HETEROCYCLES, Vol. 95, No. 1, 2017, pp. 314-321. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 4th August, 2016 , Accepted, 16th September, 2016 , Published online, 26th October, 2016
DOI: 10.3987/COM-16-S(S)22

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

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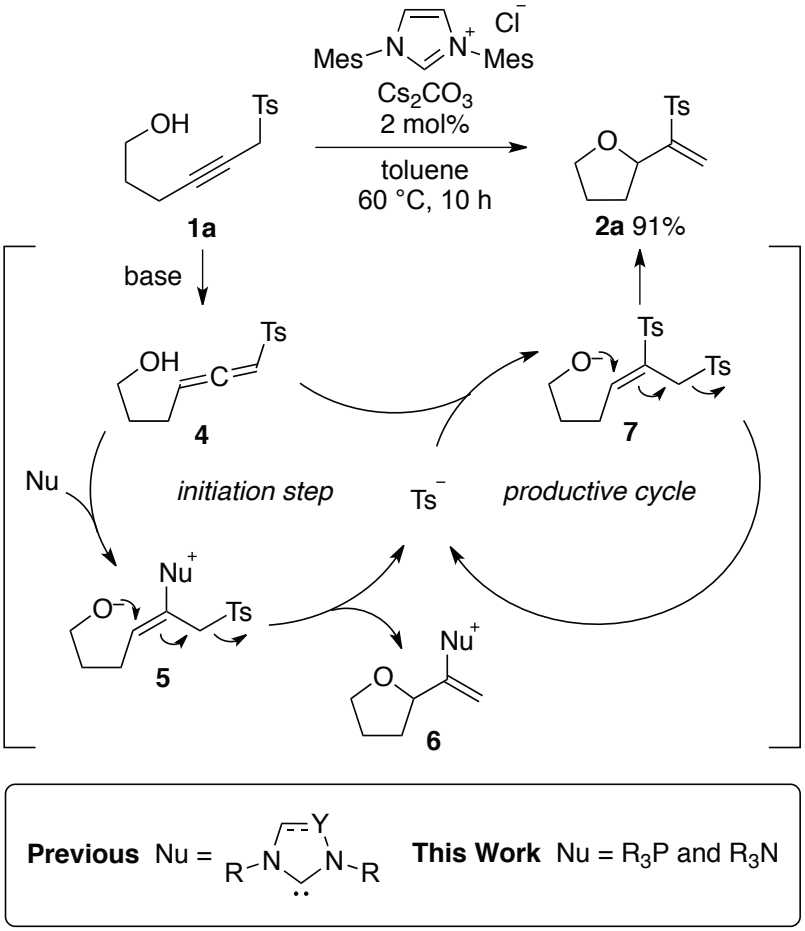
Abstract – A catalytic amount of phosphine or DMAP promoted the migrative cyclization of propargyl sulfones bearing an internal nucleophilic functionality in a γ-umpolung manner.

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]



Scheme 1. Proposed Mechanism for Migrative Cyclization

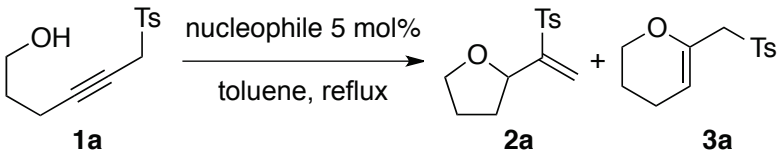
Based on the proposed mechanism, we envisioned that other nucleophiles should also induce this migrative cyclization. In the previous report, we preliminarily demonstrated that triphenylphosphine induces this transformation in the presence of cesium carbonate.[1] We herein report that *P*- and *N*-nucleophiles promote the migrative cyclization without additional bases.

RESULTS AND DISCUSSION

First, we tested several nucleophilic catalysts[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[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**,[8] 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[8] 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

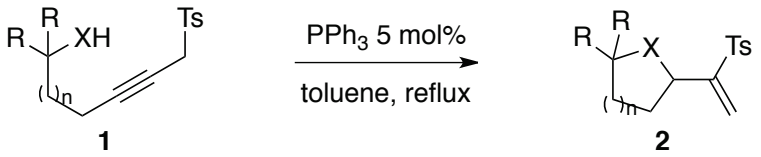


1a **2a** **3a**

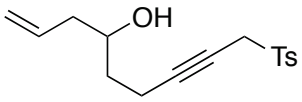
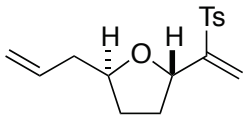
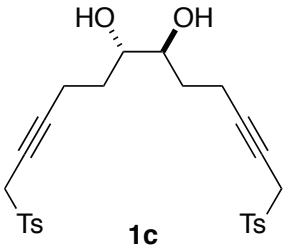
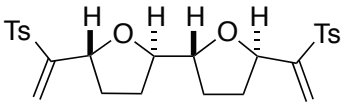
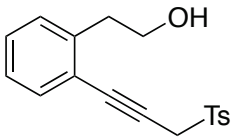
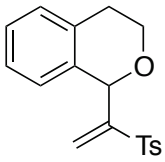
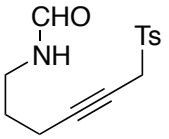
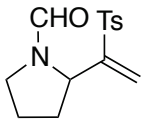
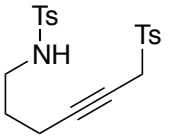
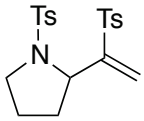
entry	nucleophile	time (h)	**2a** yield (%)	**3a** yield (%)	**1a** recovery (%)
1	Ph_3P	18	81	0	0
2	Bu_3P	24	37	0	12
3	DMAP	2	71	12	0
4	DABCO	19	0	80	0

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_2CO_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).[1] The requirement of additional base is probably due to slower S_N2' 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).[1] 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_2CO_3, formamide **1e** was smoothly converted to **2e** in 68% yield (entry 4) although the reaction failed to proceed without base. *N*-*p*-Toluenesulfonamide **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.

Table 2. Substrate Scope



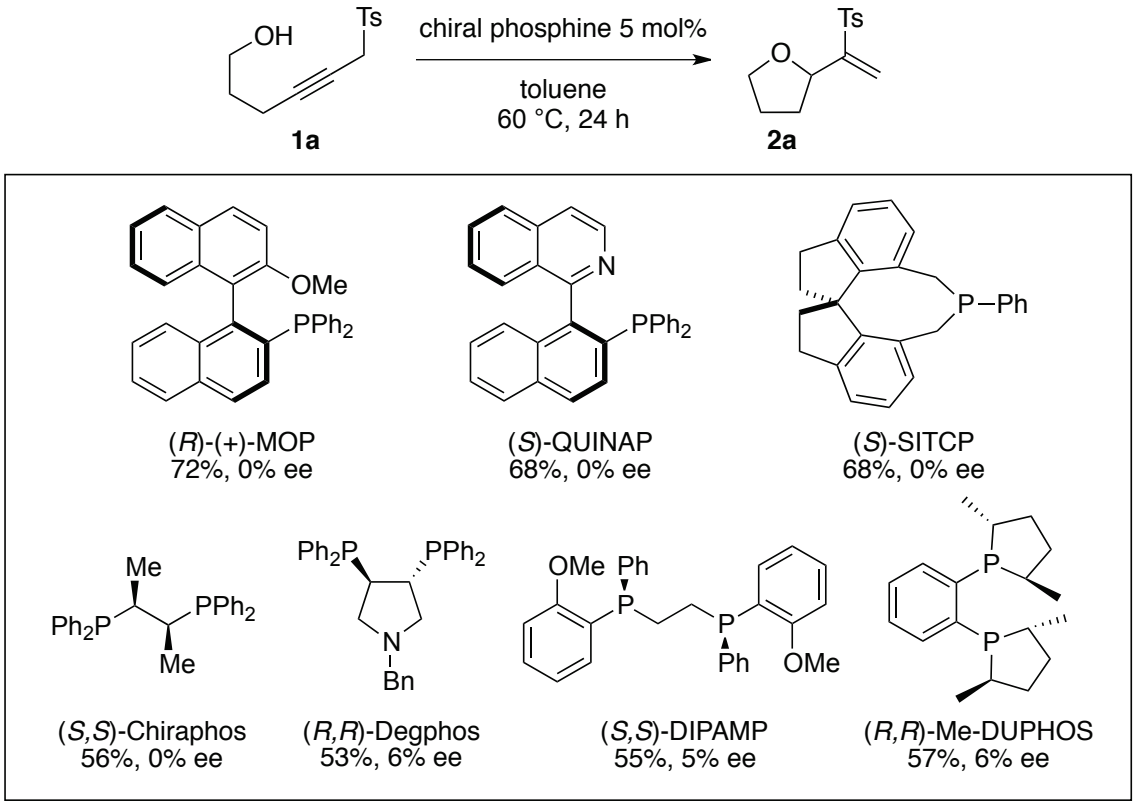
1 **2**

entry	**1**	time (h)	**2**	yield (%)[e]
1[a]	 **1b**	12	 **2b**	71[b] (81)
2	 **1c**	3	 **2c**	82[c] (88)
3	 **1d**	16	 **2d**	51 (58)
4[a]	 **1e**	16	 **2e**	68 (74)
5	 **1f**	3	 **2f**	77[d] (75)

[a] The reaction was performed using 1 mol% of Cs_2CO_3. [b] dr 5:4. [c] dr 5:3:2.
[d] The Michael adduct **3f** formed in 16% yield.
[e] For comparison, the results of previous work using NHC are shown in brackets.

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.[9] If the cation functions as a chiral counter ion of **7**, the S_N2' 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

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

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.[1] 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. ^{1}H and ^{13}C NMR spectra were recorded with JEOL ECA-500 spectrometers (500 and 125 MHz for ^{1}H and ^{13}C, 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 polarimater. Chiral HPLC analyses were performed with a Shimadzu Prominence HPLC. Column chromatography was performed on Fuji Silysia 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_2SO_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: ^1H and ^{13}C NMR, IR, and MS were in good agreement with those reported.[1]

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_2CO_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_2SO_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: ^1H 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_2O 2:1) gave a 5:3:2 mixture of the title compounds (41.2 mg, 82%) as a yellow oil: ^1H 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: ^1H 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. ^1H 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/Et_2O 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

We thank the Japan Society for the Promotion of Science (JSPS) [Grants-in-Aid for Scientific Research (B) and (C)] and the Japanese Ministry of Education, Culture, Sports, Science and Technology (Grants-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" and for Scientific Research and Platform for Drug Design, Discovery, and Development) for financial support. R.O. thanks JSPS for a postdoctoral fellowship.

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9. The formation of phosphonium species **6** was confirmed in the reaction with Ph_3P (Table 1, entry 1; the aqueous work-up omitted) by ^{31}P NMR of the crude material. The observed chemical shift (22.6 ppm) is in good agreement with that reported (23.0 ppm) for *i*-$BuPPh_3Br$: P. A. Byrne, K. V. Rajendran, J. Muldoon, and D. G. Gilheany, *Org. Biomol. Chem.*, 2012, **10**, 3531.