PHOSPHINE-PROMOTED MIGRATIVE CYCLIZATION OF SULFONYLALKYNOL AND SULFONYLALKYNAMIDE FOR THE SYNTHESIS OF OXA- AND AZACYCLES

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Abstract – A catalytic amount of phosphine or DMAP promoted the migrative cyclization of propargyl sulfones bearing an internal nucleophilic functionality in a γ-umpolung manner.

INTRODUCTION

We recently reported an oxa- and azacycle-forming reaction of sulfonylalkynols and sulfonylalkynamides utilizing an N-heterocyclic carbene (NHC).1,2 In the reaction of 1a, for example, the bond formation with the internal O-nucleophile occurred at the γ-position of the sulfone with 1,2-sulfonyl migration to give 2a in 91% yield after 10 h (Scheme 1). The latent polarity of the γ-position is negative; therefore, this transformation can be regarded as an example of γ-umpolung bond formation.3 The proposed mechanism is depicted in Scheme 1: The initiation step begins with tautomerization of propargyl sulfone 1a to generate allenyl sulfone intermediate 4,4 which undergoes conjugate addition of NHC to give alkoxide 5 after internal proton transfer (Scheme 1, initiation step). The following intramolecular S_N2’ reaction gives 6 along with p-toluenesulfinate anion (Ts^-) to initiate the productive cycle, which involves the conjugate addition of Ts^- to 4 to give 7 and the following S_N2’ cyclization to produce 2a with the regeneration of Ts^- (Scheme 1, productive cycle).5
Based on the proposed mechanism, we envisioned that other nucleophiles should also induce this migrative cyclization. In the previous report, we preliminarily demonstrated that triphenylphosphine induces this transformation in the presence of cesium carbonate.\textsuperscript{1} We herein report that $P$- and $N$-nucleophiles promote the migrative cyclization without additional bases.

**RESULTS AND DISCUSSION**

First, we tested several nucleophilic catalysts\textsuperscript{6} in the reaction of 1a. Propargyl sulfone 1a (0.10 mmol) was heated in refluxing toluene (0.5 mL) in the presence of triphenylphosphine (5 mol%). After 18 h, the migrative cyclization product 2a was obtained in 81% yield (Table 1, entry 1). The use of more nucleophilic tributylphosphine\textsuperscript{7} led to less satisfactory results than triphenylphosphine, giving 2a in 37% yield with 12% recovery of 1a after 24 h (entry 2), probably due to its lability to the autoxidation. Tributylphosphine was likely oxidized during the reaction by oxygen that invaded into the reaction tube, and no tributylphosphine but tributylphosphine oxide was observed by $^1$H NMR of the crude materials. These results would indicate that the phosphines promote this reaction not only as an initiating nucleophile but also as a base to isomerize 1a into allenyl sulfone 4, and that the isomerization became
slower after tributylphosphine was totally oxidized. An sp$^2$-N-nucleophile, 4-($N,N$-dimethylamino)pyridine (DMAP) also promoted the reaction to give 2a in 71% yield, albeit conventional adduct 3a, which was likely formed by intramolecular conjugate addition of intermediate 4, which was also produced in 12% yield (entry 3). An sp$^3$-N-nucleophile, 1,4-diazabicyclo[2.2.2]octane (DABCO) is probably too basic for this reaction and only promoted the conventional cyclization to give 3a in 80% yield without any production of the desired γ-umpolung adduct 2a (entry 4).

### Table 1. Reactions with P- or N-Nucleophiles

<table>
<thead>
<tr>
<th>entry</th>
<th>nucleophile</th>
<th>time (h)</th>
<th>2a yield (%)</th>
<th>3a yield (%)</th>
<th>1a recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph$_3$P</td>
<td>18</td>
<td>81</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Bu$_3$P</td>
<td>24</td>
<td>37</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>DMAP</td>
<td>2</td>
<td>71</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>DABCO</td>
<td>19</td>
<td>0</td>
<td>80</td>
<td>0</td>
</tr>
</tbody>
</table>

Other propargyl sulfones were subjected to the phosphine-promoted migrative cyclization condition (Table 2). Although no formation of 2b from secondary alcohol 1b was observed under the standard conditions, only giving back starting 1b after 24 h, addition of 1 mol% Cs$_2$CO$_3$ resulted in full conversion of 1b, and 2b was produced in 71% yield with diastereomeric ratio (dr 5:4, entry 1) similar to that previously observed with NHC (dr 3:2). The requirement of additional base is probably due to slower S$_N$2’ cyclization in the initiation step with the secondary alcohol. Triphenylphosphine would be completely converted into 5 or 6 before sufficient amount of Ts$^{-}$ formed to promote the productive cycle. Without involvement of additional base, isomerization of propargyl sulfone 1b to the corresponding allenyl sulfone 4b would be too slow. C$_2$-Symmetric diol 1c afforded bi-THF 2c as a mixture of diastereomers in 82% yield (entry 2). The diastereomeric ratio (dr 5:3:2) was almost the same as that observed in the reaction with NHC (dr 5:3:3). Six-membered ring formation also proceeded smoothly under the standard conditions, and isochromane 2d was produced in 51% yield (entry 3). In the presence of Cs$_2$CO$_3$, formamide 1e was smoothly converted to 2e in 68% yield (entry 4) although the reaction failed to proceed without base. N-p-Toluenesulfonylamide 1f also provided the corresponding pyrrolidine product in good isolated yield under the standard conditions (entry 5). Thus, in general, the performance of the reaction with triphenylphosphine was comparable with that using NHC.
Finally, we attempted to develop an asymmetric version of this transformation. When a chiral phosphine is used in the reaction, the initiation step should produce cation 6 possessing chirality. If the cation functions as a chiral counter ion of 7, the Sn2’ cyclization of 7 could proceed under the control of that chirality, and enantiomerically enriched 2a would be produced. Although the reaction with chiral NHC also produces chiral cation 6, the formation of NHC from its precursor requires an additional base, and

Table 2. Substrate Scope

<table>
<thead>
<tr>
<th>entry</th>
<th>1</th>
<th>time (h)</th>
<th>2</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image" alt="1b" /></td>
<td>12</td>
<td><img src="image" alt="2b" /></td>
<td>71&lt;sup&gt;b&lt;/sup&gt; (81)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="1c" /></td>
<td>3</td>
<td><img src="image" alt="2c" /></td>
<td>82&lt;sup&gt;c&lt;/sup&gt; (88)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="1d" /></td>
<td>16</td>
<td><img src="image" alt="2d" /></td>
<td>51 (58)</td>
</tr>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image" alt="1e" /></td>
<td>16</td>
<td><img src="image" alt="2e" /></td>
<td>68 (74)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="1f" /></td>
<td>3</td>
<td><img src="image" alt="2f" /></td>
<td>77&lt;sup&gt;d&lt;/sup&gt; (75)</td>
</tr>
</tbody>
</table>

<sup>a</sup> The reaction was performed using 1 mol% of Cs₂CO₃.  
<sup>b</sup> dr 5:4.  
<sup>c</sup> dr 5:3:2.  
<sup>d</sup> The Michael adduct 3f formed in 16% yield.  
<sup>e</sup> For comparison, the results of previous work using NHC are shown in brackets.
therefore, there are other cationic species, such as metal ion or ammonium ion, which should compete against chiral 6, in the reaction mixture. As shown in Scheme 2, however, no significant asymmetric induction was observed so far in the reaction of 1a despite screening of the chiral phosphines.

![Scheme 2. Attempts to Develop Asymmetric Version](image)

### CONCLUSIONS

We have tested the performance of triphenyl and tributylphosphines, DMAP, and DABCO as an initiator of a migrative oxa- and azacycle forming reaction of sulfonylalkynols and sulfonylalkynamides. Although higher temperature was required for the reaction to proceed, the results obtained with triphenylphosphine were almost comparable to those with NHCs. Interestingly, not only DMAP and DABCO but also triphenyl and tributylphosphines effectively promote the tautomerization of propargyl sulfones into allenyl sulfones. Further effort to develop an enantioselective variant is in progress in this laboratory.

### EXPERIMENTAL

All melting points were measured on YANACO MP-500P micro melting point apparatus and reported without correction. IR spectra were measured with Shimadzu IRAffinity-1. H and 13C NMR spectra were recorded with JEOL ECA-500 spectrometers (500 and 125 MHz for H and 13C, respectively). High-resolution mass spectra were recorded with a Shimadzu LCMS-IT-TOF (ESI) mass spectrometer using...
MeOH as mobile phase. Optical rotations were recorded on a JASCO P-2200 polarimeter. Chiral HPLC analyses were performed with a Shimadzu Prominence HPLC. Column chromatography was performed on Fuji Silysis BW-200 silica gel. All the reagents, including dry solvents, were purchased and used as received.

Starting Materials. Propargyl sulfones 1a–f were prepared by previously reported procedures.1

Phosphine-Promoted Migrative Cyclization of Sulfonylalkynol and Sulfonylalkynamide.

General Procedure A. 2-(1-Tosylvinyl)tetrahydrofuran (2a): A 10 mL flame-dried test tube was charged with a magnetic stirring bar, PPh$_3$ (1.4 mg, 5.0 μmol), and 1a (25.2 mg, 0.100 mmol). The test tube was filled with argon by the evacuation–refill process. After addition of dry toluene (0.5 mL), the mixture was heated under reflux for 18 h and cooled to rt. Water was added to the test tube, and the whole was extracted with CHCl$_3$ (5 mL x 3). The combined organic layers were washed with water and brine, dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by column chromatography (hexane/EtOAc 3:1) to give the title compound (20.4 mg, 81%) as a colorless oil: $^1$H and $^{13}$C NMR, IR, and MS were in good agreement with those reported.

General Procedure B. trans- and cis-2-Allyl-5-(1-tosylvinyl)tetrahydrofuran (2b): A 10 mL flame-dried test tube was charged with a magnetic stirring bar, PPh$_3$ (1.4 mg, 5.0 μmol), Cs$_2$CO$_3$ (0.4 mg, 1 μmol), and 1b (29.2 mg, 0.100 mmol). The test tube was filled with argon by the evacuation–refill process. After addition of dry toluene (0.5 mL), the mixture was heated under reflux for 12 h and cooled to room temperature. Water was added to the test tube, and the whole was extracted with CHCl$_3$ (5 mL x 3). The combined organic layers were washed with water and brine, dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by column chromatography (hexane/EtOAc 3:1) to give a 5:4 mixture of the title compounds (21 mg, 71%) as a colorless oil: $^1$H and $^{13}$C NMR, IR, and MS were in good agreement with those reported.1

cis,trans-, trans,trans-, and cis,cis-5,5'-Bis(1-tosylvinyl)octahydro-2,2'-bifuran (2c): Procedure A, using 1c (50.3 mg, 0.100 mmol) in place of 1a, and purification by column chromatography (toluene/Et$_2$O 2:1) gave a 5:3:2 mixture of the title compounds (41.2 mg, 82%) as a yellow oil: $^1$H and $^{13}$C NMR, IR, and MS were in good agreement with those reported.1

1-(1-Tosylvinyl)isochromane (2d): Procedure A, using 1d (31.4 mg, 0.100 mmol) in place of 1a, and purification by column chromatography (hexane/EtOAc 5:1) gave the title compound (18.2 mg, 58%) as a colorless oil: $^1$H and $^{13}$C NMR, IR, and MS were in good agreement with those reported.1

2-(1-Tosylvinyl)pyrrolidine-1-carbaldehyde (2e): Procedure B, using 1e (28.0 mg, 0.100 mmol) in place of 1b, and purification by column chromatography (hexane/ EtOAc 10:1) gave the title compound (19.1 mg, 68%) as a light yellow oil. $^1$H and $^{13}$C NMR, IR, and MS were in good agreement with those reported.1
1-Tosyl-2-(1-tosylvinyl)pyrrolidine (2f) and 1-Tosyl-6-(tosylmethyl)-1,2,3,4-tetrahydropyridine (3f): Procedure A, using 1f (40.6 mg, 0.100 mmol) in place of 1a, and purification by column chromatography (hexane/Et₂O 2:3) gave a mixture of the title compounds (31.6 mg, 71% and 16%, respectively) as a yellow oil: \(^1\)H and \(^{13}\)C NMR, IR, and MS were in good agreement with those reported.\(^1\)

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES


9. The formation of phosphonium species 6 was confirmed in the reaction with Ph₃P (Table 1, entry 1; the aqueous work-up omitted) by ³¹P NMR of the crude material. The observed chemical shift (22.6 ppm) is in good agreement with that reported (23.0 ppm) for i-BuPPh₃Br: P. A. Byrne, K. V. Rajendran, J. Muldoon, and D. G. Gilheany, *Org. Biomol. Chem.*, 2012, 10, 3531.