Isomerization of Allyl Ethers Initiated by Lithium Diisopropylamide
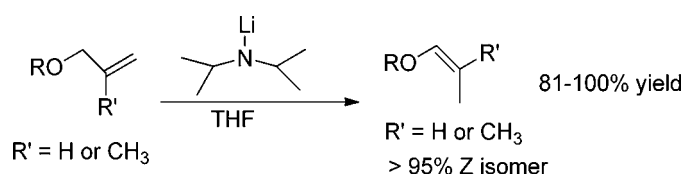
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ABSTRACT

Lithium diisopropylamide (LDA) promotes virtually quantitative conversion of allylic ethers to (*Z*)-propenyl ethers. It was discovered that allylic ethers can be isomerized efficiently with very high stereoselectivity to (*Z*)-propenyl ethers by LDA in THF at room temperature. The reaction time for the conversion increases with more sterically hindered allylic ethers. Different amides were also compared with LDA for their ability to effect this isomerization.

Vinyl ethers are important synthetic intermediates in numerous reactions such as isoxazoline synthesis,[1] cycloaddition,[2] and cross aldol reactions.[3] Moreover, vinyl ethers can be easily photopolymerized to produce polymers that are used as photocurable coatings, inks, and adhesives.[4] An efficient preparation of vinyl ethers is to prepare allyl ethers by O-alkylating an alcohol with allyl bromide followed by isomerization.[5] Such isomerization reactions have been studied and are divided into two categories: base-catalyzed[6] and transition-metal-catalyzed reactions.[7] Ruthenium and iridium complexes are reported to catalyze allyl ethers stereoselectively to *trans*-vinyl ethers.[7–9] Although it is

Scheme 1. Isomerization of Allyl Ethers Initiated by LDA
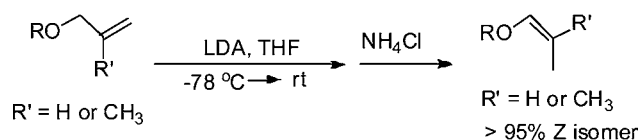
convenient to use transition metal complexes, the methods suffer from the fact that both ruthenium and iridium are expensive and are not suitable for large-scale reactions. While iron and molybdenum complex catalyzed isomerization reactions have also been reported, both reactions produced mixtures of cis and trans isomers.[5,10] For the base-catalyzed reactions, the most widely used method is to treat the allyl ethers with potassium *tert*-butoxide (*t*-BuOK) in

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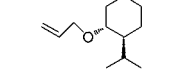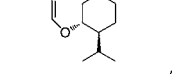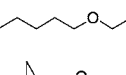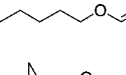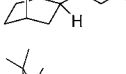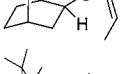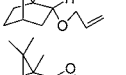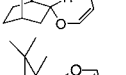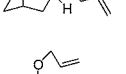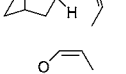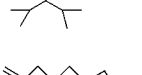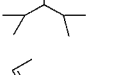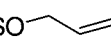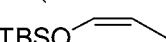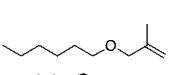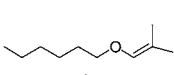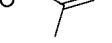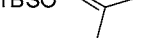
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Table 1. LDA-Catalyzed Isomerization of Various Allyl Ethers[a]

entry	allyl ether	amount of LDA	time	product	yield
1		2 equiv	0.75 h		88%
2		2 equiv	0.67 h		83%
3		2 equiv	0.75 h		88%
4		2 equiv	0.75 h		99%
5		2 equiv	0.75 h		100%
6		2 equiv	1.5 h		100%
7		2 equiv	0.67 h		92%
8		2 equiv	1.0 h		89%
9		2 equiv	1.5 h		95%
10		4 equiv	4.5 h		100%
11		6 equiv	21 h		87%
12		4 equiv	1.5 h		100%
13	TBSO	2 equiv	3.5 h	TBSO	81%
14		2 equiv	1.2 h		100%
15	TBSO	2 equiv	4 h	TBSO	85%

[a] A solution of diisopropylamine in dry THF was cooled to −78 °C; 1 equiv of *n*-BuLi in *n*-pentane was added dropwise; and the resulting solution was allowed to cool in a −78 °C bath for 5 min before the allyl ether was added drop by drop to the solution. The solution was allowed to warm and stand at room temperature for the corresponding amount of time before being quenched with saturated ammonium chloride solution.

dimethyl sulfoxide (DMSO) solution. Although the method achieved varying degrees of success,[5,11−13] it is limited by the fact that heating is usually required for the isomerization reaction.[6a,12,13] Moreover, since the reaction is exothermic, an increase in temperature will cause the equilibrium to shift

back to the allyl ethers.[14] Butyllithium has also been reported to isomerize allyl ethers,[15] but the yields were relatively low due to the fact that deallylation[16] or Wittig rearrangement[17] may occur. We report an efficient method of allyl ether isomerization initiated by LDA (Scheme 1) and a comparison

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of a series of *t*-BuOK-initiated isomerization reactions with the LDA-initiated isomerization.

In 1970, Dimmel and Gharpure reported the use of sodium amide in dimethoxyethane to isomerize allyl phenyl ether to (*Z*)-(prop-1-en-1-yloxy)benzene in 54% yield.[18] To the best of our knowledge, this is the first allyl ether isomerization using an amide base. We report that lithium diisopropylamide effects this isomerization in ethereal solvents like THF and dimethoxyethane readily. Other allyl ethers have also been investigated, and these results are summarized in Table 1.
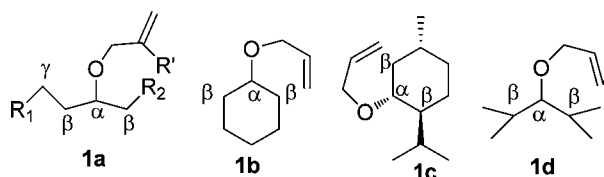

Figure 1. (a) Definition of α and β positions and R′ group of the allyl ethers. (b) An example of allyl ether without β branched chain. (c) An example of allyl ether with only one β branched chain. (d) An example of allyl ether with two β branched chains.

Branched chains at the β-position (Figure 1) of the allyl ethers reduce the speed of isomerization depending on the extent of substitution and steric bulk of the branched chain. Allyl ethers with no β branched chain (Table 1, entries 1−5, 7) isomerize much faster than other allyl ethers with β branched chains. Allyl ethers having only one β branched chain (Table 1, entries 6, 8) react faster than those with two β branched chains (Table 1, entry 10). When β branched chains are on both sides of the allyl ether (Table 1, entry 11), the isomerization rate decreases drastically. The results suggest that steric hindrance in the β position plays an important role in the rate of isomerization. Moreover, the allyl ether derived from borneol (Table 1, entry 9) isomerized much faster than that derived from isoborneol (Table 1, entry 10) presumably due to the fact that the allyl group from the former one experiences less steric hindrance than the allyl group of the latter one.

The isomerization rate slows down when R′ is a methyl group instead of a proton (Figure 1, **1a**). However, the effect of a γ branched chain (Figure 1, **1a**) on reaction rate is small compared to the effect of a β branched chain. The isomerization reaction for allyl ether derived from 3,3,5,5-tetramethylcyclohexanol (Table 1, entry 5) was done within 45 min and was much faster than that of menthol derived allyl ether (Figure 1, **1c**).

We suspect that the yields of the reactions of enol ethers with lower boiling points appear lower and are correlated with the boiling points of the enol ethers because some loss of the lower boiling products was unavoidable upon work up.

Several different amide bases have also been tested for their ability to effect this isomerization reaction. The allyl ether derived from cycloheptanol (Scheme 2) was chosen

Scheme 2. Isomerization of (Allyloxy)cycloheptane Initiated by Different Amides
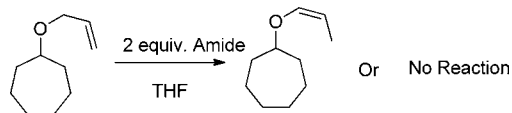
as the model substrate for surveying the effectiveness of different amides because it has no β branched chain and because of its relative high boiling point. The results are summarized in Table 2.

**Table 2.** Isomerization of (Allyloxy)cycloheptane by Different Amides

entry	amide	time	yield
1		0.75 h	100%
2		1.75 h	93%
3[a]		8 h	97%
4	NaNH$_2$		No Reaction
5	LiNH$_2$		No Reaction
6	LiHMDS		No Reaction

[a] 5 equiv if lithium amide base was used.

Lithium bis(trimethylsilyl)amide (LiHMDS) failed to initiate the reaction. Neither lithium nor sodium amide effected this rearrangement. The reaction time for entry 3 was significantly longer than that of entries 1 and 2 probably because the lithium ion was internally solvated.[19]

Several experiments using *tert*-butoxide/DMSO (Scheme 3) have been done, and the results were compared to the LDA-initiated isomerization (Table 3).

Scheme 3. Allyl Ether Isomerization Catalyzed by *t*BuOK
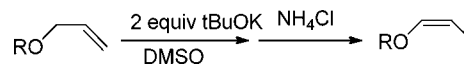
Entries 1−4 in Table 3 highlight that heating (larger than 60 °C) is required for *t*BuOK-catalyzed reactions. Although

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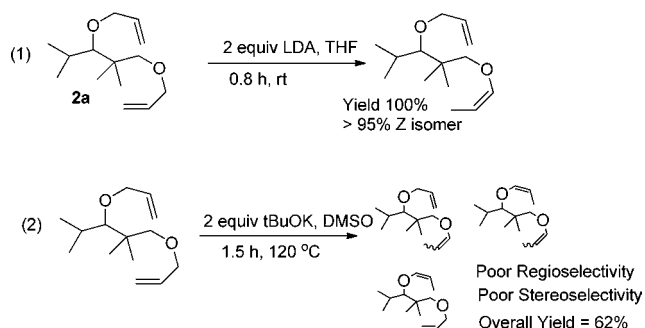
Table 3. Comparison of *t*BuOK and LDA-Initiated Isomerization

entry	allyl ether	base	time	temp	ratio[a]
1		tBuOK	1 h	60° C	0
2		tBuOK	4 h	60° C	0
3		tBuOK	2 h	120° C	2.6[b]
4		tBuOK	4 h	120° C	0.56[b]
5		LDA	0.5 h	rt	All Enol Ether
6		LDA	4 h	rt	1.5

[a] Ratio = amount of enol ether/amount of starting allyl ether. [b] The end mixture/starting allyl ether is less than 60%.

Scheme 4. Isomerization of **2a** Catalyzed by LDA and *t*BuOK

the isomerization of allyl ethers can be done at 120 °C, the rate of reaction is far slower than that of LDA-catalyzed isomerization (Table 3, entries 5 and 6). Besides, for *t*BuOK-catalyzed reactions, the mass of the resulting mixtures of enol and allyl ethers recovered was less than 60% of the starting allyl ethers. We suggest that this is likely due to the high temperature of the reaction mixtures allowing the allyl ethers to volatilize or decompose. Therefore, it is clear that the LDA-catalyzed isomerization is more effective than that which utilizes *t*BuOK.

A comparison of LDA and *t*BuOK in the isomerization of **2a** was carried out to highlight the advantage of LDA-catalyzed isomerization over *t*BuOK (Scheme 4). LDA regioselectively isomerizes the less steric hindered allyl ether group to yield Z-propenyl ether completely stereoselectivity in quantitative yield. However, the *t*BuOK-catalyzed isomerization of **2a** was not as regio- and stereoselective as the LDA-catalyzed one as shown by the ^{13}C NMR spectrum of the products (see Supporting Information). By comparing the spectrum of the product from the isomerization of **2a** by LDA with that of pure **2a**, we note that one of the two allyl groups has been selectively isomerized to a propenyl group. However, the spectrum of the products of *t*BuOK-catalyzed isomerization of **2a** shows that a mixture of *E*- and *Z*-propenyl ether isomers is formed from the less steric hindered allyl ether group. Moreover, a significant amount of the more steric hindered allyl group was isomerized to propenyl ether before the less hindered allyl group has been isomerized.

In conclusion, the LDA isomerization reaction outlined above provides a convenient, inexpensive, and highly efficient method for the isomerization of allyl ethers to propenyl ethers. Future work will focus on studying the kinetics of the reaction with a goal of unveiling a more detailed mechanism of the complexes involved in this isomerization reaction.

Supporting Information Available: Experimental procedures, reproductions of NMR, mass spectra, and gas chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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