6, 127.4, 127.5, 127.6, 128.1, 130.9, 131.7, 131.8. IR (neat): 2947, 2915, 2851, 2366, 1490, 1309, 1171, 1098, 1028. MS: *m*/*z* 400 (M + Na). Elemental Analysis: calcd. C 63.66%, H 4.77%, N 3.71%; found: C 63.37%, H 4.78%, N 3.63%.

(*S*)-2-(5-Chloropent-1-ynyl)-1-((*S*)-2-trifluoromethylbenzenesulfinyl)-pipe ridine (3g). Colorless oil (0.142 mmol, 0.054 g, 71%). $[\alpha]^{22}_D$ +10.9 (*c* 1.1, MeOH). R_f = 0.54 (diethyl ether/*n*-heptane 7/3). HPLC analysis was carried out using Exsil CN (4.6 × 250 mm); 100 Å; 5 μm; *n*-heptane:ethyl acetate = 9:1; wavelength, 254 nm; flow rate 2.0 mL/min; t_r = 6.2 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.25 (m, 1H); 1.63 (m, 5H); 1.94 (q, *J* = 6.6 Hz, 2H); 2.39 (ddd, *J* = 6.6, 2.4, 2.4 Hz, 2H); 2.74 (m, 1H); 3.11 (ddd, *J* = 12.3, 2.4, 2.4 Hz, 1H); 3.67 (t, *J* = 6.6 Hz, 2H); 4.49 (s, 1H); 7.61 (m, 1H); 7.74 (m, 2H); 8.20 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 16.1; 19.7; 25.1; 31.3; 31.7; 39.4; 43.7; 49.6; 78.4; 84.3; 126.7; 127.4; 127.5; 130.9; 131.8. IR (neat): 3068, 2930, 2856, 2239, 1591, 1436, 1312, 1254, 1170, 1133, 1092, 1032. MS: *m*/*z* 400 (M + Na). Elemental Analysis: calcd. C 54.04%, H 5.03%, N 3.70%; found: C 53.96%, H 5.05%, N 3.66%.

(*S*)-2-Pent-1-ynyl-1-((*S*)-2-trifluoromethylbenzenesulfinyl)piperidine (3h). Pale yellow oil (0.184 mmol, 0.063 g, 92%). $[\alpha]^{22}_D$ +46.8 (*c* 1.54, MeOH). R_f = 0.30 (diethyl ether/*n*-heptane 6/4). HPLC analysis was carried out using Exsil CN (4.6 × 250 mm); 100 Å; 5 μm; *n*-heptane:ethyl acetate = 95:5; wavelength, 254 nm; flow rate 2.0 mL/min; t_r = 9.0 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.97 (t, *J* = 6.6 Hz, 3H); 1.25 (m, 1H); 1.51 (m, 4H); 1.75 (m, 3H); 2.15 (ddd, *J* = 7.2, 2.1, 2.1 Hz, 2H); 2.74 (m, 1H); 3.14 (ddd, *J* = 12.6, 2.4, 2.4 Hz, 1H); 4.48 (s, 1H); 7.56 (m, 1H); 7.73(m, 2H); 8.20 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 13.5, 19.7, 20.7, 22.2, 25.2, 31.9, 39.5, 49.6, 77.3, 86.3, 121.9, 125.6, 126.6, 127.3, 127.4, 127.5, 127.8,

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130.8, 131.8, 143.1. IR (neat): 2937, 2863, 2244, 1593, 1439, 1377, 1174, 1133, 1101, 1029, 908. MS: *m*/*z* 366 (M + Na). Elemental Analysis: calcd. C 59.47%, H 5.83%, N 4.08%; found: C 59.23%, H 5.64%, N 4.11%.

(*S*)-2-(5-Methylhex-1-ynyl)-1-((*S*)-2-trifluoromethylbenzenesulfinyl)piperidine (3i). Colorless oil (0.172 mmol, 0.064 g, 86%). $[\alpha]^{22}_D$ +27.1 (*c* 1.9, MeOH). R_f = 0.30 (diethyl ether/*n*-heptane 6/4). HPLC analysis was carried out using Exsil CN (4.6 × 250 mm); 100 Å; 5 μm; *n*-heptane:ethyl acetate = 9:1; wavelength, 254 nm; flow rate 2.0 mL/min; t_r = 4.3 min ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.89 (d, *J* = 6.6 Hz, 3H); 1.26 (m, 1H); 1.38 (m, 2H); 1.55 (m, 2H); 1.65 (m, 1H); 1.75 (m, 3H); 2.18 (ddd, *J* = 7.5, 2.1, 2.1 Hz, 2H); 2.78 (m, 2H); 3.15 (ddd, *J* = 12.6, 2.4, 2.4 Hz, 1H); 4.48 (s, 1H); 7.60 (m, 1H); 7.74(m, 2H); 8.20 (d, *J* = 7.5 Hz, 1H) ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 16.8, 19.7, 22.2, 25.2, 27.3, 31.9, 37.7, 39.6, 49.5, 86.5, 126.6, 127.4, 127.5, 130.8, 131.8, 143.1. IR (neat): 2954, 2973, 2862, 2242, 1733, 1591, 1470, 1433, 1308, 1254, 1177, 1119, 1028, 907, 769. MS: *m*/*z* 394 (M + Na). Elemental Analysis: calcd. C 61.45%, H 6.47%, N 3.77%; found: C 61.42%, H 6.49%, N 3.61%.

(*S*)-2-Ethynyl-1-((*S*)-2-trifluoromethylbenzenesulfinyl)piperidine (3j). White solid (0.164 mmol, 0.049 g, 82%). mp 102 °C. $[\alpha]^{22}_D$ +67.5 (*c* 1.3, MeOH). R_f = 0.40 (diethyl ether/*n*-heptane 7/3). HPLC analysis was carried out using Exsil CN (4.6 × 250 mm); 100 Å; 5 μm; *n*-heptane:ethyl acetate = 9:1; wavelength, 254 nm; flow rate 2.0 mL/min; t_r = 7.7 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.26 (m, 1H); 1.58 (m, 3H); 1.83 (m, 2H); 2.41 (d, *J* = 2.4 Hz, 1H); 2.78 (m, 1H); 3.16 (ddd, *J* = 12.9, 2.4, 2.4 Hz, 1H); 4.54 (s, 1H); 7.63 (m, 1H); 7.77(m, 2H); 8.25 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 19.5, 24.9, 31.3, 39.3, 49.4, 74.1, 81.1, 126.7, 127.6, 127.7, 131.1, 131.9, 142.7. IR (neat): 3217, 2947, 2854, 2366,, 2108, 1307, 1264, 1138, 1119, 1028. MS: *m*/*z* 324 (M + Na). Elemental Analysis: calcd. C 55.81%, H 4.65%, N 4.65%; found: C 55.91%, H 4.91%, N 4.39%.

(*S*)-2-(3-Methylbut-3-en-1-ynyl)-1-((*S*)-2-trifluoromethylbenzenesulfinyl)piperidine (3k). Colorless oil (0.180 mmol, 0.061 g, 90%). $[\alpha]^{22}_D$ +26.9 (*c* 0.88, MeOH). R_f = 0.48 (diethyl ether/*n*-heptane 7/3). HPLC analysis was carried out using Exsil CN (4.6 × 250 mm); 100 Å; 5 μm; *n*-heptane:ethyl acetate = 9:1; wavelength, 254 nm; flow rate 2.0 mL/min; t_r = 4.7 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.32 (m, 1H); 1.68 (m, 5H); 1.82 (m, 3H); 2.87 (m, 1H); 3.16 (ddd, *J* = 12.9, 2.4, 2.4 Hz, 1H); 4.60 (t, 1H); 5.22 (d, 2H); 7.63 (m, 1H); 7.77(m, 2H); 8.25 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 19.5, 24.9, 31.3, 39.3, 49.4, 74.1, 81.1, 126.7, 127.6, 127.7, 131.1, 131.9, 142.7. IR (neat): 3098, 3062, 2942, 2860, 2212, 1612, 1594, 1440, 1334, 1259, 1213, 1174, 1100, 1030, 906. MS: *m*/*z* 364 (M + Na). Elemental Analysis: calcd. C 59.82%, H 5.28%, N 4.10%; found: C 59.88%, H 5.45%, N 4.04%.

(*S*)-2-Cyclohex-1-enylethynyl-1-((*S*)-2-trifluoromethylbenzenesulfinyl)piperidine (3l). Pale yellow oil (0.182 mmol, 0.069 g, 91%). $[\alpha]^{22}_D$ +31.8 (*c* 1.2, MeOH). R_f = 0.54 (diethyl ether/*n*-heptane 7/3). HPLC analysis was carried out using Exsil CN (4.6 × 250 mm); 100 Å; 5 μm; *n*-heptane:ethyl acetate = 9:1; wavelength, 254 nm; flow rate 2.0 mL/min; t_r = 4.9 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.32 (m, 2H); 1.68 (m, 5H); 1.82 (m, 3H); 2.1 (m, 4H); 2.80 (m, 1H); 3.16 (ddd, *J* = 12.9, 2.4, 2.4 Hz, 1H); 4.60 (t, 1H); 6.08 (m, 1H); 7.63 (m, 1H); 7.77(m, 2H); 8.25 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 19.7, 21.5, 22.2, 25.2, 25.5, 29.1, 31.7, 39.8, 49.7, 83.7, 87.8, 120.25, 126.6, 127.5, 130.8, 131.8, 134.8, 143.1. IR (neat): 3066, 2930, 2854, 2219, 1594, 1436, 1314, 1257, 1167, 1124, 1092, 1031, 905. MS: *m*/*z* 404 (M + Na). Elemental Analysis: calcd. C 62.99%, H 5.77%, N 3.67%; found: C 62.93%, H 5.87%, N 3.55%.

(*S*)-2-Pent-1-ynylpiperidine (4h). To a solution of **3h** (0.051 g, 0.15 mmol) in methanol (1 mL) at 0 °C was added 0.15 mL of aqueous HCl (3 N). The mixture was stirred 30 min at 0 °C and 1 h at room temperature. After removal of the solvent under reduced pressure, the residue was solubilized in 3 M HCl (2 mL). The aqueous layer was washed with Et_2O and evaporated to dryness. The product was obtained and used in the next step without purification. White solid (0.132 mmol, 0.025 g, 88%). mp 126 °C. $[\alpha]^{22}_D$ −16.7 (*c* 0.8, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.96 (t, 3H); 1.54 (m, 3H); 1.84 (m, 4H); 2.19 (m, 3H); 3.18 (m, 1H); 3.31 (m, 1H); 4.28 (s, 1H); 9.52(m, 1H); 9.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 13.5, 19.3, 20.7, 21.8, 22.0, 28.8, 41.0, 46.0, 73.2, 90.1. IR (neat): 3419, 2910, 2795, 2707, 2556, 2481, 2374, 2242. MS: *m*/*z* 152 $[(MH)\text{-}HCl]^+$.

(*R*)-2-Pentylpiperidine (5). Compound **4h** (0.025 g, 0.132 mmol) in methanol (1 mL) was hydrogenolyzed in the presence of 10% Pd/C at atmospheric pressure and room temperature for 12 h. The mixture was filtered through Celite 545, and the filtrate was concentrated in vacuo. The product was characterized without purification. White solid (0.119 mmol, 0.023 g, 90%). mp 148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.83 (t, 3H); 1.31 (m, 7H); 1.75 (m, 7H); 2.84 (m, 2H); 3.41 (m, 1H); 9.11(m, 1H); 9.39 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 13.9, 22.2, 22.4, 25.0, 28.0, 31.4, 33.3, 44.9, 57.3. $[\alpha]^{22}_D$ −10.4 (*c* 0.7, $CHCl_3$).(for the free base obtained after using Amberlite resin IR 120). $[\alpha]^{22}_D$ +10 (*c* 0.52, $CHCl_3$) (for the S configuration of the free base)[15]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **3a**−**h**, **4h**, and **5** are available free of charge via the Internet at http://pubs.acs.org.

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