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Brønsted Base Catalyzed [2,3]-Wittig/ Phospha-Brook Tandem Rearrangement Sequence

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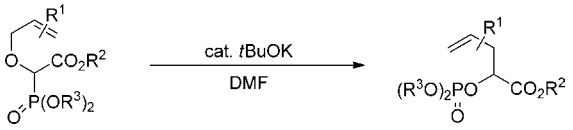
ABSTRACT



A Brønsted base catalyzed rearrangement reaction of 2-allyloxy-2-phosphonoacetate derivatives was developed. This reaction proceeded via a [2,3]-Wittig rearrangement followed by a phospha-Brook rearrangement. This is the first example of a catalytic [2,3]-Wittig rearrangement initiated by a Brønsted base.

The [2,3]-Wittig rearrangement is a useful tool in synthetic organic chemistry, especially for the total synthesis of natural products and the preparation of bioactive compounds.[1] The conventional initiation of this rearrangement is accomplished through generation of α-allyloxy carbanions by deprotonation using a stoichiometric amount of strong Brønsted bases, such as *n*BuLi and NaH, followed by [2,3] sigmatropic rearrangement to provide homoallyl alkoxides. Many reaction systems in [2,3]-Wittig rearrangement have been studied thoroughly. Among the systems investigated, catalytic rearrangements have stimulated intensive interest because they allow a reaction without the use of a stoichiometric amount of a strong Brønsted base. To develop a catalytic rearrangement, methods using a Lewis base[2] as well as a Lewis acid catalyst[3] have been reported. However, these catalytic methods require preformed silyl enol ethers of α-allyloxy esters or ketones.[4] Recently, a direct rearrangement without preparation of a preformed enolate equivalent was reported using a secondary amine catalyst.[5] Although this direct catalysis can be performed under mild reaction conditions, the substrates are inherently limited to α-allyloxy ketones because of participation of the enamine intermediate generated from the ketone and secondary amine catalyst. No direct rearrangements using Brønsted base catalysis have been reported to date. In this context, we designed a tandem rearrangement sequence to develop a novel catalytic [2,3]-Wittig rearrangement initiated by Brønsted bases. In our proposed system, a [2,3]-Wittig rearrangement is combined with a phosphonate–phosphate rearrangement, so-called phospha-Brook rearrangement,[6,7] using substrates containing a phosphono

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(3) Mikami, K.; Takahashi, O.; Tabei, T.; Nakai, T. *Tetrahedron Lett.* **1986**, *27*, 4511.

(4) Lewis acid catalyzed [2,3]-rearrangement of propargyloxy enols was reported; see: Moniz, G. A.; Wood, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 5095.

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(6) For early studies, see: (a) Fitch, S. J.; Moedritzer, K. *J. Am. Chem. Soc.* **1962**, *84*, 1876. (b) Hall, L. A. R.; Stephenes, C. W.; Drysdals, J. J. *J. Am. Chem. Soc.* **1957**, *79*, 1768. (c) Barthel, W. F.; Alexander, B. H.; Giang, P. A.; Hall, S. A. *J. Am. Chem. Soc.* **1955**, *77*, 2424. (d) Mattson, A. M.; Spillane, J. T.; Pearce, G. W. *J. Agric. Food Chem.* **1955**, *3*, 319. (e) Lorenz, W.; Henglbin, A.; Schrader, G. *J. Am. Chem. Soc.* **1955**, *77*, 2554.

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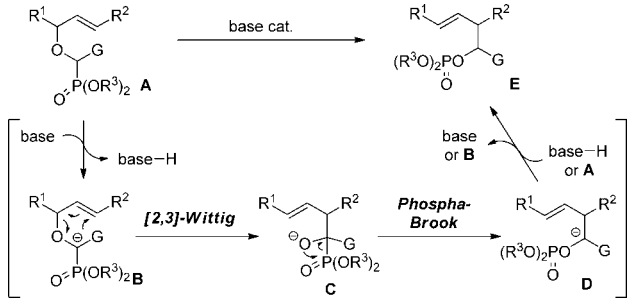
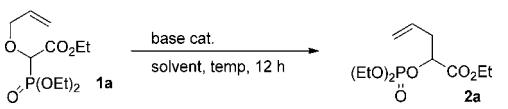
group α to an allyloxy group. The proposed reaction is shown in Scheme 1. At first, deprotonation by a Brønsted base followed by [2,3]-Wittig rearrangement provides alkoxide **C**. Conventional [2,3]-Wittig rearrangement is terminated at this point; for the designed substrate, 1,2-rearrangement of the phosphono group from carbon to oxygen, i.e., phospha-Brook rearrangement, occurs to generate carbanion **D**. Finally, carbanion **D** is protonated by the conjugated acid of the Brønsted base or substrate **A** to afford the product along with regeneration of the Brønsted base or carbanion **B**. The key step for the catalytic reaction is the last step of the catalytic cycle, which involves regeneration of the Brønsted base or α-allyloxy carbanion. For conventional [2,3]-Wittig rearrangement, this step is difficult because the acidity of the proton α to the allyloxy group of the substrate is lower than that of the hydroxy proton of the product. In contrast, the newly designed reaction system maintains the acidity of the substrate that is relatively high compared to that of the product because of the influence of an electron-withdrawing phosphono group. As a consequence, protonation of carbanion **D** to regenerate a Brønsted base or carbanion **B** can occur and reaction should proceed catalytically. This report describes the tandem rearrangement of phosphonoacetate derivatives containing an allyloxy group in the presence of a catalytic amount of a Brønsted base.

Scheme 1. Proposed Catalytic System



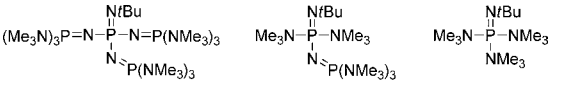
To ascertain the viability of the proposed tandem rearrangement, we attempted the reaction of ethyl 2-allyloxy-2-diethylphosphonoacetate (**1a**) as the primary substrate. An initial experiment was performed using 10 mol % of *t*BuOK in DMF at 90 °C for 12 h. Delightfully, the envisioned tandem rearrangement proceeded catalytically to afford **2a** in 89% NMR yield and 86% isolated yield (Table 1, entry 1). This preliminary result prompted us to a further screening of Brønsted bases, including

Table 1. Screening of Reaction Conditions[a]



entry	base (mol %)	solvent	temp	yield (%)[b]
1	*t*BuOK (10)	DMF	90 °C	89 (86)
2	LHMDS (10)	DMF	90 °C	81
3	Cs_2CO_3 (10)	DMF	90 °C	(86)
4	P4-*t*Bu (10)	DMF	90 °C	82 (81)
5	P2-*t*Bu (10)	DMF	90 °C	88 (85)
6	P1-*t*Bu (20)	DMF	90 °C	32
7	TBD (20)	DMF	90 °C	34
8	DBU (20)	DMF	90 °C	14
9	*t*BuOK (10)	DMF	rt	(93)
10	P2-*t*Bu (10)	DMF	rt	(86)
11	*t*BuOK (10)	DMSO	rt	(86)
12	*t*BuOK (10)	THF	rt	75
13	*t*BuOK (10)	1,4-dioxane	rt	52
14	*t*BuOK (10)	toluene	rt	0
15	*t*BuOK (10)	*t*BuOH	rt	0

[a] Reaction conditions: **1a** (0.10 mmol), base (0.010−0.020 mmol), solvent (1.0 mL), 90 °C or rt, 12 h. [b] NMR yields of **2a**. $CHBr_3$ was used as an internal standard. Isolated yields are in parentheses.



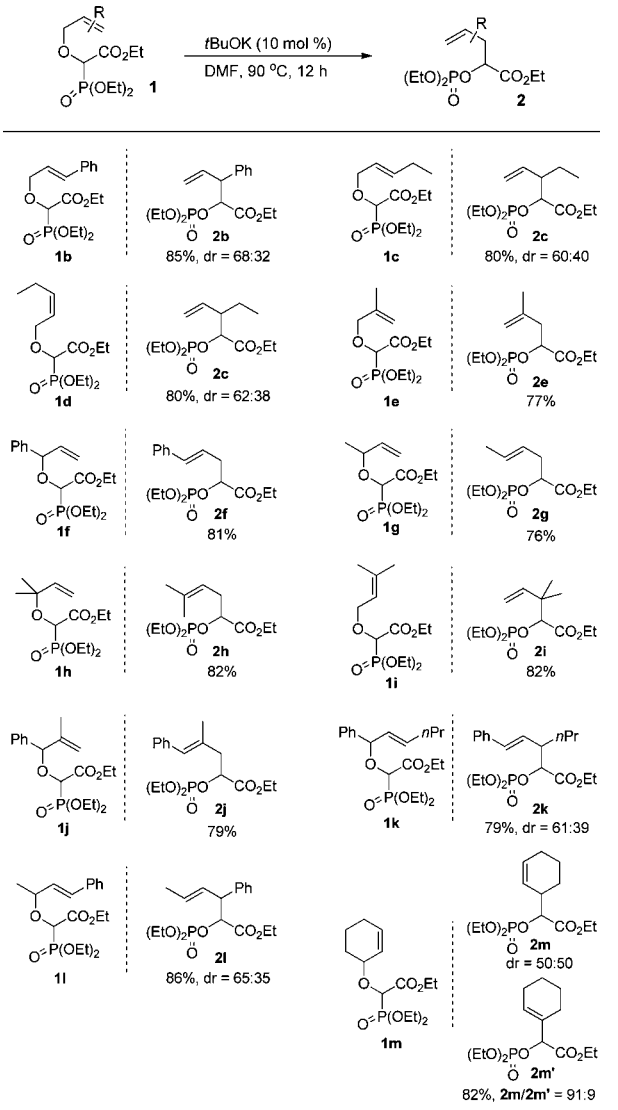
inorganic bases as well as organic bases (entries 2−8). Among them, inorganic bases, such as LHMDS and Cs_2CO_3, and phosphazene bases P2-*t*Bu and P4-*t*Bu, which are organosuperbases, provided **2a** in good yield. With these bases, *t*BuOK and P2-*t*Bu, the reaction proceeded smoothly even at room temperature (entries 9 and 10). Next, the effect of solvents was investigated with *t*BuOK at room temperature (entries 11−15). The result indicated that aprotic polar solvents such as DMF and DMSO proved to be the solvents of choice (entries 9 and 11), whereas ethereal solvents were less effective (entries 12 and 13). The use of toluene and *t*BuOH did not provide any product, and **1a** was completely recovered (entries 14 and 15).

With the optimized conditions in hand, the scope of the substrates was investigated (Scheme 2).[8] Substrates possessing a variety of substitution patterns involving an allyloxy group were subjected to the reaction conditions. Reactions of **1b** and **1c**, which have a *trans*-1,2-disubstituted alkene moiety, proceeded to provide the corresponding products **2b** and **2c**, respectively, in good yield with moderate diastereoselectivity. The *cis*-alkene **1d** gave a result similar to that of *trans*-alkene **1c**. A methallyloxy-substituted **1e** also underwent the reaction to afford **2e** in good yield. Next, the substrates containing substituents at the allylic

(7) For selected examples, see: (a) Bausch, C. C.; Johnson, J. S. *Adv. Synth. Catal.* **2005**, *347*, 1207. (b) Demir, A. S.; Reis, Ö.; İğdir, A. Ç.; Esiringü, İ.; Eymur, S. *J. Org. Chem.* **2005**, *70*, 10584. (c) Demir, A. S.; Reis, B.; Reis, Ö.; Eymür, S.; Göllü, M.; Tural, S.; Saglam, G. *J. Org. Chem.* **2007**, *72*, 7439. (d) Demir, A. S.; Esiringü, I.; Göllü, M.; Reis, Ö. *J. Org. Chem.* **2009**, *74*, 2197. (e) El Kaïm, L.; Gaultier, L.; Grimaud, L.; Dos Santos, A. *Synlett* **2005**, 2335. (f) Hayashi, M.; Nakamura, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 2249. (g) Corbett, M. T.; Uraguchi, D.; Ooi, T.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 4685.

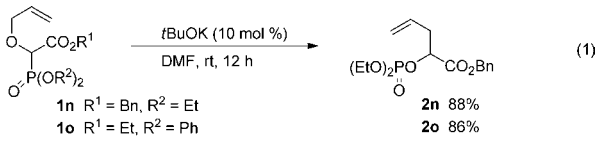
(8) The reaction was conducted at 90 °C because the reaction of the substrates possessing substituent(s) on the allyloxy moiety was very slow at room temperature.

Scheme 2. Substrate Scope[a]



[a] Reaction conditions: **1** (0.20 mmol), *t*BuOK (0.020 mmol), DMF (2.0 mL), 90 °C, 12 h. Ratios of diastereomers were determined by ^{1}H NMR analysis of a crude mixture.

position were investigated. Monosubstituted **1f** and **1g** as well as disubstituted **1h** underwent the reaction smoothly to afford the corresponding products in high yields. Note that the reaction of **1f** and **1g** proceeded with perfect *E* selectivity. Two substituents at the alkene terminus did not compromise the reaction, and **2i** was produced in good yield. The reaction of **1j** occurred in an entirely stereoselective manner to provide the corresponding stereodefined trisubstituted alkene **2j**. Finally, the substrates with a substituent at each allylic position and alkene terminus were examined. For **1k** and **1l**, the reaction proceeded in good yield with perfect *E* selectivity and moderate diastereoselectivity. In contrast, **1m** provided the corresponding product **2m**, which has a cyclic *Z* alkene moiety, as a 1:1 diastereomixture along with a small amount of isomer **2m′**. The use of phosphonoacetate is essential for this reaction (eq 1, Figure 1). The other acetate such as benzyl acetate **1n** underwent the reaction smoothly as with **1a** (eq 1). The substrate **1o**, which had a diphenylphosphono group instead of diethylphosphono group, also reacted to provide the corresponding product **2o** in high yield. In contrast, the reaction of *N*,*N*-dialkylacetamide analog **1p** and acetophenone analog **1q** did not afford the desired products (Figure 1). The reaction of an acetonitrile analog **1r** provided a complex mixture of products.



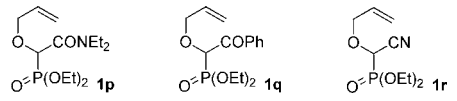
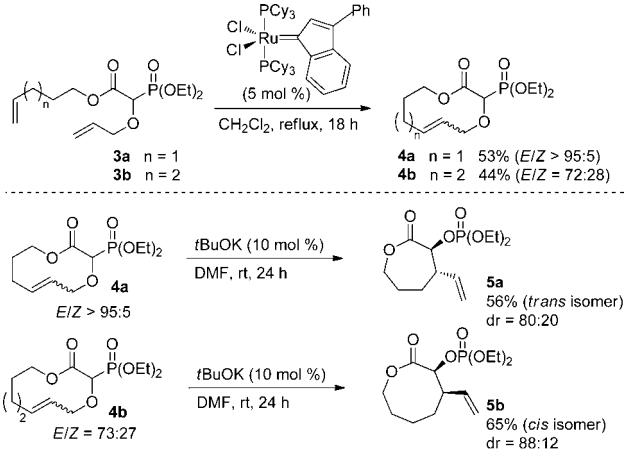


Figure 1. Unsuitable substrates for the reaction.

Additional investigation of this reaction involved application to ring contraction (Scheme 3).[9] The 11- and 12-membered substrates **4a** and **4b** were synthesized by ring-closing metathesis of dienes **3a** and **3b**, respectively.[10] The substrates obtained then were subjected to the reaction conditions. Both substrates underwent the reaction to provide the corresponding 7- and 8-membered lactones **5a** and **5b**, respectively, with good diastereoselectivity. Interestingly, in the reaction of **4a**, the *trans* isomer was obtained as the major diastereomer, while **4b** afforded the *cis* isomer as the major diastereomer.[11] These major isomers were easily isolated using silica gel column chromatography.

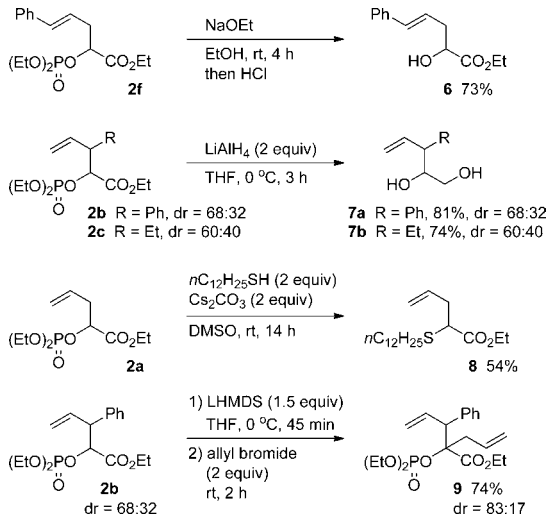
Scheme 3. Application to Ring Contractions



(9) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315.

(10) Fürstner, A.; Guth, O.; Düffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem.—Eur. J.* **2001**, *7*, 4811.

Scheme 4. Transformation of **2**



The products of this reaction possess a diethoxyphosphoryloxy group, which can function as a handle for further manipulation. Based on this functionality, several transformations were performed (Scheme 4). For example, treatment of **2f** with sodium ethoxide in ethanol provided the corresponding hydroxy ester **6** in good yield. The reduction of **2b** and **2c** with $LiAlH_4$ provided the corresponding diols **7a** and **7b**, respectively, in good yields. Nucleophilic substitution occurred by treating **2a** with dodecanethiol in the presence of cesium carbonate, where a diethoxyphosphoryloxy group served as a leaving group. Finally, allylation of the α position of an ester was conducted to yield a product containing a tetrasubstituted carbon.

In conclusion, a novel catalytic [2,3]-Wittig rearrangement was developed by utilizing phospha-Brook rearrangement, which is the first example of direct rearrangement under Brønsted base catalysis. This operationally simple reaction is applicable to substrates containing substitutions on an allyloxy moiety and can provide building blocks that are easily modified in a variety of ways. Further investigation of this methodology, including development of an enantioselective rearrangement, is now in progress.

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Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) Relative configurations of the major isomers of **5a** and **5b** were determined by NOE analysis. See Supporting Information for details.

The authors declare no competing financial interest.