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Influence of Quaternization or Coordination of Nitrogen with a Lewis Acid upon the Diastereoselectivity of 5-*exo* Ring Closure of β-Aminoalkyl Radicals

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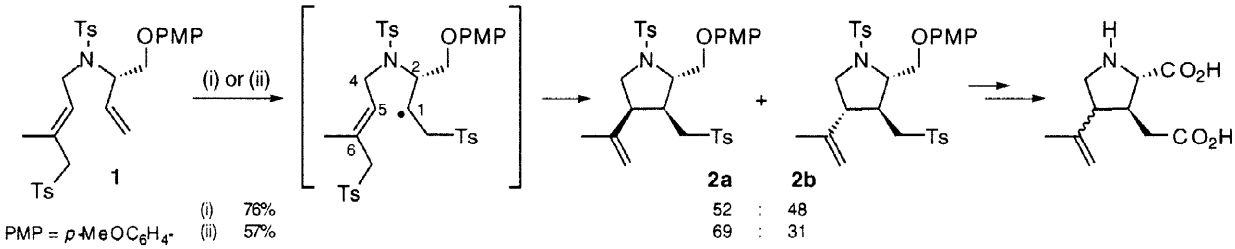
Abstract : Two methodologies, likely to enhance the diastereoselectivity of sulfonyl radical mediated cyclization of dienes **8** and **11**, were investigated. Quaternization provided the expected result whatever the nature of the radical accepting double bond, so did complexation of **11** with BF_3 or $AlMe_3$. A more strongly coordinating reagent like BH_3 was necessary to improve selectivity in the case of **8**.

Introduction

During the course of our studies on sulfonyl radical mediated cyclization of 4-aza-1,6-dienes, we investigated the rearrangement of allyl sulfone **1** as a potential route to kainoids (Scheme 1).[1] Although this process was very convenient to build in one step the properly substituted pyrrolidine, it suffered from a rather low degree of diastereoselectivity. Focusing on the 5-*exo* ring closure, it is noteworthy that whereas 1,2-stereocontrol is complete, the diastereomeric excess (d.e.) resulting from 1,5-stereocontrol is only 38% at room temperature.

Scheme 1



(i) : TsSePh (0.15 equiv.), benzene, 80 °C ; (ii) TsSePh (0.15 equiv.) benzene, hv, 19 °C.

With the aim of improving the diastereoselectivity, we have examined, using simple model substrates, the ability of two methodologies to provide the expected result. The first strategy is based on nitrogen quaternization, the second one consists of complexing nitrogen with a Lewis acid.

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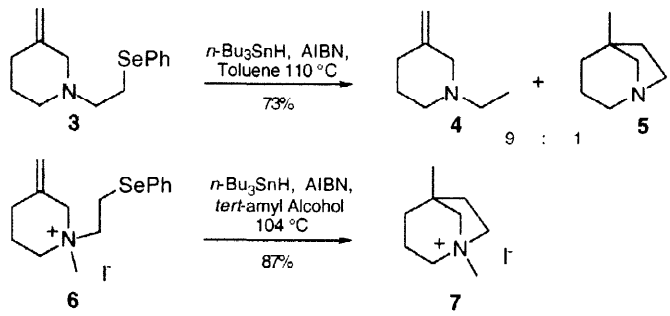
We report in this article how substrates behaved depending on the substitution of the radical accepting double bond.[2]

Cyclization of quaternary ammonium salts

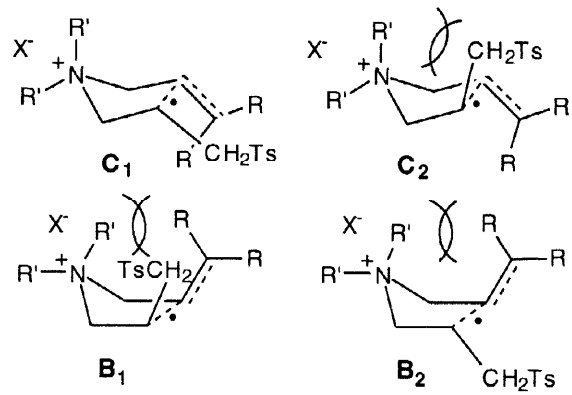
In recent studies, nitrogen quaternization has been used to increase the rate of 5-*exo* and 6-*endo* cyclizations of α- and β-aminoalkylradicals.[3,4] As shown in Scheme 2, the reduction of **3** proceeded essentially without cyclization, on the other hand, the corresponding ammonium salt **6** led to **7** as the unique product in 87% yield.[4]

Scheme 2



Because of the Thorpe-Ingold effect, quaternization affects the rate of 5-*exo* ring closure. We reasoned that quaternization should also influence the relative contribution of chair- and boat like conformers in the transition state (Figure 1) and consequently modify the diastereomeric ratio.

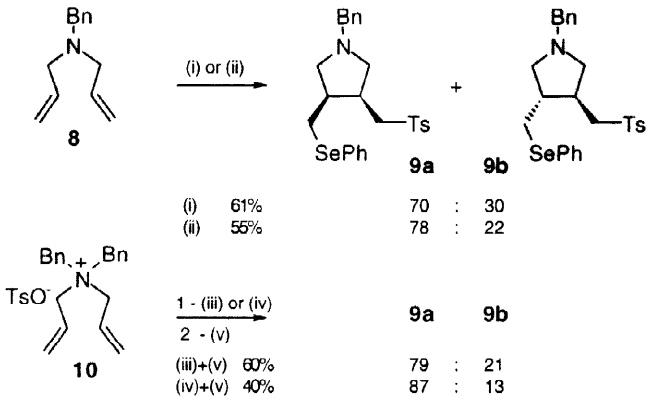
Figure 1



The extra substituent on nitrogen should strongly destabilize not only the boat conformers but also the chair conformer C_2 (due to 1,3-diaxial interactions), thus favouring the formation of the *cis* product through C_1.

As expected, a significant increase in d.e. (18%) compared to the parent amine **8** was observed for the addition of TsSePh to **10** (Scheme 3).[5] Dequaternization was effected through reduction with $NaBH_4$.[6] The two-step formation of pyrrolidines **9a** and **9b** proceeded essentially with the same yield as the cyclization of **8**, which indicated that the rate of ring closure was significantly enhanced.

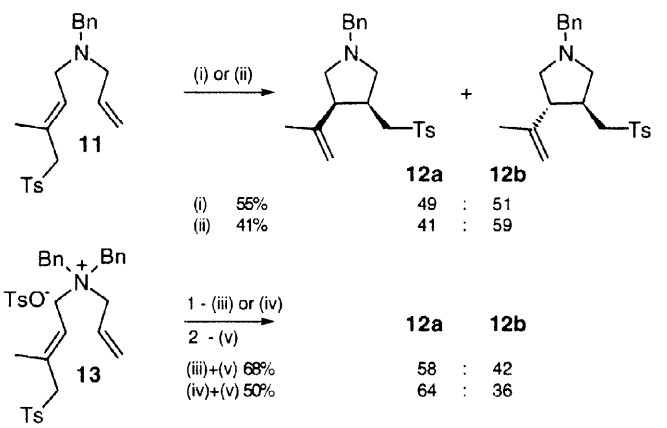
Scheme 3



(i) TsSePh (1 equiv.), benzene, 80 °C ; (ii) TsSePh (1 equiv.) benzene, hv, 19 °C;
(iii) TsSePh (1 equiv.), CH_3CN, 80 °C; (iv) TsSePh (1 equiv.) CH_3CN, hv, 19 °C;
(v) $NaBH_4$, isopropyl alcohol .

As depicted in Scheme 4, the ammonium salt **13** derived from **11** behave similarly. It is interesting to note that the cyclization of the parent amine gave very poor stereoselectivity (8% d.e. at room temperature) in favour of the *trans* isomer (**12b**), whereas the cyclization of **13** resulted in a 28% d.e. in favour of the *cis* isomer (**12a**) at the same temperature.[5]

Scheme 4



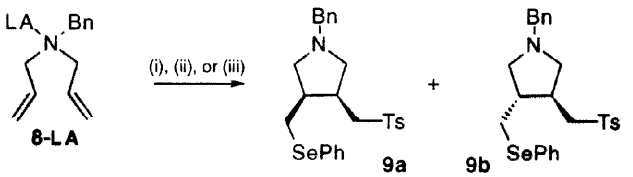
(i) TsSePh (cat.), benzene, 80 °C ; (i) TsSePh (cat.), benzene, hv, 19 °C ;
(iii) TsSePh (cat.), CH_3CN, 80 °C; (iv) TsSePh (cat.) CH_3CN, hv, 19 °C;
(v) $NaBH_4$, isopropyl alcohol .

It seems reasonable to consider that when the double bond bears two alkyl groups on its terminus, the preferential formation of **12b** from **11** should result from repulsive interactions between the alkyl groups and the tosylmethyl group on the radical center which contribute to destabilize $\mathbf{C_1}$ and $\mathbf{B_1}$. The selectivity difference between the amine and quaternary salt relies on the stronger destabilization of $\mathbf{C_2}$ (and at the same time of both boat conformers) when nitrogen bears an axial substituent.

Cyclization of tertiary amines complexed with a Lewis acid.

The use of Lewis acids in radical reactions has dramatically expanded over the last decade, allowing considerable progress in the control of diastereoselectivity.[7]

Scheme 5



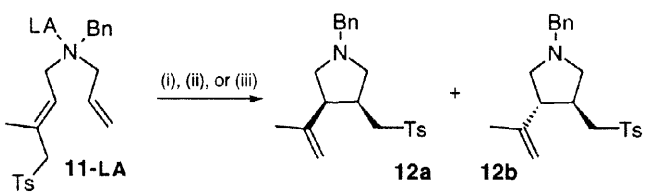
LA = $BF_3.Et_2O$	(i)	67%	70	:	30
	(ii)	66%	80	:	20
$AlMe_3$	(iii)	57%	78	:	22

(i) TsSePh (1 equiv.), Lewis acid (1 equiv.), CH_3CN, 80 °C ;
(ii) TsSePh (1 equiv.), Lewis acid (1 equiv.), CH_2Cl_2, hv, 19 °C;
(iii) TsSePh (1 equiv.), Lewis acid (1 equiv.), CH_3CN, hv, 19 °C.

Since the complexation of the amine with a Lewis acid might be expected to lead to the same selectivity improvement as demonstrated by quaternization, and moreover would suppress the inconveniency of an overall three-step procedure, we explored the effect of various complexing reagents. Following on ^1H NMR studies (measurement of the deshielding of the protons α to nitrogen), BF_3 and $AlMe_3$ were selected to perform the radical reactions. As shown in Scheme 5, no improvement of the diastereomeric excess was registered in the experiments carried out with **8** as the starting material.

However, a very significant increase in the abundance of the *cis* isomer was observed with amine **11**, even under thermal initiation. The highest selectivity was obtained with BF_3 at room temperature (Scheme 6).

Scheme 6



LA = $BF_3.Et_2O$	(i)	68%	60	:	40
	(ii)	55%	73	:	27
$AlMe_3$	(iii)	64%	58	:	42

(i) TsSePh (cat), $BF_3.Et_2O$ (1 equiv.),CH_3CN, 80 °C ;
(ii) TsSePh (cat), $BF_3.Et_2O$ (1 equiv.),CH_2Cl_2, hv, 19 °C;
(iii) TsSePh (cat), $AlMe_3$, CH_2Cl_2, hv, 19 °C.

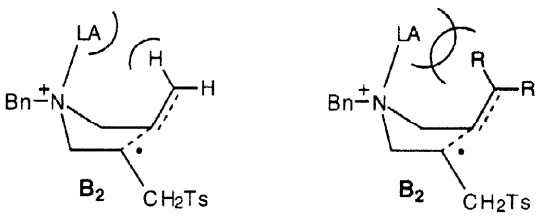
Thus, when the double bond was monosubstituted, complexation was inefficient compared to quaternization in increasing the diastereoselectivity. Interestingly, complexation appeared to be at least as efficient as quaternization when the double bond was trisubstituted.

These results can be interpreted if one assumes that the Lewis acid preferentially occupies an axial position in the transition state. If that was not the case, the benzyl group would lie in the axial position and therefore the diastereoselectivity should be identical to the one observed starting from quaternary ammonium salts whatever the substitution of the double bond.

In order to increase the *cis:trans* ratio, the coordinating reagent has to minimize, at the same time, the contribution of the transition structure $\mathbf{C_2}$ and of both boat conformers. The experimental results suggest that the efficiency of the Lewis acid (LA) is likely to be less related to its steric bulk than to the strength of its association with nitrogen. Consequently its influence should be correlated to the N-LA bond length.

The bond length in the complexes (1.85 Å in Me_3N-$AlMe_3$; 1.99 Å in Me_3N-BF_3, according to AM1 calculations[8]) is longer than the N-C bond in quaternary ammonium salts (1.50 Å[9]). In a manner, the distance would be insufficient to strongly destabilize boat transition structures when the double bond bears hydrogen atoms on its terminus, but the N-LA bond length would be short enough to introduce strong steric interactions between the Lewis acid and the *cis* alkyl group on the trisubstituted double bond as depicted in Figure 2 (for sake of clarity only transition structures of type $\mathbf{B_2}$ have been drawn, $\mathbf{B_1}$ being more energetic than $\mathbf{B_2}$ in any case; the same effects should also apply to $\mathbf{C_2}$).

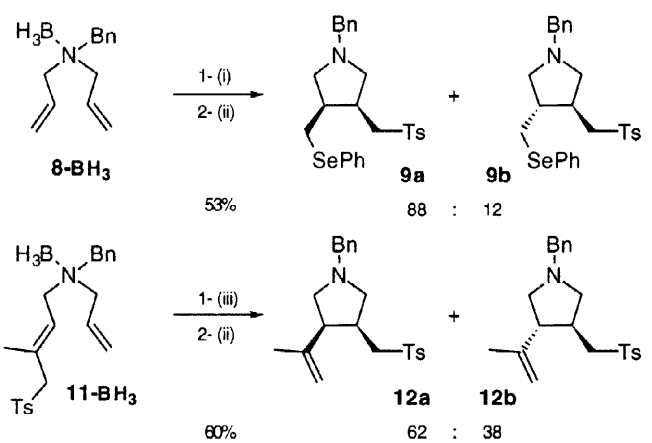
Figure 2



If this hypothesis is correct, then a Lewis acid more strongly associated to nitrogen should induce the same increase of selectivity, as quaternization, in the case of a monosubstituted radical accepting double bond. Amine-borane complexes are very stable. According to AM1 calculations the N-B bond length in Me_3N-BH_3 is 1.66 Å. We investigated the addition of TsSePh to amine **8** previously complexed with borane. The amine-borane complex is known to be a very good hydrogen donor towards electrophilic radicals like *t*-BuO$^{\bullet}$.[10] However the reduction of Ts$^{\bullet}$ is less probable since sulfonyl radicals are far less electrophilic than alkoxyl radicals.[11] This was verified since the overall yields were more or less similar to the yields obtained in the previous experiments.

The results are given in Scheme 7. At room temperature, the diastereomeric excess reached 76%, which is comparable to the selectivity observed with **10**. In the case of **11**, the results were also comparable to those obtained *via* quaternization (in this case no argument allows to conclude whether BH_3 occupies an axial position or an equatorial position).

Scheme 7



(i) TsSePh (1 equiv.), CH_2Cl_2, hv, 19 °C ; (ii) HCl 6N/ MeOH;
(iii) TsSePh (cat), CH_2Cl_2, hv, 19 °C .

Conclusion

Throughout this work, quaternization was shown to allow a significant, but limited, increase of the diastereomeric excess in 5-*exo* ring closure of 3-aza-5-hexenyl radicals substituted in position 1. The gain in stereoselectivity was similar, or even slightly better when the radical accepting double bond was trisubstituted (taking into account that the selectivity was reversed with respect to the parent amine in this case). However the formation of pyrrolidines *via* this procedure needed two additional steps (quaternization and dequaternization) compared to the direct cyclization of the parent amines.

An alternative and much more simple protocol was illustrated by complexing the tertiary amine with a Lewis acid such as BF_3 or $AlMe_3$. The results are consistent with the complexing reagent occupying preferentially a pseudoaxial position in the transition structure. The cyclizations afforded the same selectivity as those performed on quaternary ammonium salts, provided the double bond was trisubstituted. When the intramolecular addition took place on a terminal olefin, a more strongly coordinating reagent like BH_3 was able to provide a selectivity essentially similar to that reached through amine quaternization. These conclusions are likely to be general and should apply to other types of cyclization involving β-aminoalkyl radicals.

Experimental Section

General procedures.

^1H NMR spectra were recorded in $CDCl_3$ at 200 or 400 MHz and ^{13}C NMR spectra in $CDCl_3$ at 50 or 100 MHz as indicated. Chemical shifts (δ) are in ppm downfield from tetramethylsilane and coupling constants (*J*) are in Hz. All solvents were distilled by standard techniques. Semi-preparative HPLC were performed on a Waters Model 610 apparatus, fitted in series with two columns (25 x 100 mm) Prep Nova-Pak, HR silica 6 μm 60 Å, and coupled to a R 401 refractometer. Diallylbenzylamine (**8**)[12] was prepared by alkylating diallylamine with benzyl bromide.

Addition of TsSePh to 8.

- Thermal conditions : A solution of **8** (100 mg, 0.53 mmol), TsSePh (183 mg, 0.059 mmol), and AIBN (3 mg) in degassed benzene (41 mL) was heated at reflux for 3.5 h under inert atmosphere (after 90 min an additional portion of AIBN (3 mg) was added). After concentration, the residue was purified by flash chromatography on silica gel (EtOAc/pentane, 15/85 to 30/70). This led to a 70/30 mixture of **9a** and **9b** (160 mg, 0.32 mmol; 61%) in that order of elution. The diasteromeric ratio was determined, on the crude reaction mixture, by analytical HPLC (EtOAc/2,2,3-trimethylpentane, 20/80; 0.8 mL/min) and (or) by ^1H NMR *via* the integration of the signals of benzylic protons. Anal. calcd for $C_{26}H_{29}NO_2SSe$: C, 62.64; H, 5.86; N, 2.81. Found : C, 62.54; H, 5.79; N, 2.79. Further separation of pure samples of the two isomers was achieved by semi-preparative HPLC (EtOAc/2,2,3-trimethylpentane, 20/80; 13 mL/min).

(3S*,4R*)-1-Benzyl-3-phenylselanylmethyl-4-*p*-toluenesulfonylmethyl-pyrrolidine (9a).

^1H NMR ($CDCl_3$) (400 MHz): 7.75 (d, J = 8.3, 2H); 7.46-7.20 (m, 12H); 3.58 (AB quartet, J_{AB} = 13.1, $\Delta\nu$ = 9 Hz, 2H); 3.32 (dd, J = 13.9 and 4.0, 1H); 3.13 (dd, J = 13.9 and 10.0, 1H); 2.93-2.83 (m, 3H); 2.72 (dd, J = 11.4 and 9.7, 1H); 2.70-2.62 (m, 1H); 2.55-2.46 (m, 2H); 2.42 (s, 3H); 2.35-2.42 (m, 1H).

^{13}C NMR ($CDCl_3$) (50 MHz): 144.8 (C); 138.7 (C); 136.5 (C); 133.0 (CH); 130.0 (CH); 129.2 (CH); 128.7 (CH); 128.3 (CH); 128.1 (CH); 127.2 (CH); 127.1 (C); 127.0 (CH); 59.9 (CH_2); 59.4 (CH_2); 58.7 (CH_2); 56.5 (CH_2); 40.3 (CH, C3); 35.3 (CH, C4); 28.6 (CH_2Se); 21.7 (CH_3).

(3R*,4R*)-1-Benzyl-3-phenylselanylmethyl-4-*p*-toluenesulfonylmethyl-pyrrolidine (9b).

^{1}H NMR ($CDCl_3$) (400 MHz): 7.73 (d, J = 8.3, 2H); 7.40-7.19 (m, 12H); 3.51 (AB quartet, J_{AB} = 13.0, $\Delta\nu$ = 12 Hz, 2H); 3.25 (dd, J = 14.1 and 4.4, 1H); 3.13 (dd, J = 14.1 and 9.4, 1H); 2.98 (dd, J = 12.0 and 6.6, 1H); 2.89 (dd, J = 12.0 and 8.0, 1H); 2.80 (pseudo t, J = 8.7, 1H); 2.72 (pseudo t, J = 8.7, 1H); 2.49-2.40 (m, 1H); 2.41 (superimposed s, 3H); 2.28 (dd, J = 9.4 and 6.0, 1H); 2.35-2.25 (superimposed m, 1H); 2.10 (pseudo sext, J = 8.3, 1H).

^{13}C NMR ($CDCl_3$) (50 MHz): 144.7 (C); 139.1 (C); 136.6 (C); 132.6 (CH); 130.0 (CH); 129.2 (CH); 128.7 (CH); 128.3 (CH); 128.0 (CH); 127.1 (CH); 127.0 (CH); 65.9 (CH_2SO_2); 61.0 (NCH_2); 59.7 (NCH_2); 59.4 (NCH_2); 44.4 (CH, C3); 39.3 (CH, C4); 32.5 (CH_2Se); 21.6 (CH_3).

- **Photochemical conditions :** A solution of **8** (50 mg, 0.27 mmol), TsSePh (91 mg, 0.29 mmol) and AIBN (3 mg) in degassed benzene was irradiated for 3 h, under inert atmosphere, with a mercury lamp (after 90 min an additional portion of AIBN (3 mg) was added). The temperature was maintained at 19 °C by external cooling. After evaporating the solvent, the residue was purified under the previously described conditions, which led to a 78/22 mixture of **9a** and **9b** (74 mg, 0.14 mmol; 55%).

Diallyl-dibenzyl-ammonium *p*-toluenesulfonate (10).

Benzyl *p*-toluenesulfonate (708 mg, 2.7 mmol) was added to a solution of **8** (500 mg, 2.7 mmol) in chloroform (10 mL). The reaction mixture was heated at reflux for 2 h. After solvent evaporation, the ammonium salt was precipitated by adding Et_2O (10 mL) to the residue. After filtering and drying, **10** (800 mg, 1.8 mmol; 67%) was isolated. Anal. calcd for $C_{27}H_{31}NO_3S$: C, 72.13; H, 6.95; N, 3.12. Found : C, 72.14; H, 6.92; N, 3.08.

^{1}H NMR ($CDCl_3$) (200 MHz): 7.85 (d, J = 8.1, 2H); 7.63-7.25 (m, 10H); 7.10 (d, J = 8.1, 2H); 5.92-5.72 (m, 2H); 5.62 (d, J = 16.4, 2H); 5.46 (d, J = 10.2, 2H); 4.79 (s, 4H); 4.05 (d, J = 7.3, 4H); 2.30 (s, 3H).

^{13}C NMR ($CDCl_3$) (50 MHz): 144.3 (C); 138.9 (C); 133.4 (CH); 130.5 (CH); 126.1 (CH); 128.5 (CH); 127.8 (C); 127.7 (CH_2); 126.1 (CH); 125.6 (CH); 65.0 (CH_2); 61.5 (CH_2); 21.2 (CH_3).

Addition of TsSePh to 10 :

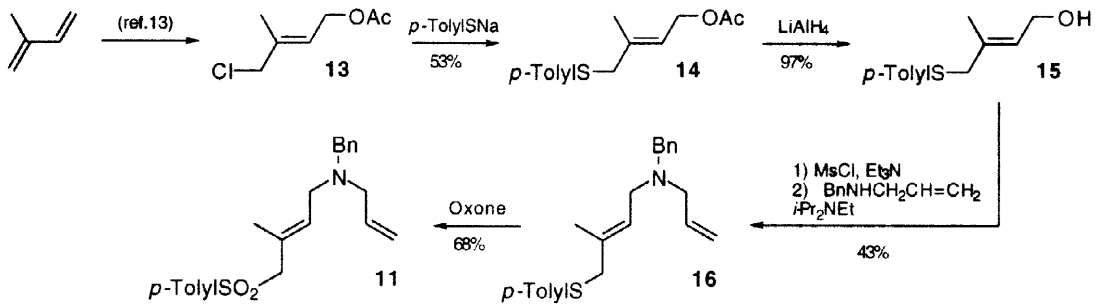
- **Thermal conditions :** A solution containing **10** (45 mg, 0.1 mmol), TsSePh (37 mg, 0.12 mmol), and AIBN (1 mg) in degassed acetonitrile (3 mL) was heated at reflux, under inert atmosphere, for 7 h (every 90 min, 1 mg of AIBN was added). After evaporating the solvent, the residue was dissolved in isopropanol (5 mL) and $NaBH_4$ (15 mg, 0.4 mmol) was added. The mixture was heated at reflux overnight and then concentrated. H_2O and EtOAc were added to the crude product, after extraction, the combined organic phases were dried over Na_2SO_4. The residue was purified by flash chromatography as above, which led to a 79/21 mixture of **9a** and **9b** (30 mg, 0.06 mmol; 60%).

- **Photochemical conditions :** A solution of **10** (45 mg, 0.1 mmol), TsSePh (37 mg, 0.12 mmol) and AIBN (1 mg) in degassed acetonitrile (3 mL) was irradiated for 4 h under inert atmosphere at 19 °C (warming was prevented by an external cooling). After evaporation of the solvent, the reduction with $NaBH_4$ and subsequent treatment and purification were carried out as above. This led to a 87/13 mixture of **9a** and **9b** (20 mg, 0.04 mmol; 40%).

Synthesis of 11.

The preparation of **11** was realized as summarized in Scheme 8, starting from 4-chloro-3-methyl-but-2-enyl acetate **13** (easily available from isoprene[13]).

Scheme 8



- 3-Methyl-4-*p*-toluenesulfanyl-but-2-enyl acetate (14).

p-Thiocresol (4.72 g, 38 mmol) was added to a solution of NaOEt in EtOH (20 mL) previously prepared from metallic sodium (874 mg, 38 mmol). The solution was stirred at room temperature for 30 min before adding over 1 h a solution of **13** (6.17 g, 38 mmol) in EtOH (10 mL). After one night at room temperature, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (EtOAc/pentane, 2/98) which led to **14** (4.9 g, 20 mmol; 53%). Anal. calcd for $C_{14}H_{18}O_2S$: C, 67.17; H, 7.25. Found : C, 67.16 ; H, 7.19.

^{1}H NMR ($CDCl_3$) (200 MHz) : 7.23 (d, J = 8.3, 2H); 7.16 (d, J = 8.3, 2H); 5.31 (t, J = 7.1, 1H); 4.51 (d, J = 7.1, 2H); 3.44 (s, 2H); 2.30 (s, 3H); 2.00 (s, 3H); 1.82 (s, 3H).

^{13}C NMR ($CDCl_3$) (50 MHz): 170.8 (C=O); 137.2 (C); 136.7 (C); 131.9 (C); 131.6 (CH); 129.5 (CH); 122.1 (CH); 60.9 (OCH_2); 44.5 (SCH_2); 21.0 (CH_3); 20.9 (CH_3); 15.5 (CH_3).

- 3-Methyl-4-*p*-toluenesulfanyl-but-2-en-1-ol (15).

To a solution of $LiAlH_4$ (68 mg, 1.8 mmol) in dry THF (4 mL), **14** (0.8 mg, 3.2 mmol) was added at 0 °C. After stirring for 2 h at 0 °C, Na_2SO_4 10 H_2O (1.3 g) was added to the reaction mixture, before filtering over anhydrous Na_2SO_4. The solution was concentrated and the crude product (**15**) (640 mg, 3.1 mmol; 97%) was used without further purification.

^{1}H NMR ($CDCl_3$) (200 MHz) : 7.23 (d, J = 8.3, 2H); 7.16 (d, J = 8.3, 2H); 5.35 (t, J = 6.6, 1H); 4.02 (d, J = 6.6, 2H); 3.43 (s, 2H); 2.28 (s, 3H); 1.75 (s, 3H).

^{13}C NMR ($CDCl_3$) (50 MHz) : 136.5 (C); 134.1 (C); 132.0 (C); 131.2 (CH); 129.5 (CH); 127.2 (CH); 58.9 (OCH_2); 44.3 (SCH_2); 20.9 (CH_3); 15.2 (CH_3).

- Allyl-(3-methyl-4-*p*-toluenesulfanyl-but-2enyl)-benzylamine (16).

Methanesulfonyl chloride (172 mg, 1.5 mmol) was added at 0 °C to a solution of **15** (200 mg, 0.97 mmol) and Et_3N (202 mg, 2 mmol) in dichloromethane (3 mL). The reaction mixture was stirred for 30 min and poured onto a 10% solution of $NaHCO_3$. After decantation, the organic phase was dried over Na_2SO_4 and concentrated. The crude mesylate was added, at 0 °C, to a solution of N-allylbenzylamine (141 mg, 0.95 mmol) and diisopropylethylamine (149 mg, 1.15 mmol) in acetonitrile (10 mL). The reaction mixture was stirred overnight at room temperature. After treating with a 20% solution of Na_2CO_3 and extracting with three portions of dichloromethane, the combined organic phases were dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (EtOAc/pentane, 3/97) which led to **16** (140 mg, 0.41 mmol; 43%). Anal. calcd for $C_{22}H_{27}NS$: C, 78.29; H, 8.06; N, 4.15. Found : C, 78.14 ; H, 8.11; N, 4.12.

^{1}H NMR ($CDCl_3$) (200 MHz) : 7.40-7.16 (m, 7H); 7.10-6.97 (m, 2H); 5.94-5.71 (m, 1H); 5.48-5.08 (m, 3H); 3.46 (s, 2H); 3.38 (s, 2H); 3.52-3.43 (m, 2H); 2.90 (d, J = 6.4, 2H); 2.23 (s, 3H); 1.74 (s, 3H).

- Allyl-(3-methyl-4-*p*-tolylsulfonyl-but-2enyl)-benzylamine (11).

A solution of oxone® (3.5 g, 5.7 mmol) in water (18 mL) was added to a solution of **16** (640 mg, 1.9 mmol) in methanol (18 mL). After stirring for 3 h at room temperature, water was added up to complete dissolution of the salts and the solution was extracted twice with chloroform. The combined organic phases were washed with brine. After drying over Na_2SO_4, the solvent was evaporated and the crude product was purified by flash chromatography on silica gel (EtOAc/pentane, 10/90 to 20/80) which led to **11** (480 mg, 1.3 mmol; 68%). Anal. calcd for $C_{12}H_{27}NSO_2$: C, 71.51; H, 7.36; N, 3.79. Found : C, 71.38; H, 7.33; N, 3.77.

^1H NMR ($CDCl_3$) (200 MHz) : 7.63 (d, J = 8.3, 2H); 7.08-7.24 (m, 7H); 5.70 (m, 1H); 5.19-4.98 (m, 3H); 3.66 (s, 2H); 3.25 (s, 2H); 2.89 (d, J = 6.4, 2H); 2.78 (d, J = 6.4, 2H); 2.22 (s, 3H); 1.67, J = 1.0, 3H).

^{13}C NMR ($CDCl_3$) (50 MHz) : 144.5 (C); 139.0 (C); 135.3 (CH); 135.3 (C); 133.6 (CH); 129.6 (CH); 128.8 (CH); 128.3 (CH); 128.1 (CH); 126.8 (CH); 117.5 (CH_2); 66.1 (CH_2); 57.7 (CH_2); 56.5 (CH_2); 21.6 (CH_3); 17.0 (CH_3).

Addition of TsSePh to 11.

- Thermal conditions : A solution of **11** (100 mg, 0.27 mmol) in degassed benzene (10 mL) was heated at reflux for 9 h under inert atmosphere. A 3 mg portion of a mixture containing AIBN (2 mg, 12 mmol) and TsSePh (17 mg, 55 mmol) were added at the beginning of the reaction and then every 90 min. The solvent was evaporated and the residue was purified by flash chromatoraphy on silica gel (EtOAc/pentane, 20/80 to 30/70) which led to a mixture of **12a** and **12b** (55 mg, 0.15 mmol); 55%) in that order of elution. The diasteromeric ratio (49:51) was determined by GPC on the crude reaction mixture. Anal. calcd for $C_{22}H_{27}NSO_2$: C, 71.51; H, 7.36; N, 3.79. Found : C, 71.55; H, 7.25; N, 3.69. Further separation was achieved by semi-preparative HPLC (EtOAc/2,2,3-trimethylpentane, 20/80, 35 mL/min) which allowed to isolate a pure sample of **12a**.

1-Benzyl-3-isoprenyl-4-*p*-toluenesulfonylmethyl-pyrrolidine (12a).

^1H NMR ($CDCl_3$) (400 MHz): 7.72 (d, J = 8.2, 2H); 7.32-7.19 (m, 7H); 4.84 (s, 1H); 4.63 (s, 1H); 3.60 (s, 2H); 3.05-2.96 (m, 2H); 2.95-2.80 (m, 2H); 2.74-2.65 (m, 2H); 2.60-2.51 (m, 2H); 2.41 (s, 3H); 1.58 (s, 3H).

^{13}C NMR ($CDCl_3$) (100 MHz): 144.8 (C); 143.0 (C); 136.8 (C); 130.1 (CH); 128.9 (CH); 128.5 (CH); 128.2 (CH); 127.3 (CH); 113.6 (CH_2); 60.3 (CH_2); 59.3 (CH_2); 57.6 (CH_2); 55.5 (CH_2); 48.3 (CH, C3); 35.0 (CH, C4); 23.1 (CH_3); 21.8 (CH_3).

1-Benzyl-3-isoprenyl-4-*p*-toluenesulfonylmethyl-pyrrolidine (12b).

Characteristic signals of **12b** were deduced from the spectra of the 1:1 mixture of the two diastereomers.

^1H NMR ($CDCl_3$) (400 MHz): 4.72 (s, 1H); 4.66 (s, 1H); 3.61-3.75 (m, 2H); 2.41 (s, 3H); 1.59 (s, 3H).

^{13}C NMR ($CDCl_3$) (100 MHz): 113.3 (CH_2); 59.7 (CH_2); 59.6 (CH_2); 56.8 (CH_2); 56.0 (CH_2); 51.5 (CH, C3); 35.7 (CH, C4); 21.8 (CH_3); 19.6 (CH_3).

- Photochemical conditions : A solution of **11** (100 mg, 0.27 mmol) and AIBN (1 mg) in degassed benzene (10 mL) was irradiated for 8 h under inert atmosphere. The temperature was maintained at 19 °C by external cooling. Every 60 min, 2 mg of a mixture containing AIBN (2 mg, 12 mmol) and TsSePh (17 mg, 55 mmol) were added. The solvent was evaporated and the crude product was purified as above which led to a 41/59 mixture of **12a** and **12b** (40 mg, 0.11 mmol; 41%).

Allyl-(3-methyl-4-*p*-toluenesulfonyl-but-2-enyl)-dibenzyl-ammonium *p*-toluenesulfonate (13). Benzyl-*p*-toluenesulfonate (219 mg, 0.84 mmol) was added to a solution of **11** (280 mg, 0.76 mmol) in acetonitrile (3 mL). The reaction mixture was stirred for 48 h at room temperature. After the solvent was evaporated, the crude salt was washed four times with portions of Et_2O (5 mL). The salt was dried under vacuum and **13** (390 mg, 0.62 mmol; 81%) was isolated. ^1H and ^{13}C NMR spectra were useless due to signals broadening (possibly because of an accidental incorporation of paramagnetic impurities to the solid).

Addition of TsSePh to 13.

- **Thermal conditions :** A solution of **13** (72 mg, 0.11 mmol) in degassed acetonitrile (4 mL) was heated at reflux for 7 h under inert atmosphere. At the beginning of the reaction and every 60 min, 2 mg portions of a mixture containing AIBN (1 mg, 6 mmol) and TsSePh (6 mg, 19 mmol) were added. After concentration the residue was dissolved in isopropanol (5 mL) and $NaBH_4$ (15 mg, 0.4 mmol) was added. The mixture was refluxed overnight. The solvent was then evaporated and water and EtOAc were added to the crude product. After extraction with EtOAc, drying the combined organic phases over Na_2SO_4, and concentration, the residue was purified by chromatography on silica gel (EtOAc/pentane, 20/80). This led to a 58/42 mixture of **12a** and **12b** (28 mg, 0.07 mmol; 68%).

- **Photochemical conditions :** A solution of **13** (72 mg, 0.11 mmol) in degassed acetonitrile (4 mL) was irradiated for 8 h with a mercury lamp (the temperature was maintained stationary by external cooling). Reaction with $NaBH_4$ and following treatment were carried out as above. This led to isolate a 64/36 mixture of **12a** and **12b** (20 mg, 0.054 mmol; 50%).

Addition of TsSePh to 8 in the presence of Lewis acids.

- **Thermal conditions :** A solution of **8** (46 mg, 0.24 mmol) and $BF_3.Et_2O$ (35 mg, 0.24 mmol) in degassed acetonitrile (10 mL) was stirred for 5 min. Then TsSePh (90 mg, 0.29 mmol) and AIBN (1 mg) were added and the resulting solution was refluxed for 6 h under inert atmosphere (every 90 min portions of AIBN (1 mg) were added). The solution was stirred with a 20% solution of Na_2CO_3 before extracting with Et_2O and the combined organic phases were then washed with brine. After drying over Na_2SO_4, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (*vide supra*), which led to a 70/30 mixture of **9a** and **9b** (85 mg, 0.17 mmol; 67%).

- **Photochemical conditions :**

a) **$BF_3.Et_2O$** : A solution of **8** (50 mg, 0.27 mmol) and $BF_3.Et_2O$ (38 mg, 0.27 mmol) in degassed dichloromethane (10 mL) was stirred for 5 min. TsSePh (93 mg, 0.30 mmol) and AIBN (1 mg) were added and the solution was irradiated for 6 h, at 19 °C, under inert atmosphere, with an external mercury lamp (every 60 min additional portions of AIBN (1 mg) were added). The solution was successively washed with a 20% solution of Na_2CO_3 and with brine and then dried over Na_2SO_4 before the solvent was evaporated. Purification on silica gel led to a 80/20 mixture of **9a** and **9b** (89 mg, 0.18 mmol; 66%).

b) **$AlMe_3$** : A 2M solution of $AlMe_3$ in hexane.(75 mL, 0.15 mmol) was added to a solution of **8** (28 mg, 0.15 mmol) in degassed acetonitrile (4 mL). The resulting mixture was stirred for 5 min before TsSePh (56 mg, 0.18 mmol) and AIBN (1 mg) were added. Then the solution was irradiated for 5 h, at 19 °C (every 60 min additional portions of AIBN (1 mg) were added). The solution was stirred overnight with a 20% solution of Na_2CO_3. After extraction with Et_2O, the combined organic phases were washed with brine and dried. Purification on silica gel led to a 78/22 mixture of **9a** and **9b** (43 mg, 0.09 mmol; 57%).

c) BH_3 : A 2M solution of $BH_3.Me_2S$ in toluene (67 mL, 0.13 mmol) was added to a solution of **8** (24 mg, 0.12 mmol) in dry degassed dichloromethane (4 mL). The resulting mixture was stirred for 5 min before TsSePh (45 mg, 0.14 mmol) and AIBN (0.5 mg) were added. The reaction mixture was irradiated for 8h at 19 °C under inert atmosphere (every 60 min additional portions (0.5 mg) of AIBN were added). The solvent was evaporated and the residue was dissolved in methanol (3 mL). This solution was refluxed for 3 h in the presence of 6N HCl (6 mL) and basified, after cooling, with a 20% solution of NaOH. After extraction with dichloromethane and drying over Na_2SO_4, the solvent was evaporated and the crude product was purified by flash chromatography on silica gel, as previously described. This led to a 88/12 mixture of **9a** and **9b** (32 mg, 0.06 mmol; 53%).

Addition of TsSePh to 11 in the presence of Lewis acids.

- Thermal conditions : A solution of **11** (140 mg, 0.38 mmol) and $BF_3.Et_2O$ (46 mL, 0.38 mmol) in dry degassed acetonitrile (15 mL) was stirred for 5 min before 2 mg of a mixture of TsSePh (47 mg, 15 mmol) and AIBN (6 mg) were added. The solution was refluxed for 6 h (every 90 min additional portions (2 mg) of the above mixture were added). The solution was stirred for 30 min with a 20% solution of Na_2CO_3 and then extracted with Et_2O, the combined organic phases were washed with brine and dried over Na_2SO_4. Chromatographic purification led to a 60/40 mixture of **12a** and **12b** (96 mg, 0.25 mmol; 68%).

- Photochemical conditions :

a) $BF_3.Et_2O$: A solution of **11** (50 mg, 0.13 mmol) and $BF_3.Et_2O$ (16 mL, 0.18 mmol) in dichloromethane (4 mL) was stirred for 5 min before 2 mg of a mixture of TsSePh (12 mg, 38 mmol) and AIBN (2mg) were added. The solution was irradiated at 19 °C for 7 h (every 90 min additional portions (2 mg) of the above mixture were added). The solution was stirred for 30 min with a 20% solution of Na_2CO_3 and then washed with brine and dried. Purification on silicagel led to a 73/27 mixture of **12a** and **12b** (26 mg, 0.07 mmol; 55%).

b) $AlMe_3$: A 2M solution of $AlMe_3$ in hexane.(68 mL, 0.13 mmol) was added to a solution of **11** (50 mg, 0.13 mmol) in dry degassed dichloromethane (5mL). The reaction mixture was irradiated for 7 h according to the above procedure. After treatment and chromatographic purification a 58/42 mixture of **12a** and **12b** (31 mg, 0.08 mmol; 64%) was isolated.

c) BH_3 : A 2M solution of $BH_3.SMe_2$ in toluene was added to a solution of **11** (50 mg, 0.13 mmol) in dry degassed dichloromethane (4 mL). The solution was stirred for 5 min before 2 mg of a mixture of TsSePh (12 mg, 38 mmol and AIBN (2 mg) were added. The solution was irradiated at 19 °C for 7 h (every 60 min additional portions (2 mg) of the above mixture were added). After solvent evaporation, the residue was dissolved in methanol and refluxed for 3 h in the presence of 6N HCl (6 mL). After cooling the solution was treated with a 20% solution of NaOH. The aqueous phase was extracted with dichloromethane and the organic phases were dried over Na_2SO_4. The solution was concentrated and the residue was purified by flash chromatography on silica gel (*vide supra*) which led to a 62/38 mixture of **12a** and **12b** (29 mg, 0.08 mmol; 60%).

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