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Base-promoted [1,4]-Wittig rearrangement of chalcone-derived allylic ethers leading to aromatic β-benzyl ketones†

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n-BuLi-promoted [1,4]-Wittig rearrangement of allylic ethers was developed successfully in this work, in which the Wittig rearrangement reaction provided a facile approach to the synthesis of aromatic β -benzyl ketones under mild reaction conditions.

Since Wittig and Löhmann reported the first example of 1,2alkyl migration from an oxygen atom to a carbanion center in the rearrangement reaction of benzylic ethers with phenyllithium in 1942,¹ Wittig arrangement of ethers to alcohols has been proven to be a synthetically useful reaction in organic synthesis.² Especially in the past years, [1,2]- and [2,3]-Wittig rearrangements are a particularly attractive for the synthesis of secondary alcohols with both variations having found widespread use in synthesis.^{3,4} In this context, we have ever reported a facile and practical methodology for the preparation of chiral alcohols via [1,2]-Wittig rearrangement, in which the axially chiral monoalkylated BINOLs could be converted into optically pure 1,1'-binaphthalene-2-a-arylmethanol-2'-ols (Ar-BINMOLs) with axial and sp³-central chirality through the axial-to-central chirality transfer during the neighbouring lithium-assisted [1,2]-Wittig rearrangement (NLAWR).⁵ This work provided a springboard for the synthesis and application of a series of Ar-BINMOL-based chiral ligands in versatile catalytic asymmetric transformations.⁶ Although the earlier investigation on [1,4]-Wittig rearrangement of allylic ethers have also been demonstrated in the past decades,⁷ relative to its [1,2]- and [2,3]-counterparts, the research work of [1,4]-Wittig rearrangement remained limited because of its narrow scope of this method and imperfect chemoselectivity. Notably, different from [2,3]-and [1,2]-Wittig rearrangement, [1,4]-Wittig rearrangement is unique in its ability to generate stereodefined enolates and the ketone derivatives (Scheme 1).⁸ And it has been demonstrated that the role of base and solvent was key to the reactivity and different reaction pathways, [1,4]- or [2,3]-Wittig rearrangement.^{8d} In this regard, Maleczka and coworkers have recently reported their findings on the [1,4]-Wittig rearrangement of α -benzyloxyallylsilanes or α -alkoxysilanes to α substituted acylsilanes, in which the [1,4]-Wittig rearrangement provided a unique method for the synthesis of a variety of synthetically useful acylsilanes.⁹ Nonetheless, the substrate scope of the [1,4]-Wittig rearrangement of allylic ethers is not well documented and thus its potential in synthetic organic chemistry needs to be further elucidated.

To the best of our knowledge, no reports of base-mediated [1,4]-Wittig rearrangement of general allylic benzyl ethers, and the Wittig rearrangement of chalcone-derived allylic ethers with benzylic groups is unclear (Scheme 2). On the basis of our previous findings on [1,2]-Wittig rearrangement of THP (tetra-hydropyran) acetal compounds¹⁰ and monoalkylated BINOLs,^{5,6}



Scheme 1 Possible pathways for the different variations of Wittig rearrangement of allylic ethers with benzylic group.

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Scheme 2 What's the product of base-promoted Wittig rearrangement of chalcone-derived allylic ether (1a)?

we continued to establish a simple Wittig rearrangement of chalcone-derived allylic ethers to the facile synthesis of aromatic β-benzyl ketones. Fortunately, we successfully find the [1,4]-Wittig rearrangement was the major pathway for this transformation of carbon-oxygen bond cleavage and subsequent new carbon-carbon bond-forming reaction.

Initially, the rearrangement precursor 1a was prepared by the allylic alkylation of allylic acetate with benzylic alcohols in the presence of palladium catalyst.11 Then the Wittig rearrangement of allylic ether 1a was investigated under different condition showed in Table 1. Employing, 1.2 equivalents of n-BuLi in hexane as base, allylic ether 1a was rearrangement smoothly under low temperature (-40 °C). Good yield (80%) of the β -benzyl ketone 2a was achieved via [1,4]-Wittig rearrangement. With this preliminary study complete, we tested different lithium, sodium, or potassium bases in the Wittig rearrangement of allylic ether 1a. The control experiments revealed that other strong bases, such as NaOtBu, LiHDMS, KOtBu, and

Table 1 Optimizing the [1,4]-Wittig rearrangement of chalconederived allylic ether 1a

Ph.

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Ph Ph Ph Ph	Ph +	Ph OH Ph
1a	2a	За
Base	Solvent	Yield of $2\mathbf{a}^{b}$ (%)
<i>n</i> -BuLi	THF	80
NaOtBu	DCM	<5
LiHDMS	DCM	42
KOtBu	DCM	<5
<i>n</i> -BuLi	Et_2O	65
<i>t</i> -BuLi	THF	33
NaOtBu	THF	<5
KOtBu	THF	<5
<i>n</i> -BuLi	DCM	57
<i>n</i> -BuLi	MeCN	24
<i>n</i> -BuLi	DMAc	68
<i>n</i> -BuLi	Toluene	77
	Ph Ph Ph Ph? Ph? Ph? Ph Ph? Ph Ph? Ph Ph? Ph Ph? Ph Ph? Ph Ph? Ph Ph? Ph Ph? Ph?	Base Ph 2 Ph 2 Ph 2 Ph 2 Ph 2 Ph 2 Ph 2 Ph 4 Ph 4

^a The Wittig rearrangement was carried out with 0.5 mmol of allylic ether 1a, 0.6 mmol of *n*-BuLi in hexane, in THF, at -40 °C, for 6 h. ^b Isolated yield of **2a**, and the selectivity was perfect because product 3a of [2,3]-Wittig rearrangement was not detected in this reaction.

t-BuLi, gave low or moderate yields at the same reaction temperature. The use of sodium and potassium bases led to almost no [1,4]-Wittig rearrangement reaction. When LiHDMS or t-BuLi was used as base in this reaction, only moderate yield was obtained (33-42% yields). Thus n-BuLi proved to be superior to t-BuLi and other lithium bases, leading to high conversion of the allylic ether 1a. Notably, the THF was found to be better solvent than Et₂O in this reaction. And interestingly, we did not find the formation of 3a that could be obtained via [2,3]or [1,2]-Wittig rearrangement in the presence of *n*-BuLi. The ketone 2a could be isolated as the only product in this rearrangement reaction. These results showed the strong base and relative thermodynamic stabilities of C1' and C2 anions might favor the [1,4]-Wittig rearrangement over [2,3]-Wittig rearrangement.^{2c,9,15c} Although deprotonation at benzylic carbon center (Ph-CH₂(C1')-O) is associated with [2,3]-Wittig rearrangement as well, we suggested the deprotonation at the benzylic carbon center (C1') led to the formation of a higher reactive benzylic anion than that of allylic carbon (Ph-CH(C2)-CH=CH) anion because of steric repulsion. Thus the method allows providing a straightforward alternative for preparing the rather elusive γ -arylated ketones that are synthetically useful intermediates in organic synthesis and have been found in as basic backbone in natural products.12

With the optimized conditions in hand, the scope of the allylic ethers was investigated in the next study. As shown in Scheme 3, various chalcone-derived allylic ethers (1) possessing a variety of substitution pattern involving a benzylic group were subjected to the reaction conditions. Reactions of 1b and 1c, which have para-substituted methyl or methoxyl group on benzylic ether moiety, proceeded to provide the corresponding products 2b and 2c, respectively, in good yield. The substrate 1d with steric group on two ortho-substituted methyl groups also gave good yield of product 2d. Interestingly, the trifluoromethoxyl group on the allylic ether did not affect the [1,4]-Wittig rearrangement obviously due to the promising conversion (62% isolated yield) in this reaction. Not surprisingly, substituted chalcones with electron-donor group as starting material for the construction of corresponding allylic ether substrates, were also exhibited to be good substrates in the [1,4]-Wittig rearrangement. However, the allylic ethers with electrondeficient substituents, such as CF₃, NO₂, and halides (Cl, Br, I) were not suitable substrates because of poor conversions or dehalogenation.

In order to synthesize the chiral aromatic β -benzyl ketone, additional investigation of such [1,4]-Wittig rearrangement involved application to possible enantioselective transformation of chiral allylic ether. In our previous report, we demonstrated successfully its effectiveness of our novel chiral phosphine ligand (CycloN2P2-Phos) in palladium-catalyzed asymmetric allylic etherification (AAE) of general alcohols and silanols (Scheme 4), which afforded the corresponding allylic ethers with excellent enantioselectivities (93-99% ee).13 Thus we applied the chiral allylic ether (R)-1a (96% ee) in the [1,4]-Wittig rearrangement. Unfortunately, the [1,4]-Wittig rearrangement of chiral allylic ether resulted in racemic product 2a. On the other hand, the result illustrated in Scheme 5 provides



Scheme 3 [1,4]-Wittig rearrangement of chalcone-derived allylic ethers to aromatic β -benzyl ketones.



Scheme 4 Synthesis of chiral allylic ethers through Pd/CycloN2P2-Phos-catalyzed asymmetric allylic etherification of various alcohols with allylic acetates.

considerable information about the likely radical mechanism of the Wittig rearrangement.¹⁴ The conversion of chiral substrate **1a** to racemic product **2a** suggests this mechanism of this unusual rearrangement involves the formation of enolate intermediate that make the stereogenic sp³ carbon-center to sp² carbon center.



Scheme 5 [1,4]-Wittig rearrangement of chiral allylic ether 1a (96% ee).



Scheme 6 Possible mechanism of base-promoted [1,4]-Wittig rearrangement of allylic ether 1.

On the basis of these results and previous reports on basemediated benzylic rearrangement,2,3,5,15 a plausible mechanism for the conversion of allylic ether **1** to aromatic β -benzyl ketone 2 is illustrated in Scheme 6. In the radical pathway (Path A), the treatment of allylic benzyl ether 1 with strong base (such as *n*-BuLi) leads to the formation of allylic or benzylic anion (I) by deprotonation at the benzylic position, which is a common intermediate for variations of Wittig rearrangement. And then the dissociative process involving the formation of a pair of radicals and subsequent recombination occur to form the enolate (III). Upon workup, protonation of the enolate would generate the intermediate IV and the total product 2a. The alternative reaction pathway looks possibly for the intramolecular nucleophilic addition of benzylic anion to double bond, and then performs a Claisen-like 1,4-sigamatropic rearrangement followed protonation of enolate intermediate to form the observed product 2a (Path B). However, the [1,4]-Wittig rearrangement of chiral allylic ether 1a revealed that the Path B is not reasonable or major pathway because there is no ee value for the desired product 2a. In addition, we found that the [1,4]-Wittig rearrangement did not occur in the presence of 2,2,4,4tetramethyl-1-piperidinyloxy (TEMPO), in which the direct evidence supported the radical pathway (Path A) in the proposed mechanism.

Conclusions

In summary, we have discovered an unusual [1,4]-Wittig rearrangement reaction of chalcone-derived allylic ethers upon deprotonation with *n*-BuLi. The reactions produce potentially useful aromatic β -benzyl ketone in moderate to good yields with unprecedented selectivity. It appears to proceed *via* radical alkylation and enolate intermediate. Further studies will be directed toward improving enantioselectivity of [1,4]-Wittig rearrangement and expanding the scope of these transformations.

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