



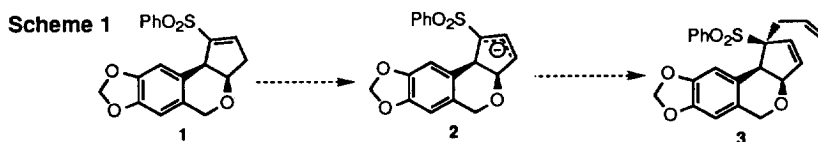
## Use of Phosphazene Base and Phase-Transfer Conditions for Regiospecific Alkylative Isomerization of Vinyl Sulfones Capable of Undergoing $\beta$ -Elimination Reactions.<sup>1</sup>

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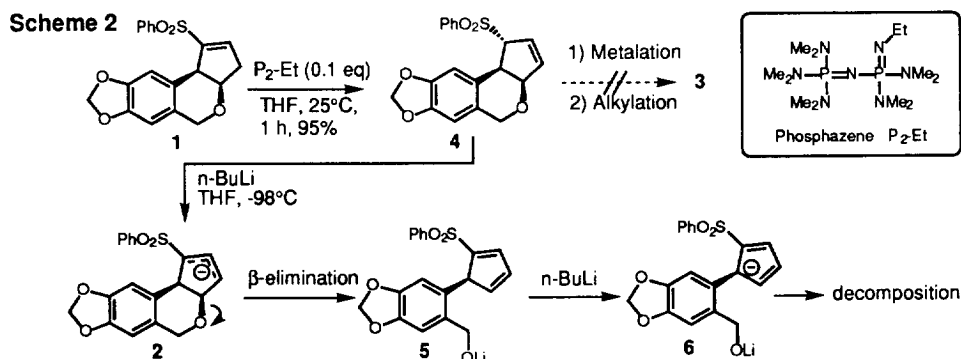
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**Abstract:** Using phosphazene base,  $P_4$ -t-Bu or basic phase-transfer catalyst conditions, vinyl sulfones were regiospecifically alkylated at the  $\alpha$ -position. No  $\beta$ -elimination products were observed in a system capable of undergoing anion-promoted  $\beta$ -elimination. The scope and limitations of these reactions were studied. Copyright © 1996 Elsevier Science Ltd

In conjunction with a project directed toward improving our existing synthesis<sup>2</sup> of the *cephalotaxus* alkaloids, we wished to effect the construction of compound **3** by alkylation of allyl sulfonyl anion **2** which was projected to be formed via  $\gamma$ -deprotonation of the readily available<sup>3</sup> vinyl sulfone **1** under low temperature, strongly basic conditions (Scheme 1).

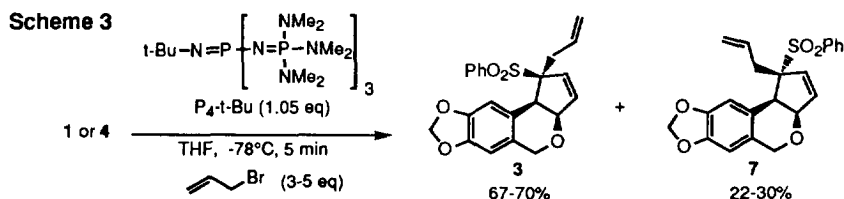


Many strong ionic bases were screened without success. Even those bases which did react generated many products, and compound **3** was never detected. Therefore, a two-step approach was adopted. Isomerization of vinyl sulfone **1** to allyl sulfone **4** was accomplished using 0.1 eq of the Schwesinger phosphazene base  $P_2$ -Et.<sup>4,5</sup> Attempts to effect sequential metalation-alkylation of **4** using  $n$ -BuLi at low temperature led to a plethora of products. An anion-promoted  $\beta$ -elimination is believed to be responsible for the failure although the reaction failed to produce any identifiable products (Scheme 2).

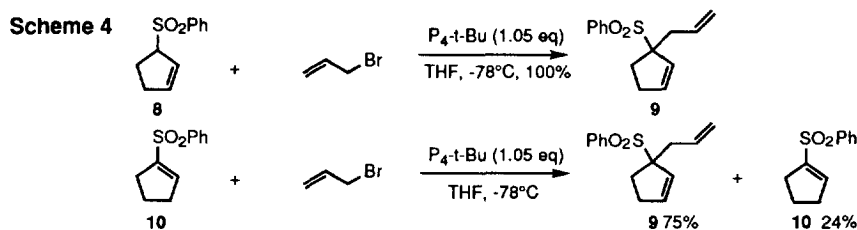


Since no  $\beta$ -elimination was observed during the isomerization of **1** to **4** using the phosphazene bases, we speculated that the nature of  $\pi$ -base extended "counterion" might be of

crucial importance in determining the lifetime of allylic anions like **2**. This possibility derives further support from our earlier observation of DBU-mediated isomerization of a sulfolene derivative known to fragment under standard metalation conditions.<sup>6</sup> Since  $P_2$ -Et was not strong enough to enable alkylation,  $P_4$ -t-Bu was employed for the desired alkylation since it is about a factor of  $10^{17}$  stronger than DBU.<sup>4</sup> In the presence of 3-5 eq of allyl bromide at  $-78^\circ\text{C}$ , 1.05 eq of  $P_4$ -t-Bu was added to the solution of allyl sulfone **4** in THF. A rapid reaction took place which was complete in less than 5 minutes. A pair of diastereomeric allylated products (**3,7**) was isolated in near-quantitative yield. Under the same conditions, vinyl sulfone **1** provided the same mixture of allylated sulfones (Scheme 3). As expected,  $P_4$ -t-Bu promotes decomposition of the intermediate anion when the reaction is conducted in the absence of allyl bromide, even at  $-98^\circ\text{C}$ .



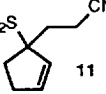
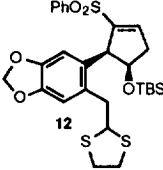
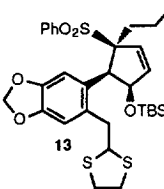
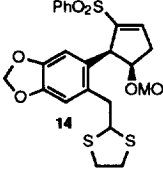
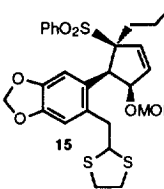
The success of the phosphazene base mediated alkylative isomerization prompted us to further investigate the generality of this type of reaction. Under the above conditions, allyl sulfone **8** provided allylated product **9** in quantitative yield, but vinyl sulfone **10** gave only 75% of compound **9** accompanied by 24% of recovered starting material (Scheme 4). The incomplete reaction is presumably due to competitive alkylation of the  $P_4$ -t-Bu by allyl bromide. Therefore, the direct alkylation of allyl sulfones with  $P_4$ -t-Bu seems to be general, but the alkylative isomerization depends upon the kinetics of the competitive processes. This finding, coupled with the high cost of  $P_4$ -t-Bu, inspired a search for other alternatives.

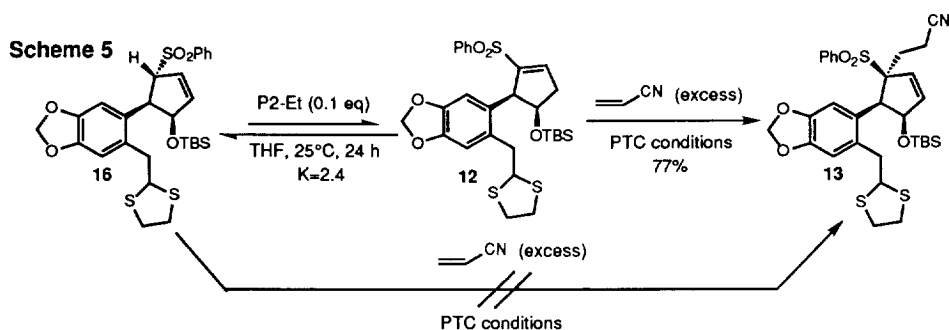


It is known that acyclic allyl sulfones can be alkylated under basic phase-transfer catalyst conditions,<sup>7</sup> but this method has not been extended to cyclic allyl sulfones. In the presence of 50% aqueous KOH solution and 0.2 eq of  $\text{Bu}_4\text{NBr}$  in THF, allyl sulfone **4** was converted to a pair of two diastereomers **3** and **7** in 97% combined yield without any accompanying  $\beta$ -elimination product (Table, entry 1). Extending this protocol to vinyl sulfone **1** was also successful (Table, Entry 2). Although vinyl sulfone **10** failed to react with allyl bromide, it could be isomerized and subsequently undergo conjugate addition to acrylonitrile to afford compound **11** in good yield. Some additional examples are shown in the table.<sup>8</sup> No  $\beta$ -elimination products were isolated in

entries 6, and 7. It was also interesting to observe that vinyl sulfone **12** and allyl sulfone **16** exist as an equilibrium mixture under the basic conditions with an equilibrium constant  $K=2.4$  (favoring allyl sulfone). Furthermore, allyl sulfone **16** failed to react with acrylonitrile under the basic phase-transfer catalyst conditions presumably due to steric hindrance of the  $\alpha$ -proton (Scheme 5).

Table

Entry	Substrates	Electrophiles	Conditions	Products
1	<b>4</b>	allyl bromide (10 eq)	50% aq. KOH, THF Bu <sub>4</sub> NBr (0.2 eq), 5 min	<b>3</b> (67%)+ <b>7</b> (30%)
2	<b>1</b>	allyl bromide (10 eq)	50% aq. KOH, THF Bu <sub>4</sub> NBr (0.2 eq), 5 min	<b>3</b> (70%) + <b>7</b> (23%)
3	<b>8</b>	allyl bromide (20 eq)	50% aq. KOH, CH <sub>3</sub> CN Bu <sub>4</sub> NBr (0.2 eq), 5 min	<b>9</b> (20%) + <b>8</b> (80%)
4	<b>10</b>	allyl bromide (20 eq)	50% aq. KOH, CH <sub>3</sub> CN Bu <sub>4</sub> NBr (0.2 eq)	No reaction
5	<b>10</b>	acrylonitrile (20 eq)	50% aq. KOH, CH <sub>3</sub> CN Bu <sub>4</sub> NBr (0.2 eq), 1 hr	 <b>11</b> 82%
6	 <b>12</b>	acrylonitrile (50 equiv.)	50% aq. KOH Bu <sub>4</sub> NBr (0.2 eq) CH <sub>3</sub> CN, 1 hr	 <b>13</b> 77%
7	 <b>14</b>	acrylonitrile (50 equiv.)	50% aq. KOH Bu <sub>4</sub> NBr (0.2 eq) CH <sub>3</sub> CN, 1 hr	 <b>15</b> 80%



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### References and notes

<sup>1</sup>Synthesis via vinyl sulfones 65.

<sup>2</sup>(a) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, *110*, 2341; (b) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1990**, *112*, 9601.

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<sup>4</sup>(a) Schwesinger, R.; Schlemper, H. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1167; (b) Schwesinger, R. *Chimia* **1985**, *39*, 269; (c) Pietzonka, T.; Seebach, D. *Chem. Ber.* **1991**, *124*, 1837; (d) Schwesinger, Willaredt, J., R.; Schlemper, H., Keller, M., Schmitt, D., Fritz H. *Chem. Ber.* **1994**, *127*, 2435; and references cited therein.

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<sup>6</sup>Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208.

<sup>7</sup>(a) Golinski, J.; Jonczyk, A.; Makosza, M. *Synthesis* **1979**, 461; (b) Jonczyk, A.; Radwan-Pytlewski, T. *J. Org. Chem.* **1983**, *48*, 910.

<sup>8</sup> **Experimental:** To a vigorously stirred solution of vinyl sulfone **14** (0.395 mmol, 200 mg), tetrabutylammonium bromide (0.2 eq, 0.079 mmol, 25.5 mg), and acrylonitrile (10 eq, 3.95 mmol, 0.21 g, 0.2 mL), in 3 mL of CH<sub>3</sub>CN at 25°C was added 11 mL of 50% aq. KOH solution in one portion. The reaction mixture was stirred at 25°C for ~3 minutes, and then more acrylonitrile was added to the reaction via syringe pump (5 mL syringe) at the rate of 1.7 mL/h. Acrylonitrile addition is continued until disappearance of the vinyl sulfone starting material is complete as assayed by TLC. After removal of the solvent, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and H<sub>2</sub>O was added to dissolve some of the solids. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> until TLC showed no product in the H<sub>2</sub>O layer, washed with brine, the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent was removed *in vacuo*. The crude residue was first purified by a short flash column chromatography on silica gel to give a mixture of the desired product, HOCH<sub>2</sub>CH<sub>2</sub>CN (large excess), O(CH<sub>2</sub>CH<sub>2</sub>CN)<sub>2</sub> (large excess) and some minor side products. This mixture was further purified via Kugelrohr distillation (0.02 mm Hg at 130°C) to afford a mixture of the desired product and small amounts of the side products which can be further purified by flash column chromatography on silica gel to give 180 mg of pure adduct **15** (81%).

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