DOI: 10.1002/ejoc.200901372

Broadening the Synthetic Scope of the Iron(III)-Catalyzed Aza-Prins Cyclization

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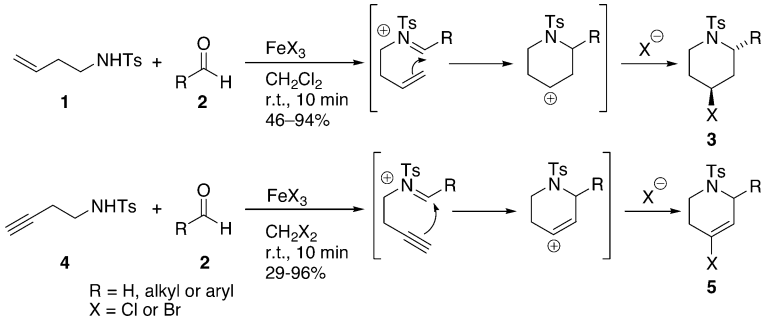
Keywords: Iron / Homogeneous catalysis / Sulfonamides / Cyclization / Heterocycles

The nature and influence of the *N*-sulfonyl group in aza-Prins cyclization and the reactivity of the six-membered aza-cycle generated has been studied. The aza-Prins cyclization of γ,δ-unsaturated amines with a tosyl group at the nitrogen atom produces 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines with a halovinyl function, extraordinarily stable to further derivatization and detosylation conditions. To modulate the reactivity of such aza-cycles, a general study of the aza-Prins cyclization reaction was performed with several sulfonamides. Ring formation occurs satisfactorily with both *N*-nosyl and *N*-mesylamines providing optimal conditions for further synthetic transformations. To exemplify the scope of this methodology, a short synthesis of the alkaloid coniine was successfully carried out.

Introduction

The Prins cyclization reaction is one of the most powerful methodologies for generating heterocycles through concomitant carbon–heteroatom and carbon–carbon bond formation, showing great potential in organic synthesis.[1] The aza-Prins cyclization is the nitrogen version of the reaction, which permits a rapid access to aza-cycles of natural and synthetic products, but it has received less attention than the oxygen version.[2] The pioneering work of Speckamp and co-workers in this field[3] opened the way to Overman and co-workers to develop an excellent methodology that has been applied in the synthesis of several natural products.[4]

Recently we described the direct aza-Prins cyclization reaction between γ,δ-unsaturated tosylamines and aldehydes in the presence of inexpensive, environmentally friendly, and stable iron(III) halides to give six-membered aza-cycles **3** and **5** in good-to-excellent yields (Scheme 1). The process is based on the consecutive generation of a γ-unsaturated iminium ion and subsequent nucleophilic attack by the unsaturated C–C bond.[5] Homoallyl(tosyl)amine (**1**) gave *trans*-2-alkyl-4-halo-1-tosylpiperidine **3** as the major isomer. In addition, the alkyne aza-Prins cyclization reaction between homopropargyl(tosyl)amine (**4**) and aldehydes gave 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines **5** as the only cyclic products.



Scheme 1. Aza-Prins cyclization of γ,δ-unsaturated tosylamines.

A further step in the optimization of the Prins cyclization reaction was the development of a catalytic version in which the stoichiometric amounts of the iron(III) halide were re-

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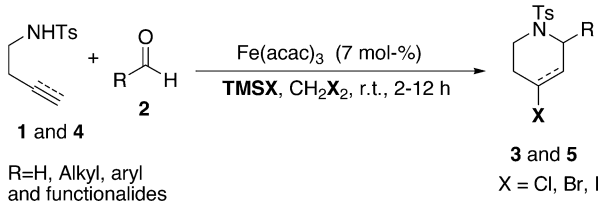
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901372.

placed. The key finding for this protocol was the catalytic effect of a combination of the iron source [FeX_3 or Fe(acac)$_3$] and TMSCl.[6] This catalytic method also allows the construction of chloro-, bromo-, and iodo-substituted heterocycles by choosing a suitable combination of the iron(III) source, the corresponding trimethylsilyl halide, and the solvent.[7] Overall, this process leads to the formation of one carbon–carbon bond, one heteroatom–carbon bond, one halogen–carbon bond, and a ring in a regioselective and efficient manner (Scheme 2).



Scheme 2. Iron-catalyzed aza-Prins cyclization of γ,δ-unsaturated tosylamines.

On the other hand, in our research directed at the development of novel antitumor drugs[8] we have determined the antiproliferative activity of a series of *trans*-2-alkyl-4-halopiperidines **3** and 2-alkyl-4-halo-1,2,5,6-tetrahydropyridines **5**. These in vitro activities were examined in the human solid tumor cell lines A2780 (ovarian cancer), SW1573 (non-small cell lung cancer), and WiDr (colon cancer). The values of the biological activities revealed that, in general, analogues of 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridine **5** are more potent than derivatives of *trans*-2-alkyl-4-halopiperidine **3**. A remarkable selectivity of the most active aza compound **7** for the resistant cell line WiDr was observed (Figure 1).

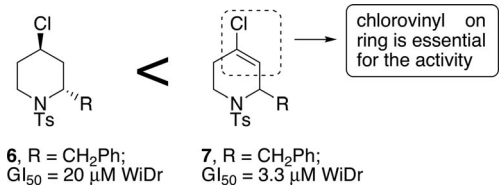
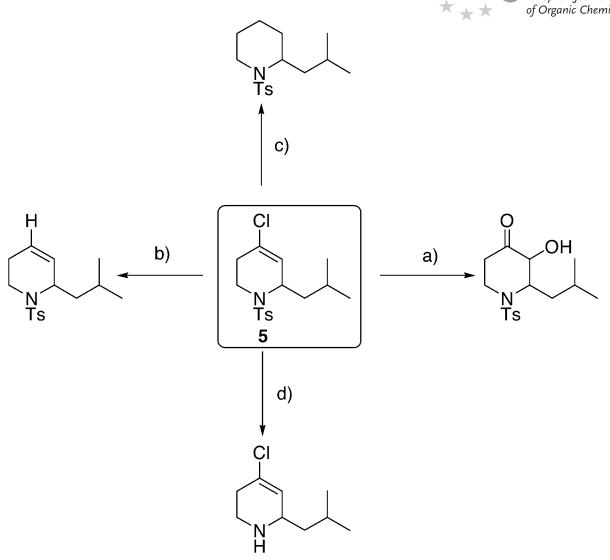


Figure 1. Structures of antiproliferative six-membered aza-cycles.

To test the reactivity of this kind of aza-cycle and with the obtention of large diverse synthetic libraries to be evaluated as bioactive compounds as a final objective,[9] we decided to derivatize this kind of heterocycle, particularly the 2-alkyl-4-halo-1,2,5,6-tetrahydropyridines **5**. Based on our previous results with six-membered oxa-cycles, we applied the strategy to the halovinyl double bond and attempted to remove the protecting tosyl group.[8a,10]

Unfortunately, all attempts at dihydroxylation and *N*-sulfonyl deprotection were fruitless.[11] Under hydrogenation and dehalogenation conditions, the chlorovinyl system was also stable. The methods used to remove the *N*-tosyl group were also fruitless (Scheme 3).



Scheme 3. Chemical stability of 2-isobutyl-4-chloro-1-tosyl-1,2,5,6-tetrahydropyridine. Reagents and conditions: a) $RuCl_3 \cdot H_2O$ (7 mol-%), $NaIO_4$, EtOAc/CH_3CN/H_2O (3:3:1), 0 °C; b) *tert*-BuLi, Et_2O; c) H_2, Pd/C, EtOAc; d) Na, naphthalene, DME, –78 °C.

The high stability of sulfonamides, although rendering them attractive candidates for general amine protection, clearly poses the conundrum of their eventual removal, usually at a late stage in a synthetic scheme. Thus, there is a widespread perception that the *N*-tosyl group is difficult to remove. In fact, this depends on the substrate type, experimental conditions (usually harsh), and the functional groups present in the molecule.[12] In our case we assumed that methods involving radical mechanisms are not compatible with the halogen groups in the aza-cycle. Moreover, we suspected that the *N*-tosyl group may have a direct influence on the reactivity of the rest of the functional groups.

In this article we describe our studies on the influence of *N*-sulfonyl groups on the aza-Prins cyclization reaction and subsequent derivatization of the six-membered ring. We used *p*-nitrobenzenesulfonyl (nosyl) and methanesulfonyl (mesyl) and compared these with our previous results obtained with the *p*-toluenesulfonyl group (tosyl). We found that the nosyl and mesyl sulfonamide groups had advantages over the tosyl group. The nosyl group led to improved selectivity of the reaction and was easily removed in the presence of the halogen and halovinyl function. The smaller mesyl group permitted aza-Prins cyclization, giving very good yields, and had a positive influence on the derivatization of the resulting aza-cycles.

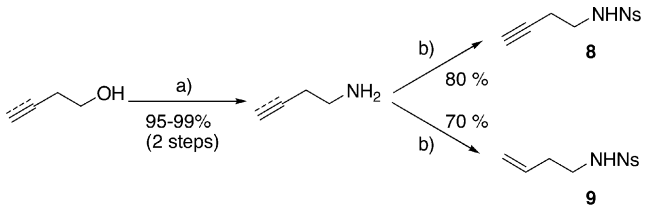
Results and Discussion

The general aim of this study was to find stable sulfonamides that could be used in the aza-Prins cyclization, that permitted the further derivatization of the six-membered aza-cycles, and that were more easily deprotected than the tosyl group.

Use of the *N*-Nosyl Group in the Aza-Prins Cyclization Reaction

Because of the inefficient conditions required for the removal of *N*-tosyl groups, we first decided to explore the replacement of the *N*-tosyl group by other more labile *N*-sulfonyl groups. We focused our efforts on *p*-nitrobenzenesulfonyl (nosyl) because its removal proceeds under much milder conditions, that is, by the attack of a thiophenolate anion at the sulfonyl *ipso* position.[13]

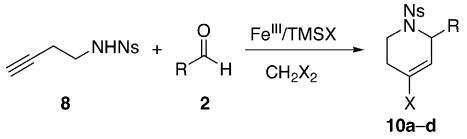
To initiate our study, we synthesized the homopropargyl- and homoallyl(nosyl)amines starting from the corresponding homopropargyl and homoallyl alcohols. The syntheses proceeded via the corresponding phthalimides, obtained by Mitsunobu reaction,[14] hydrolysis, and further sulfonylation (Scheme 4).



Scheme 4. Synthesis of γ,δ-unsaturated nosylamines. Reagents and conditions: a) i) Phthalimide, PPh_3/DEAD, THF, 0 °C, ii) $NH_2NH_2{\cdot}H_2O$, EtOH/Δ, b) NsCl/Et_3N, CH_2Cl_2.

As a model study for the optimization of the reaction conditions, we first chose the alkyne aza-Prins cyclization of homopropargyl(nosyl)amine (**8**) and isovaleraldehyde to give 2-alkyl-4-halo-1-nosyl-1,2,5,6-tetrahydropyridines **10** (Table 1, entries 1–10). We used our previously described conditions based on stoichiometric amounts of $FeCl_3$ and the catalytic systems FeX_3/TMSX or $Fe(acac)_3$/TMSX.[5,6] We found complete conversion to the desired product when an excess of aldehyde was used (Table 1, entries 4, 7, and 10). In the stoichiometric reaction an excess of FeX_3 was necessary to obtain better yields (Table 1, entries 3 vs. 4). With the FeX_3/TMSCl system, we found that it was possible to increase the yields with 1.5 equiv. of TMSCl (Table 1, entries 6 and 7), whereas with $Fe(acac)_3$/TMSCl 2.0 equiv. of TMSCl were necessary (Table 1, entry 10). With regard to catalyst loading, 15 mol-% of FeX_3 and 20 mol-% of $Fe(acac)_3$ were found to provide the best conditions (Table 1, entries 7 and 10).

Table 1. Synthesis of 2-alkyl-4-halo-1-nosyl-1,2,5,6-tetrahydropyridines from homopropargyl(nosyl)amine and aldehydes using iron(III) salts as catalysts.



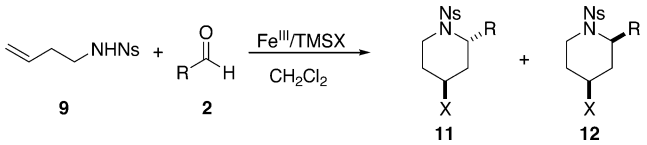
Entry	R	X	RCHO [equiv.]	FeX_3 [mol-%]	$Fe(acac)_3$ [mol-%]	TMSX [equiv.]	% Yield[a]
1	*i*Bu	Cl	1.0	100	0	0	65[b]
2	*i*Bu	Cl	1.2	100	0	0	69[b]
3	*i*Bu	Cl	1.5	100	0	0	80[b]
4	*i*Bu	Cl	**1.5**	**150**	**0**	**0**	**91**[b]
5	*i*Bu	Cl	1.0	10	0	1.0	65[b]
6	*i*Bu	Cl	1.2	10	0	1.2	70[b]
7	*i*Bu	Cl	**1.5**	**15**	**0**	**1.5**	**86**[b]
8	*i*Bu	Cl	1.0	0	10	1.0	47[b]
9	*i*Bu	Cl	1.2	0	10	1.5	50[b]
10	*i*Bu	Cl	**2.0**	**0**	**20**	**2.0**	**83**[b]
11	*i*Bu	Br	1.5	150	0	0	74[c]
12	*i*Bu	Br	1.5	15	0	1.5	97[c]
13	*i*Bu	Br	2.0	0	20	2.0	83[c]
14	**Bn**	**Cl**	**1.5**	**150**	**0**	**0**	**49**[d]
15	Bn	Cl	1.5	15	0	1.5	29[d]
16	Bn	Cl	2.0	0	20	2.0	35[d]
17	**Ph**	Cl	**1.5**	**150**	**0**	**0**	**14**[e]
18	Ph	Cl	1.5	15	0	1.5	14[e]
19	Ph	Cl	2.0	0	20	2.0	18[e]

[a] Isolated yield. [b] **10a**: R = *i*Bu, X = Cl. [c] **10b**: R = *i*Bu, X = Br. [d] **10c**: R = Ph, X = Cl. [e] **10d**: R = Ph, X = Br.

Compared with the *N*-tosyl aza-cycles, we obtained similar yields when isovaleraldehyde was used. However, 2-phenylacetaldehyde and benzaldehyde gave lower yields.[5,6]

With these results in hand, we extended our studies to homoallyl(nosyl)amine as the unsaturated amine. Table 2 summarizes the results obtained in this study.

Table 2. Cyclization of homoallyl(nosyl)amine and aldehydes using iron(III) salts as catalysts.[a]

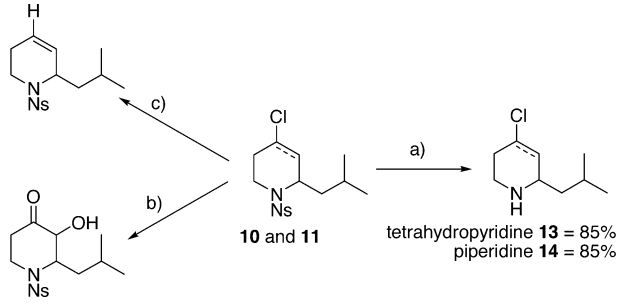


Entry	R	X	% Yield (**11**/**12**)		
			FeX_3[b]	FeX_3/TMSX[c]	$Fe(acac)_3$/TMSX[d]
a	*i*Bu	Cl	96 (>99:1)	80 (>99:1)	88 (>99:1)
b	*i*Bu	Br	84 (>99:1)	70 (>99:1)	84 (>99:1)
c	Bn	Cl	32 (90:10)	26 (90:10)	67 (90:10)
d	Ph	Cl	56 (85:15)	74 (85:15)	67 (90:10)

[a] For the best reaction conditions see the Supporting Information. [b] Reaction conditions: **9** (1.0 equiv.), **2** (1.0 equiv.), FeX_3 (1.0 equiv.), CH_2Cl_2 (0.1 M), room temp., 1 h. [c] Reaction conditions: **9** (1.0 equiv.), **2** (1.5 equiv.), FeX_3 (0.1 equiv.), TMSX (1.0 equiv.), CH_2Cl_2 (0.1 M), room temp., 2–12 h. [d] Reaction conditions: **9** (1.0 equiv.), **2** (1.0 equiv.), $Fe(acac)_3$ (0.075 equiv.), TMSX (1.0 equiv.), CH_2Cl_2 (0.1 M), room temp., 2–12 h.

With homoallyl(nosyl)amine (**9**), the three promoter systems gave similar yields and diastereoselectivity (Table 2). In all cases, the *trans* diastereomer **11** was obtained as the major stereoisomer and its stereochemistry was established by NOE experiments.[15] The stability of the γ-unsaturated iminium ion controls the stereochemical course of the alkene Prins cyclization reaction. Thus, the more stable *E* iminium intermediate led to the more stable *trans* isomer. The *Z* iminium ion becomes a more stable intermediate when R bears an aromatic ring. This fact explains the increase in the *cis* isomer when an aromatic ring is used. Interestingly, all the *trans* compounds were more stable than their corresponding *cis* isomers.[5] The best promoter system was Fe(acac)$_3$/TMSX, which worked well with both aliphatic and aromatic aldehydes. Catalyst loadings of 10 mol-% of $FeCl_3$ and 7.5 mol-% of Fe(acac)$_3$ were found to be optimal (Table 2). With the nosyl group the aza-Prins cyclization gave better diastereoselectivity but the yields were slightly lower.[16]

The removal of the *N*-nosyl group under previously reported conditions[12a] was satisfactorily performed leaving intact the halovinyl system. However, the halovinyl moiety continued to be unreactive under other derivatization conditions (Scheme 5).



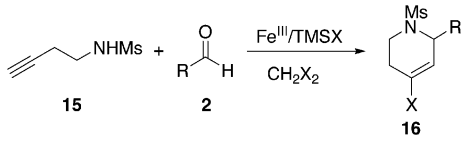
Scheme 5. Deprotection of 4-chloro-2-isobutyl-1-nosyl-1,2,5,6-tetrahydropyridine and *trans*-4-chloro-2-isobutyl-1-nosylpiperidine. Reagents and conditions: a) K_2CO_3/CH_3CN, DMSO/PhSH, 50 °C; b) [$RuCl_3 \cdot H_2O$] (7 mol-%), $NaIO_4$, EtOAc/CH_3CN/H_2O (3:3:1), 0 °C; c) *t*BuLi, Et_2O.

Use of the *N*-Mesyl Group in the Aza-Prins Cyclization Reaction

Although we succeeded in removing the *N*-nosyl group, the reactivity of the halovinyl system of the protected amine continued to be too low for practical use. Thus, we pondered the use of methanesulfonyl (mesyl) as the protecting group because of its small size and the expectation of a positive influence on the reactivity of the halovinyl system.

The γ,δ-unsaturated mesylamines were synthesized in good yields following a similar protocol to that described in Scheme 4.[17] The next step was to check the alkyne aza-Prins cyclization using *N*-(but-3-ynyl)methanesulfonamide (**15**) as the nucleophile. The results of this study are summarized in Table 3. We found that the corresponding 2-alkyl-4-halo-1-mesyl-1,2,5,6-tetrahydropyridines **16** were formed in good yields. The three promoter systems worked well giving almost the same yields as those obtained with the nosyl series.

Table 3. Synthesis of 2-alkyl-4-halo-1-mesyl-1,2,5,6-tetrahydropyridines from homopropargyl(mesyl)amine and aldehydes using iron(III) salts as catalysts.[a]



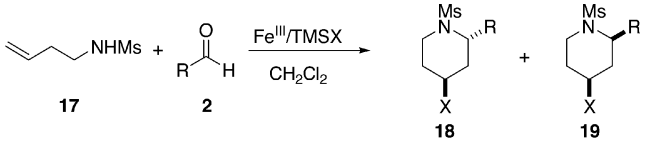
15 **2** **16**

Entry	R	X	% Yield		
			FeX_3[b]	FeX_3/TMSX[c]	Fe(acac)$_3$/TMSX[d]
a	*i*Bu	Cl	82	80	78
b	*i*Bu	Br	82	82	79
c	Bn	Cl	61	55	57
d	Ph	Cl	18	14	18

[a] For the best reaction conditions, see the Supporting Information. [b] Reaction conditions: **15** (1.0 equiv.), **2** (1.0 equiv.), FeX_3 (1.0 equiv.), CH_2Cl_2 (0.1 M), room temp., 1 h. [c] Reaction conditions: **15** (1.0 equiv.), **2** (1.0 equiv.), FeX_3 (0.1 equiv.), TMSX (1.0 equiv.), CH_2Cl_2 (0.1 M), room temp., 2–12 h. [d] Reaction conditions: **15** (1.0 equiv.), **2** (1.5 equiv.), Fe(acac)$_3$ (0.15 equiv.), TMSX (1.5 equiv.), CH_2Cl_2 (0.1 M), room temp., 2–12 h.

With *N*-(but-3-enyl)methanesulfonamide (**17**) the aza-Prins cyclization worked very well, affording as the major compound the *trans* diastereomer **18** in excellent yields. The best promoter system was FeX_3/TMSX, which gave almost quantitative yields with isovaleraldehyde and 2-phenylacetaldehyde (Table 4, entries a–c). This promoter system also worked well with aromatic aldehydes (Table 2 and Table 4, entry d). With *N*-mesylamines the yields of the aza-Prins cyclization reactions increased and the stereoselectivities decreased with respect to *N*-nosylamines (Table 2). In the case of aldehydes with an aromatic ring, the *trans*/*cis* (**18**/**19**) ratios were the same as those observed with *N*-tosyl- and *N*-nosyl-protected amines (Table 4, entries c and d).[5,6]

Table 4. Cyclization of homoallyl(mesyl)amine and aldehydes using iron(III) salts as catalysts.[a]



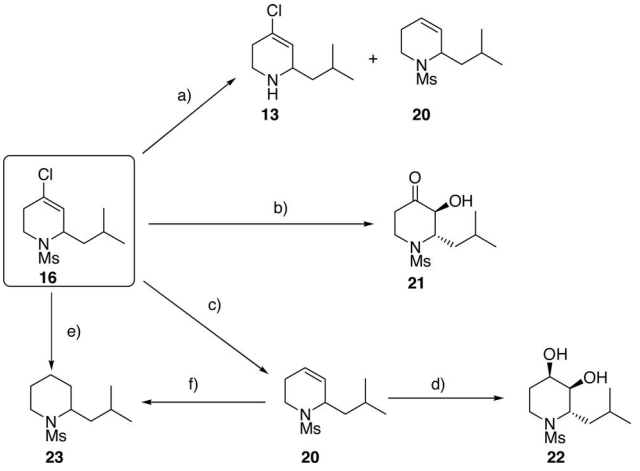
17 **2** **18** **19**

Entry	R	X	% Yield (**18**/**19**)		
			FeX_3[b]	FeX_3/TMSX[c]	Fe(acac)$_3$/TMSX[d]
a	*i*Bu	Cl	99 (90:10)	99 (90:10)	99 (88:12)
b	*i*Bu	Br	99 (90:10)	99 (85:15)	90 (87:13)
c	Bn	Cl	97 (90:10)	99 (85:15)	75 (85:15)
d	Ph	Cl	56 (85:15)	76 (85:15)	58 (85:15)

[a] For the best reaction conditions, see the Supporting Information. [b] Reaction conditions: **17** (1.0 equiv.), **2** (1.0 equiv.), FeX_3 (1.0 equiv.), CH_2Cl_2 (0.1 M), room temp., 1 h. [c] Reaction conditions: **17** (1.0 equiv.), **2** (1.0 equiv.), FeX_3 (0.1 equiv.), TMSX (1.0 equiv.), CH_2Cl_2 (0.1 M), room temp., 2–12 h. [d] Reaction conditions: **17** (1.0 equiv.), **2** (1.5 equiv.), Fe(acac)$_3$ (0.15 equiv.), TMSX (1.5 equiv.), CH_2Cl_2 (0.1 M), room temp., 2–12 h.

With these results in hand, we moved forward to explore the deprotection of the *N*-mesyl group and the derivatization of the halovinyl system.

The reductive cleavage of the *N*-mesyl group was carried out with Red-Al leading to the demesylated tetrahydropyridine **13** in 42% yield.[18] Unfortunately, under these conditions, the dehalogenated *N*-mesyltetrahydropyridine **20** was also obtained as a minor compound in 22% yield (Scheme 6). However, 6-isobutyl-1-mesyl-1,2,3,6-tetrahydropyridine (**20**) was obtained as the sole product by using $LiAlH_4$ instead of Red-Al as the reducing agent.[19] From these experiments it can be concluded that the presence of the chloro has a direct influence on the cleavage of the *N*-mesyl group. In fact, *N*-mesyl deprotection was successful when the chlorovinyl system was not present in the six-membered ring (Scheme 7).



Scheme 6. Deprotection and reactivity of the 4-chloro-2-isobutyl-1-mesyl-1,2,5,6-tetrahydropyridine. Reagents and conditions: a) Red-Al, C_7H_8, **13/20** (2:1) 64%; b) $RuCl_3{\cdot}H_2O$ (7 mol-%), $NaIO_4$, EtOAc/CH_3CN/H_2O (3:3:1), 0 °C, 75%; c) $LiAlH_4$/THF, 75%; d) OsO_4/NMO, THF/H_2O (1:1), 85%; e) $Pd(OH)_2$/C, HCO_2NH_4, MeOH, 65 °C, 96%; f) $Pd(OH)_2$/C, H_2, MeOH, 83%.

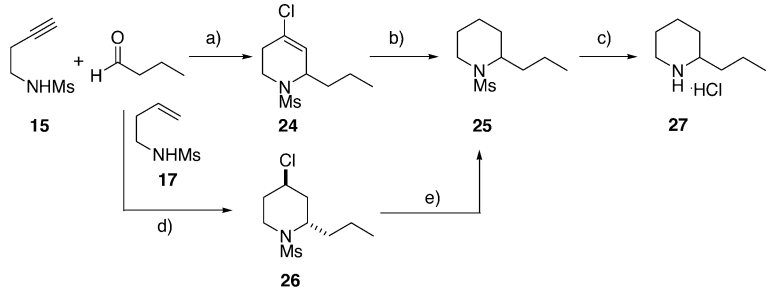
With regard to the reactivity of the halovinyl system, we first looked at dihydroxylation. When the chlorovinyl azacycle **16** was submitted to ruthenium-catalyzed *cis* hydroxylation, the *trans*-3-hydroxy-2-isobutyl-1-(methylsulfonyl)piperidin-4-one (**21**) was stereoselectively produced as the sole stereoisomer.[8a] An additional functionality was incorporated into the aza-cycle framework by osmium-catalyzed *cis* hydroxylation of the tetrahydropyridine **20**, giving the diol **22** as the sole stereoisomer. Furthermore, **20** was hydrogenated by using $Pd(OH)_2$/C as the catalyst to give the piperidine **23** in 83% yield, which was also synthesized by catalytic transfer hydrogenation of 4-chloro-6-isobutyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridine (**16**). Hydrogenation of the chlorovinyl system was possible in 96% yield by using ammonium formate as the hydrogen source.

As we can see from Scheme 6, the *N*-mesyltetrahydropyridines are probably more reactive than the corresponding *N*-tosyl and *N*-nosyl derivatives due to the smaller volume of the *N*-mesyl group compared with the *N*-tosyl and *N*-nosyl groups.[20]

Finally, to explore the synthetic scope of this methodology and concomitantly to broaden the library of potential bioactive compounds, we synthesized the racemic coniine by using the homopropargyl- and homoallyl(mesyl)amine approaches (Scheme 7). Thus, the tetrahydropyridine **24** was obtained in 85% yield from an alkyne aza-Prins cyclization reaction using $FeCl_3$ as the promoter and butanal as the aldehyde. The chlorovinyl system in **24** was hydrogenated by using $Pd(OH)_2$/C as the catalyst and ammonium formate as the hydrogen source, which gave the *N*-mesylpiperidine **25** in 90% yield. Deprotection of the *N*-mesyl group with Red-Al in toluene led to (*R*,*S*)-coniine hydrochloride (**27**) in 85% yield. The approach through the alkene aza-Prins cyclization using the catalytic system $FeCl_3$/TMSCl led to the piperidine **26** in 72% yield. The *N*-mesylpiperidine **25** was obtained in 90% yield by treatment with Bu_3SnH and AIBN.

Conclusions

We have shown the direct influence of the *N*-sulfonyl group on the reactivity of the halovinyl system of six-membered-ring aza-cycles. The halovinyl reactivity increases as the volume of the sulfonyl group decreases. Thus, the tetrahydropyridines protected with the smaller *N*-mesyl group are chemically more reactive than the corresponding *N*-tosyl or *N*-nosyl derivatives. The combination of a readily available and inexpensive iron source [$Fe(acac)_3$ or FeX_3] and TMSCl catalyzed the aza-Prins cyclization of γ,δ-unsaturated (alkyne and alkene) sulfonamides with different aldehydes. The reaction worked very well with *N*-tosyl, *N*-



Scheme 7. Synthesis of (*R*,*S*)-coniine by the aza-Prins cyclization reaction. Reagents and conditions: a) $FeCl_3$, CH_2Cl_2, 85%; b) $Pd(OH)_2$/C, HCO_2NH_4, MeOH, 65 °C, 90%; c) Red-Al, C_7H_8, 85%; d) $FeCl_3$/TMSCl, CH_2Cl_2, 72%; e) AIBN, Bu_3SnH, THF, Δ, 90%.

nosyl, and *N*-mesyl groups. With the *N*-nosyl group, the aza-Prins cyclization reaction led to better diastereoselectivity and its deprotection was possible keeping intact the halovinyl system of the aza-cycle, which is essential for biological activity. With the *N*-mesyl group, further derivatization of the six-membered ring and sulfonyl deprotection were possible.

Experimental Section

General: ^{1}H NMR spectra were recorded at 300, 400, and 500 MHz and ^{13}C NMR spectra were recorded at 75 and 100 MHz (VTU 298.0 K). Chemical shifts are reported in parts per million. The residual solvent peak was used as an internal reference. For analytical thin-layer chromatography, silica gel ready-foils were used and developed with 254 nm UV light and/or by spraying with a solution of ninhydrin (10% w/v in EtOH) or vanillin in EtOH/H_2SO_4/AcOH (15:1:1.3) and heating at 200 °C. Column chromatography was performed using silica gel (0.015–0.04 mm) and *n*-hexane/EtOAc solvent systems. All reagents were obtained from commercial sources and used without further purification. Solvents were dried and distilled before use.

General Procedure for the FeX_3-Promoted Nosyl Aza-Prins Cyclization Reactions [Homopropargyl(nosyl)amine]: Anhydrous FeX_3 (1.5 equiv.) was added in one portion to a solution of homopropargyl(nosyl)amine (1.0 equiv.) and aldehyde (1.5 equiv.) in dry CH_2X_2 (0.1 M). The reaction was stirred at room temperature until analysis by TLC showed complete formation of the product. The reaction was then quenched by the addition of water with stirring and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems).

General Procedure for the FeX_3/TMSX-Catalyzed Nosyl Aza-Prins Cyclization Reactions: Anhydrous FeX_3 (0.15 equiv.) and TMSX (1.5 equiv.) were added to a solution of homopropargyl(nosyl) amine (1.0 equiv.) in dry CH_2X_2 (0.1 M). Aldehyde (1.5 equiv.) was then added to the reaction mixture, which was stirred at room temperature until analysis by TLC showed complete formation of the product. The reaction was then quenched by the addition of water with stirring and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems).

General Procedure for the $Fe(acac)_3$/TMSX-Catalyzed Nosyl Aza-Prins Cyclization Reactions: $Fe(acac)_3$ (0.2 equiv.) and TMSX (2.0 equiv.) were added to a solution of homopropargyl(nosyl)-amine (1.0 equiv.) in dry CH_2X_2 (0.1 M). Aldehyde (2.0 equiv.) was then added to the reaction mixture, which was stirred at room temperature until analysis by TLC showed complete formation of the product. The reaction was then quenched by the addition of water with stirring and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems).

Starting Materials

***N*-(But-3-ynyl)-4-nitrobenzenesulfonamide [Homopropargyl(nosyl)-amine, 8]:** Et_3N (11.34 mL, 81 mmol) and 4-nitrobenzene-1-sulfonyl chloride (7.20 g, 32.4 mmol) were added to a solution of but-3-yn-1-amine[21] (2.85 g, 27 mmol) in CH_2Cl_2 (135 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then diluted with CH_2Cl_2 and washed with H_2O, dried with $MgSO_4$, and concentrated. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems) to give **8** (5.47 g, 21.6 mmol) in 80% yield.[22]

***N*-(But-3-enyl)-4-nitrobenzenesulfonamide [Homoallyl(nosyl)amine, 9]:** Et_3N (11.34 mL, 81 mmol) and 4-nitrobenzene-1-sulfonyl chloride (7.20 g, 32.4 mmol) were added to a solution of but-3-en-1-amine[23] (2.90 g, 27 mmol) in CH_2Cl_2 (135 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then diluted with CH_2Cl_2 and washed with H_2O, dried with $MgSO_4$, and concentrated. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems) to give **9** (4.84 g, 18.9 mmol) in 70% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.37 (d, J = 8.9 Hz, 2 H), 8.0 (d, J = 8.8 Hz, 2 H), 5.62 (m, 1 H), 5.07 (m, 2 H), 4.47 (br. s, 1 H), 3.09 (q, J = 6.5 Hz, 2 H), 2.24 (d, J = 6.7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 149.8 (C), 145.7 (C), 133.4 (CH), 128.1 (2 CH), 124.2 (2 CH), 118.5 (CH_2), 42.0 (CH_2), 33.5 (CH_2) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 3263.6, 1519.5, 1345.6, 1309.7, 1159.5 cm^{-1}. $C_{10}H_{12}N_2O_4S$ (256.28): calcd. C 46.87, H 4.72, N 10.93; found C 46.95, H 4.56, N 10.86.

***N*-(But-3-ynyl)methanesulfonamide [Homopropargyl(mesyl)amine, 15]:** Et_3N (11.34 mL, 81 mmol) and methanesulfonyl chloride (2.6 mL, 32.4 mmol) were added to a solution of but-3-yn-1-amine (2.85 g, 27 mmol) in CH_2Cl_2 (135 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then diluted with CH_2Cl_2 and washed with H_2O, dried with $MgSO_4$, and concentrated. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems) to give **15** (2.79 g, 18.9 mmol) in 70% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.95 (br. s, 1 H), 3.27 (dd, J = 6.4, 12.9 Hz, 2 H), 2.98 (s, 3 H), 2.47 (td, J = 2.7, 6.5 Hz, 2 H), 2.06 (t, J = 2.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 80.3 (C), 70.8 (C), 41.5 (CH_2), 40.6 (CH_3), 20.1 (CH_2) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 3277.3, 1307.1, 1142.9, 640.5, 516.6 cm^{-1}. $C_5H_9NO_2S$ (147.20): calcd. C 40.80, H 6.16, N 9.52; found C 40.50, H 6.25, N 9.46.

***N*-(But-3-enyl)methanesulfonamide [Homoallyl(mesyl)amine, 17]:** Et_3N (3.9 mL, 27.9 mmol) and methanesulfonyl chloride (7.2 g, 870 μL) were added to a solution of but-3-en-1-amine (1.0 g, 9.3 mmol) in CH_2Cl_2 (43 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then diluted with CH_2Cl_2 and washed with H_2O, dried with $MgSO_4$, and concentrated. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems) to give **17** (765 mg, 5.12 mmol) in 55% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.75 (m, 1 H), 5.16 (m, 2 H), 4.40 (br. s, 1 H), 3.20 (br. d, J = 6.4 Hz, 2 H), 2.95 (s, 3 H), 2.33 (d, J = 6.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 133.9 (CH), 118.1 (CH_2), 42.0 (CH_2), 40.2 (CH_3), 34.0 (CH_2) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 3289.5, 2934.1, 1641.9, 1315.8, 1150.2 cm^{-1}. $C_5H_{11}NO_2S$ (149.21): calcd. C 40.25, H 7.43, N 9.39; found C 39.99, H 7.63, N 9.19.

Final Products

4-Chloro-6-isobutyl-1-(4-nitrophenylsulfonyl)-1,2,3,6-tetrahydropyridine (10a): (Table 1, entries 1–10). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.32 (d, J = 8.7 Hz, 2 H), 7.99 (d, J = 8.7 Hz, 2 H), 5.77 (br. s, 1 H), 4.47 (br. s, 1 H), 3.92 (dd, J = 5.3, 14.8 Hz, 1 H), 3.29 (m, 1 H), 2.02 (m, 2 H), 1.69 (sept, J = 6.7 Hz, 1 H), 1.43 (m, 2 H), 0.93 (m, 6 H) ppm. ^{13}C NMR (CDCl3, 75 MHz): δ = 149.7 (C), 146.5 (C), 129.5 (C), 127.9 (2 CH), 124.8 (CH), 124.1 (2 CH), 53.0 (CH), 43.2 (CH_2), 38.5 (CH_2), 30.4 (CH_2), 24.4 (CH), 22.4 (CH_3), 22.0

(CH_3) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2951.2, 1655.7, 1527.4, 1349.3, 1317.6, 1159.5, 739.8 cm^{-1}. $C_{15}H_{19}ClN_2O_4S$ (358.84): calcd. C 50.21, H 5.34, N 7.81; found C 50.42, H 5.30, N 7.62.

4-Bromo-6-isobutyl-1-(4-nitrophenylsulfonyl)-1,2,3,6-tetrahydropyridine (10b): (Table 1, entries 11–13). ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.32 (d, J = 8.9 Hz, 2 H), 7.98 (d, J = 8.9 Hz, 2 H), 5.59 (br. s, 1 H), 4.41 (m, 1 H), 3.87 (m, 1 H), 3.30 (td, J = 6.5, 13.6 Hz, 1 H), 2.12 (m, 2 H), 1.68 (m, 1 H), 1.14 (m, 2 H), 0.91 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 149.7 (C), 146.4 (C), 129.0 (CH), 127.9 (2 CH), 124.1 (2 CH), 118.8 (C), 54.1 (CH), 43.0 (CH_2), 39.1 (CH_2), 32.5 (CH_2), 24.4 (CH), 22.4 (CH_3), 22.0 (CH_3) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 3103.5, 1650.9, 1528.9, 1343.4, 1159.5, 610.9 cm^{-1}. $C_{15}H_{19}BrN_2O_4S$ (403.29): calcd. C 44.67, H 4.75, N 6.95; found C 44.70, H 4.72, N 6.99.

6-Benzyl-4-chloro-1-(4-nitrophenylsulfonyl)-1,2,3,6-tetrahydropyridine (10c): (Table 1, entries 14–16). ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.12 (d, J = 8.9 Hz, 2 H), 7.71 (d, J = 8.9 Hz, 2 H), 7.26 (m, 3 H), 7.11 (m, 2 H), 5.79 (br. s, 1 H), 4.70 (m, 1 H), 3.86 (dd, J = 6.3, 14.8 Hz, 1 H), 3.19 (m, 1 H), 2.90 (dd, J = 1.0, 7.0 Hz, 2 H), 2.36 (m, 1 H), 2.10 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 149.6 (C), 146.0 (C), 136.2 (C), 130.5 (C), 129.2 (2 CH), 128.5 (2 CH), 127.8 (2 CH), 126.8 (CH), 124.1 (2 CH), 124.0 (CH), 55.8 (CH), 40.9 (CH_2), 39.0 (CH_2), 31.1 (CH_2) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2975.4, 1652.4, 1527.4, 1349.4, 1317.3, 1156.7 cm^{-1}. $C_{18}H_{17}ClN_2O_4S$ (392.86): calcd. C 55.03, H 4.36, N 7.13; found C 55.09, H 4.35, N 7.21.

***trans*-4-Chloro-2-isobutyl-1-(4-nitrophenylsulfonyl)piperidine (11a):** (Table 2, entry a). ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.35 (d, J = 8.8 Hz, 2 H), 8.00 (d, J = 8.8 Hz, 2 H), 4.24 (q, J = 6.9 Hz, 1 H), 4.05 (m, 1 H), 3.88 (m, 1 H), 3.10 (t, J = 13.3 Hz, 1 H), 2.04 (m, 2 H), 1.66 (m, 1 H), 1.55–1.23 (m, 4 H), 0.88 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 149.7 (C), 146.8 (C), 127.9 (2 CH), 124.3 (2 CH), 52.4 (CH), 52.0 (CH), 40.4 (CH_2), 39.1 (CH_2), 38.6 (CH_2), 35.3 (CH_2), 24.6 (CH), 22.3 (CH_3), 22.0 (CH_3) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2963.2, 1526.3, 1347.2, 1319.3, 1156.7, 746.3 cm^{-1}. $C_{15}H_{21}ClN_2O_4S$ (360.86): calcd. C 49.93, H 5.87, N 7.76; found C 50.06, H 6.01, N 7.55.

***trans*-4-Bromo-2-isobutyl-1-(4-nitrophenylsulfonyl)piperidine (11b):** (Table 2, entry b). ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.35 (d, J = 7.7 Hz, 2 H), 8.00 (d, J = 8.2 Hz, 2 H), 4.16 (br. s, 2 H), 3.82 (m, 1 H), 3.10 (t, J = 13.7 Hz, 1 H), 2.13 (br. d, J = 8.4 Hz, 2 H), 1.89 (m, 1 H), 1.67 (m, 1 H), 1.41 (m, 3 H), 0.85 (br. s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 149.7 (C), 146.7 (C), 127.9 (2 CH), 124.3 (2 CH), 53.1 (CH), 42.7 (CH), 41.2 (CH_2), 39.5 (CH_2), 38.8 (CH_2), 36.1 (CH_2), 24.5 (CH), 22.3 (CH_3), 22.1 (CH_3) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2954.3, 1529.4, 1355.3, 1311.4, 1147.0, 600.2 cm^{-1}. $C_{15}H_{21}BrN_2O_4S$ (405.31): calcd. C 44.45, H 5.22, N 6.91; found C 44.56, H 5.35, N 6.72.

***trans*-2-Benzyl-4-chloro-1-(4-nitrophenylsulfonyl)piperidine (11c):** (Table 2, entry c). ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.13 (d, J = 8.5 Hz, 2 H), 7.60 (d, J = 8.5 Hz, 2 H), 7.18 (m, 5 H), 4.52 (br. s, 1 H), 4.38 (br. d, J = 5.8 Hz, 1 H), 3.76 (br. d, J = 14.1 Hz, 1 H), 3.62 (t, J = 12.9 Hz, 1 H), 3.17 (m, 2 H), 2.04 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 149.3 (C), 146.0 (C), 138.2 (C), 129.1 (2 CH), 128.4 (2 CH), 127.8 (2 CH), 126.4 (CH), 123.9 (2 CH), 54.3 (CH), 54.1 (CH), 38.6 (CH_2), 35.9 (CH_2), 34.0 (CH_2), 33.2 (CH_2) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2927.7, 1522.3, 1344.8, 1310.1, 1156.7, 690.7 cm^{-1}. $C_{18}H_{19}ClN_2O_4S$ (394.87): calcd. C 54.75, H 4.85, N 7.09; found C 54.99, H 4.90, N 7.15.

***trans*-4-Chloro-1-(4-nitrophenylsulfonyl)-2-phenylpiperidine (11d):** (Table 2, entry d). ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.36 (d, J = 8.8 Hz, 2 H), 8.02 (d, J = 8.8 Hz, 2 H), 7.27 (m, 5 H), 5.42 (br. s, 1 H), 3.96 (m, 2 H), 3.15 (m, 1 H), 2.78 (br. d, J = 13.6 Hz, 1 H), 2.06–1.87 (m, 2 H), 1.61 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 149.7 (C), 146.3 (C), 136.4 (C), 128.9 (2 CH), 127.9 (2 CH), 127.6 (CH), 126.2 (2 CH), 124.4 (2 CH), 56.4 (CH), 51.9 (CH), 41.6 (CH_2), 38.2 (CH_2), 35.2 (CH_2) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2939.5, 1519.6, 1341.2, 1319.2, 1159.2, 567.6 cm^{-1}. $C_{17}H_{17}ClN_2O_4S$ (380.85): calcd. C 53.61, H 4.50, N 7.36; found C 53.80, H 4.65, N 7.40.

***cis*-4-Chloro-1-(4-nitrophenylsulfonyl)-2-phenylpiperidine (12d):** (Table 2, entry d). ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.17 (d, J = 9.0 Hz, 2 H), 7.68 (d, J = 9.0 Hz, 2 H), 7.13 (m, 5 H), 4.79 (t, J = 6.0 Hz, 1 H), 4.20 (sept, J = 4.1 Hz, 1 H), 4.00 (m, 1 H), 3.56 (m, 1 H), 2.51 (m, 1 H), 2.36–2.19 (m, 2 H), 2.00 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 149.4 (C), 146.0 (C), 137.8 (C), 128.0 (2 CH), 128.0 (2 CH), 127.5 (CH), 127.2 (2 CH), 123.7 (2 CH), 58.1 (CH), 53.2 (CH), 41.8 (CH_2), 39.2 (CH_2), 34.2 (CH_2) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2921.5, 1524.6, 1341.2, 1310.2, 1159.9, 601.6 cm^{-1}. $C_{17}H_{17}ClN_2O_4S$ (380.85): calcd. C 53.61, H 4.50, N 7.36; found C 53.56, H 4.68, N 7.55.

4-Chloro-6-isobutyl-1,2,3,6-tetrahydropyridine (13): PhSH (432 μL, 4.2 mmol), K_2CO_3 (800 mg, 5.6 mmol), and DMSO (0.7 mL) were added to a stirred solution of 4-chloro-6-isobutyl-1-(4-nitrophenylsulfonyl)-1,2,3,6-tetrahydropyridine (**10a**; 500 mg, 1.4 mmol) in dry MeCN (16.8 mL). The reaction mixture was stirred at 50 °C for 24 h and then the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (EtOAc/*n*-hexane solvent systems) to afford compound **13** (207 mg, 1.18 mmol, 85%). ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.75 (br. s, 1 H), 3.39 (m, 1 H), 3.16 (ddd, J = 3.1, 5.8, 12.5 Hz, 1 H), 2.91 (ddd, J = 4.8, 8.5, 12.7 Hz, 1 H), 2.40 (m, 1 H), 2.20 (m, 1 H), 1.74 (sept, J = 6.5 Hz, 1 H), 1.50 (s, 1 H), 1.30 (m, 2 H), 0.91 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 130.4 (C), 128.4 (CH), 52.6 (CH), 44.8 (CH_2), 42.6 (CH_2), 33.4 (CH_2), 24.3 (CH), 22.8 (CH_3), 22.0 (CH_3) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2955.7, 2921.5, 1604.9, 1527.5, 1048.6 cm^{-1}. $C_9H_{16}ClN$ (173.68): calcd. C 62.24, H 9.29, N 8.06; found C 62.25, H 9.18, N 8.13.

***trans*-4-Chloro-2-isobutylpiperidine (14):** PhSH (432 μL, 4.2 mmol), K_2CO_3 (800 mg, 5.6 mmol), and DMSO (0.7 mL) were added to a stirred solution of *trans*-4-chloro-2-isobutyl-1-(4-nitrophenylsulfonyl)piperidine (**11**; 500 mg, 1.39 mmol) in dry MeCN (16.8 mL). The reaction mixture was stirred at 50 °C for 24 h and then the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (EtOAc/*n*-hexane solvent systems) to afford compound **14** (207 mg, 1.18 mmol, 85%). ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.53 (br. s, 1 H), 3.12 (m, 1 H), 4.05 (m, 1 H), 2.91 (dt, J = 3.3, 12.1 Hz, 1 H), 2.05 (br. s, 1 H), 1.92 (m, 3 H), 1.56 (m, 2 H), 1.22 (m, 2 H), 0.90 (s, 3 H), 0.88 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 57.9 (CH), 47.7 (CH), 45.3 (CH_2), 40.5 (CH_2), 40.3 (CH_2), 33.9 (CH_2), 24.0 (CH), 22.8 (CH_3), 22.2 (CH_3) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 3409.2, 2958.8, 2869.9, 1628.9, 1022.7 cm^{-1}. $C_9H_{18}ClN$ (175.70): calcd. C 61.52, H 10.33, N 7.97; found C 61.66, H 10.20, N 7.99.

4-Chloro-6-isobutyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridine (16a): (Table 3, entry a). ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.87 (br. s, 1 H), 4.26 (br. s, 1 H), 3.89 (dd, J = 6.4, 14.9 Hz, 1 H), 3.25 (br. t, J = 12.2 Hz, 1 H), 2.84 (s, 3 H), 2.59 (m, 1 H), 2.19 (br. d, J = 17.9 Hz, 1 H), 1.71 (m, 1 H), 1.49 (m, 1 H), 1.36 (m, 1 H), 0.92 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 129.8 (C), 125.7 (CH), 52.3 (CH), 43.1 (CH_2), 39.9 (CH_3), 38.3 (CH_2), 31.0 (CH_2), 24.4 (CH), 22.5 (CH_3), 22.0 (CH_3) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ =

2931.9, 1659.2, 1326.9, 1150.4, 775.0, 611.4 cm^{-1}. $C_{10}H_{18}ClNO_2S$ (251.77): calcd. C 47.70, H 7.21, N 5.56; found C 47.71, H 7.37, N 5.56.

4-Bromo-6-isobutyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridine (16b): (Table 3, entry b). ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.10 (br. s, 1 H), 4.20 (br. s, 1 H), 3.83 (dd, J = 6.2, 14.7 Hz, 1 H), 3.26 (br. t, J = 12.4 Hz, 1 H), 2.83 (s, 3 H), 2.68 (m, 1 H), 2.32 (m, 1 H), 1.70 (m, 1 H), 1.48 (m, 1 H), 1.35 (m, 1 H), 0.92 (s, 3 H), 0.90 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 129.7 (CH), 118.9 (C), 53.3 (CH), 42.9 (CH_2), 39.8 (CH_3), 38.9 (CH_2), 33.1 (CH_2), 24.3 (CH), 22.5 (CH_3), 21.9 (CH_3) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2953.7, 1658.2, 1329.36, 1147.5, 619.5 cm^{-1}. $C_{10}H_{18}BrNO_2S$ (296.22): calcd. C 40.55, H 6.12, N 4.73; found C 40.65, H 6.29, N 4.74.

6-Benzyl-4-chloro-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridine (16c): (Table 3, entry c). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.30–7.19 (m, 5 H), 5.84 (br. s, 1 H), 4.54 (br. s, 1 H), 3.86 (dd, J = 5.3, 13.9 Hz, 1 H), 3.19 (m, 1 H), 2.87 (m, 2 H), 2.63 (m, 1 H), 2.41 (s, 3 H), 2.19 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 136.9 (C), 130.7 (C), 129.3 (2 CH), 128.4 (2 CH), 126.8 (CH), 124.5 (CH), 55.7 (CH), 40.6 (CH_2), 39.9 (CH_3), 38.7 (CH_2), 31.8 (CH_2) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2937.6, 1646.5, 1329.4, 1148.4, 678.6 cm^{-1}. $C_{13}H_{16}ClNO_2S$ (285.79): calcd. C 54.63, H 5.64, N 4.90; found C 54.58, H 5.73, N 4.75.

4-Chloro-1-(methylsulfonyl)-6-phenyl-1,2,3,6-tetrahydropyridine (16d): (Table 3, entry d). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.38 (m, 5 H), 6.04 (br. s, 1 H), 5.47 (br. s, 1 H), 3.81 (m, 1 H), 3.19 (m, 1 H), 2.78 (m, 1 H), 2.62 (m, 3 H), 2.37 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 137.5 (C), 131.2 (C), 128.6 (2 CH), 128.4 (CH), 128.1 (2 CH), 123.2 (CH), 56.7 (CH), 39.4 (CH_3), 38.4 (CH_2), 31.8 (CH_2) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2945.2, 1660.5, 1339.4, 1150.8, 554.6 cm^{-1}. $C_{12}H_{14}ClNO_2S$ (271.76): calcd. C 53.03, H 5.19, N 5.15; found C 53.13, H 5.29, N 5.15.

***trans*-4-Chloro-2-isobutyl-1-(methylsulfonyl)piperidine (18a):** (Table 4, entry a). ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.09 (m, 2 H), 3.75 (br. d, J = 11.7 Hz, 1 H), 3.04 (br. t, J = 2.7, 15.0 Hz, 1 H), 2.86 (s, 3 H), 2.10 (t, J = 12.7 Hz, 2 H), 1.83 (m, 2 H), 1.54 (m, 2 H), 1.31 (m, 1 H), 0.90 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 52.7 (CH), 51.7 (CH), 40.6 (CH_3), 39.9 (CH_2), 39.2 (CH_2), 39.1 (CH_2), 35.9 (CH_2), 24.6 (CH), 22.4 (CH_3), 21.9 (CH_3) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2954.5, 1326.2, 1152.3, 785.3, 567.5 cm^{-1}. $C_{10}H_{20}ClNO_2S$ (253.79): calcd. C 47.33, H 7.94, N 5.52; found C 47.34, H 8.22, N 5.53.

***cis*-4-Chloro-2-isobutyl-1-(methylsulfonyl)piperidine (19a):** (Table 4, entry a). ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.49 (m, 1 H), 4.09 (q, J = 6.7 Hz, 1 H), 3.62 (br. d, J = 13.4 Hz, 1 H), 3.47 (br. t, J = 2.5, 12.1 Hz, 1 H), 2.88 (s, 3 H), 2.23–1.57 (m, 7 H), 0.93 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.4 (CH), 50.1 (CH), 41.1 (CH_2), 40.5 (CH_3), 35.4 (CH_2), 34.4 (CH_2), 33.3 (CH_2), 25.1 (CH), 22.3 (CH_2), 22.0 (CH_2) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2950.5, 1332.2, 1149.3, 788.3, 565.5 cm^{-1}. $C_{10}H_{20}ClNO_2S$ (253.79): calcd. C 47.33, H 7.94, N 5.52; found C 47.53, H 7.84, N 5.72.

***trans*-4-Bromo-2-isobutyl-1-(methylsulfonyl)piperidine (18b):** (Table 4, entry b). ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.23 (m, 1 H), 4.08 (br. s, 1 H), 3.70 (br. d, J = 14.5 Hz, 1 H), 3.05 (m, 1 H), 2.87 (s, 3 H), 2.25–1.87 (m, 4 H), 1.55 (m, 2 H), 1.33 (m, 1 H), 0.90 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 52.5 (CH), 43.6 (CH), 40.8 (CH_2), 40.7 (CH_3), 40.1 (CH_2), 38.9 (CH_2), 36.7 (CH_2), 24.6 (CH), 22.4 (CH_3), 22.0 (CH_3) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2944.5, 1326.2, 1147.4, 665.0, 539.9 cm^{-1}. $C_{10}H_{20}BrNO_2S$ (298.24): calcd. C 40.27, H 6.76, N 4.70; found C 40.41, H 7.00, N 4.72.

***trans*-2-Benzyl-4-chloro-1-(methylsulfonyl)piperidine (18c):** (Table 4, entry c). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.26 (m, 5 H), 4.40 (br. s, 1 H), 4.26 (m, 1 H), 3.86 (br. d, J = 12.8 Hz, 1 H), 3.12 (m, 1 H), 2.95 (m, 1 H), 2.82 (m, 1 H), 2.22 (m, 5 H), 1.98 (m, 1 H), 1.86 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 137.7 (C), 128.9 (2 CH), 128.6 (2 CH), 126.8 (CH), 55.8 (CH), 52.6 (CH), 40.0 (CH_2), 40.0 (CH_3), 39.0 (CH_2), 36.7 (CH_2), 36.4 (CH_2) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2915.2, 1449.3, 1328.6, 1145.3, 743.6, 571.2 cm^{-1}. $C_{13}H_{18}ClNO_2S$ (287.81): calcd. C 54.25, H 6.30, N 4.87; found C 54.23, H 6.39, N 4.61.

***trans*-4-Chloro-1-(methylsulfonyl)-2-phenylpiperidine (18d):** (Table 4, entry d). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.34 (m, 5 H), 5.33 (br. s, 1 H), 4.00 (m, 1 H), 3.90 (br. d, J = 14.6 Hz, 1 H), 3.09 (m, 1 H), 2.96 (s, 3 H), 2.87 (br. d, J = 13.6 Hz, 1 H), 2.17 (m, 2 H), 1.89 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 137.1 (C), 128.9 (2 CH), 127.4 (CH), 126.3 (2 CH), 55.8 (CH), 52.4 (CH), 41.1 (CH_2), 40.8 (CH_3), 38.6 (CH_2), 35.8 (CH_2) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2869.5, 1449.3, 1323.8, 1141.6, 784.2, 706.4 cm^{-1}. $C_{12}H_{16}ClNO_2S$ (273.78): calcd. C 52.64, H 5.89, N 5.12; found C 53.00, H 6.09, N 5.18.

6-Isobutyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridine (20): 4-Chloro-6-isobutyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridine (**16**; 100 mg, 0.39 mmol) was added to a stirred solution of $LiAlH_4$ (18 mg, 0.47 mmol) in dry THF (0.5 mL) at room temperature. The reaction mixture was stirred until TLC showed complete conversion of the substrate and then quenched by the addition of water (carefully added). $MgSO_4$ was then added. The reaction mixture was filtered through a Celite pad and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica gel column chromatography (EtOAc/*n*-hexane solvent systems) to afford compound **20** (63 mg, 0.29 mmol, 75%). ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.83 (m, 1 H), 5.74 (m, 1 H), 4.14 (s, 1 H), 3.84 (dd, J = 6.4, 14.6 Hz, 1 H), 3.20 (m, 1 H), 2.84 (s, 3 H), 2.31 (m, 1 H), 1.97 (m, 1 H), 1.77 (sept, J = 6.6 Hz, 1 H), 1.52 (m, 1 H), 1.37 (m, 1 H), 0.94 (d, J = 6.4 Hz, 3 H), 0.93 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 128.6 (CH), 124.5 (CH), 51.4 (CH), 43.4 (CH_2), 39.6 (CH_3), 37.6 (CH_2), 24.3 (CH), 23.2 (CH_2), 22.6 (CH_3), 22.0 (CH_3) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2934.2, 1645.3, 1334.4, 1155.9, 916.9 cm^{-1}. $C_{10}H_{19}NO_2S$ (217.33): calcd. C 55.27, H 8.81, N 6.44; found C 55.30, H 8.80, N 6.47.

(2*SR*,3*SR*,4*RR*)-2-Isobutyl-1-(methylsulfonyl)piperidine-3,4-diol (22): *N*-Methylmorpholine *N*-oxide (NMO; 191 mg, 1.41 mmol) and OsO_4 (cat.) were added to a stirred solution of 6-isobutyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridine (**20**; 100 mg, 0.47 mmol) in THF (1.5 mL) and H_2O (1.5 mL) at room temperature. The reaction mixture was stirred until TLC showed complete conversion of the substrate and then quenched by the addition of $Na_2S_2O_4$ and diluted with AcOEt. The mixture was dried with $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (EtOAc/*n*-hexane solvent systems) to afford compound **22** (100 mg, 0.40 mmol, 85%). ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.16 (m, 1 H), 3.86 (m, 1 H), 3.74 (m, 2 H), 3.06 (m, 4 H), 2.74 (br. s, 1 H), 2.10 (br. s, 1 H), 1.82 (m, 1 H), 1.68 (m, 2 H), 1.52 (m, 1 H), 1.20 (m, 1 H), 0.93 (d, J = 6.0 Hz, 3 H), 0.92 (d, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 70.4 (CH), 66.2 (CH), 57.3 (CH), 40.3 (CH_3), 38.8 (CH_2), 37.5 (CH_2), 27.6 (CH_2), 24.4 (CH), 23.0 (CH_3), 21.6 (CH_3) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 3470.6, 2956.2, 2932.6, 1308.7, 1145.2 cm^{-1}. $C_{10}H_{21}NO_4S$ (251.34): calcd. C 47.79, H 8.42, N 5.57; found C 47.65, H 8.37, N 5.44.

2-Isobutyl-1-(methylsulfonyl)piperidine (23): $Pd(OH)_2/C$ (20%, 28 mg, 0.04 mmol) and HCO_2NH_4 (500 mg, 7.9 mmol) were added to a stirred solution of 4-chloro-6-isobutyl-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridine (**16**; 100 mg, 0.395 mmol) in dry MeOH

(3.9 mL) at room temperature. The reaction mixture was stirred at 65 °C for 14 h. Then it was allowed to cool down to room temperature and the mixture was diluted with AcOEt (5 mL), filtered, and the solvent removed under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (EtOAc/*n*-hexane solvent systems) to afford compound **23** (83 mg, 0.38 mmol, 96%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.05 (m, 1 H), 3.65 (br. d, J = 13.7 Hz, 1 H), 3.01 (t, J = 12.7 Hz, 1 H), 2.85 (s, 3 H), 1.60 (m, 8 H), 1.36 (m, 1 H), 0.92 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 50.6 (CH), 40.5 (CH_3), 40.1 (CH_2), 38.4 (CH_2), 28.2 (CH_2), 25.0 (CH_2), 24.6 (CH), 22.4 (CH_3), 22.3 (CH_3) 18.3 (CH_2) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2941.6, 2872.2, 1326.4, 1145.2, 773.2 cm^{-1}. $C_{10}H_{21}NO_2S$ (219.34): calcd. C 54.76, H 9.65, N 6.39; found C 54.70, H 9.63, N 6.43.

4-Chloro-1-(methylsulfonyl)-6-propyl-1,2,3,6-tetrahydropyridine (24): Anhydrous $FeCl_3$ (1.47 g, 9.05 mmol) was added in one portion to a solution of homopropargyl(mesyl)amine (1.3 g, 9.05 mmol) and butyraldehyde (650 mg, 9.05 mmol) in dry CH_2Cl_2 (0.1 M). The reaction mixture was stirred at room temperature until analysis by TLC showed complete formation of the product. The reaction mixture was then quenched by the addition of water with stirring and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems) to give **24** (1.83 g, 7.69 mmol) in 85% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.90 (br. s, 1 H), 4.20 (s, 1 H), 3.91 (dd, J = 4.7, 11.1 Hz, 1 H), 3.25 (m, 1 H), 2.85 (s, 3 H), 2.60 (m, 1 H), 2.20 (dd, J = 3.5, 13.4 Hz, 1 H), 1.55 (m, 2 H), 1.43 (m, 2 H), 0.93 (t, J = 2.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 129.9 (C), 125.5 (CH), 54.1 (CH), 40.0 (CH_3), 39.7 (CH_2), 36.5 (CH_2), 31.3 (CH_2), 19.3 (CH_2), 13.7 (CH_3) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2956.2, 1652.3, 1327.4, 1150.9, 785.5 cm^{-1}. $C_9H_{16}ClNO_2S$ (237.75): calcd. C 45.47, H 6.78, N 5.89; found C 45.48, H 6.74, N 5.84.

1-(Methylsulfonyl)-2-propylpiperidine (25) (24 as Starting Material): $Pd(OH)_2$/C (20%, 516 mg, 0.74 mmol) and HCO_2NH_4 (39.4 g, 147.4 mmol) were added to a stirred solution of 4-chloro-1-(methylsulfonyl)-6-propyl-1,2,3,6-tetrahydropyridine (**24**; 1.75 g, 7.37 mmol) in dry MeOH (74 mL) at room temperature. The reaction mixture was stirred at 65 °C for 14 h. Then it was allowed to cool to room temperature and the mixture was diluted with AcOEt (90 mL), filtered, and the solvent removed under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (EtOAc/*n*-hexane solvent systems) to afford compound **25** (1.36 g, 6.63 mmol, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.94 (br. s, 1 H), 3.65 (br. d, J = 14.2 Hz, 1 H), 2.99 (t, J = 13.0 Hz, 1 H), 2.84 (s, 3 H), 1.61 (m, 6 H), 1.48 (m, 2 H), 1.32 (m, 2 H), 0.91 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 52.6 (CH), 40.7 (CH), 40.4 (CH_2), 31.8 (CH_2), 28.2 (CH_2), 25.2 (CH_2), 19.7 (CH_2), 18.5 (CH_2) 13.9 (CH_3) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2941.8, 2868.8, 1356.9, 1156.8, 775.8 cm^{-1}. $C_9H_{19}NO_2S$ (205.32): calcd. C 52.65, H 9.33, N 6.82; found C 52.64, H 9.32, N 6.89.

***trans*-4-Chloro-1-(methylsulfonyl)-2-propylpiperidine (26):** Anhydrous FeX_3 (10.9 mg, 0.07 mmol) and TMSCl (72.8 mg, 0.67 mmol) were added to a solution of homoallyl(mesyl)amine (100 mg, 0.67 mmol) in dry CH_2Cl_2 (0.1 M). Butyraldehyde (72.5 mg, 1.01 mmol) was then added to the reaction mixture, which was stirred at room temperature until analysis by TLC showed complete formation of the product. The reaction was then quenched by the addition of water with stirring and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems) to afford compound **26** (115.7 mg, 0.48 mmol, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.14 (m, 2 H), 3.83 (br. d, J = 12.4 Hz, 1 H), 3.09 (t, J = 12.8 Hz, 1 H), 2.92 (s, 3 H), 2.18 (m, 2 H), 1.94 (dt, J = 5.2, 12.8 Hz, 1 H), 1.81 (dq, J = 4.9, 12.8 Hz, 1 H), 1.65 (m, 1 H), 1.50 (m, 1 H), 1.38 (m, 2 H), 0.96 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.8 (CH), 52.8 (CH), 40.9 (CH_3), 40.1 (CH_2), 39.2 (CH_2), 36.2 (CH_2), 32.6 (CH_2), 19.7 (CH_2), 13.7 (CH_3) ppm. FTIR ($CHCl_3$): $\tilde{\nu}$ = 2960.6, 1327.7, 1149.8, 670.1, 537.3 cm^{-1}. $C_9H_{18}ClNO_2S$ (239.76): calcd. C 45.08, H 7.57, N 5.84; found C 45.40, H 7.18, N 6.20.

1-(Methylsulfonyl)-2-propylpiperidine (25) (26 as Starting Material): α,α′-Azoisobutyronitrile (AIBN) (13 mg, 0.08 mmol) and tributyltin hydride (210 μL, 0.78 mmol) were added to a stirred solution of 4-chloro-2-propyl-1-(methylsulfonyl)piperidine (**26**; 94 mg, 0.39 mmol) in dry toluene (4 mL) at room temperature. The reaction mixture was heated at reflux for 3 h. Then it was allowed to cool to room temperature, and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography (EtOAc/*n*-hexane solvent systems) to afford compound **25** (73 mg, 0.35 mmol, 90%).

2-Propylpiperidine (*RS*-Coniine, 27): Red-Al (3.5 M in toluene, 2.4 mL, 7.3 mmol) was added to a stirred solution of 1-(methylsulfonyl)-2-propylpiperidine (**25**; 300 mg, 1.46 mmol) in toluene (1.5 mL) at room temperature. The reaction mixture was stirred until TLC showed complete conversion of the substrate and then it was quenched by the addition of water (carefully added) and diluted with diethyl ether (5 mL). Then HCl (5%) was added and the water layer was separated. NaOH (5%) and diethyl ether were added to this layer. The organic layer was separated and dried with $MgSO_4$ and the solvent was removed under reduced pressure. This alkaloid **27** (203 mg, 1.24 mmol, 85%) was isolated as the hydrochloride salt.[24]

Supporting Information (see also the footnote on the first page of this article): Optimization tables, ^{1}H and ^{13}C NMR spectra for the homoallyl and homopropargyl sulfonamides **8**, **9**, **15**, and **17** and the compounds of Tables 1–4 as well as for compounds **13**, **14** and **20**–**25**.

Acknowledgments

This research was supported by the Ministerio de Ciencia e Innovación (MICINN) of Spain, co-financed by the European Regional Development Fund (Project CTQ2008-06806-C02-01/BQU), the Ministerio de Sanidad y Consumo (MSC) (Projects RTICC RD06/0020/1046 and RD06/0020/0041), the Agencia Canaria de Investigación, Innovación y Sociedad de la Información (ACIISI) of the Canary Islands (Project PI 2007/022), the Fundación Canaria de Investigación y Salud (FUNCIS) (Grant REDESFAC PI 01/06), the Consejo Superior de Investigaciones Científicas (CSIC) (Project PIE 200880I032) and the Fundación Instituto Canario de Investigación del Cáncer (FICIC) (Grant-G.I. No. 08/2007). R. M. C. thanks the Ministerio de Educación y Ciencia (MEC) for a predoctoral fellowship. G. V. thanks the Agencia Nacional de investigación e Innovación (ANII) of Uruguay for a predoctoral fellowship. M. P. was supported by the Programme Alban, the European Union Programme of High Level Scholarships for Latin America (scholarship no. E07D402567AR).

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Received: November 26, 2009
Published Online: March 9, 2010

