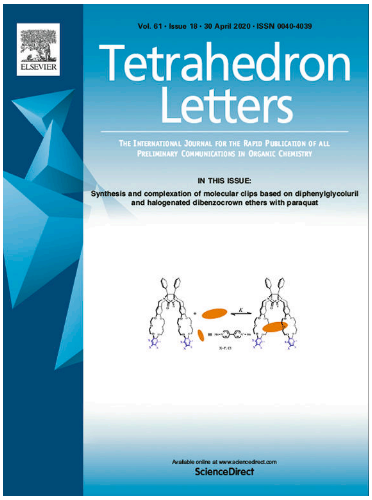

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Graphical Abstract

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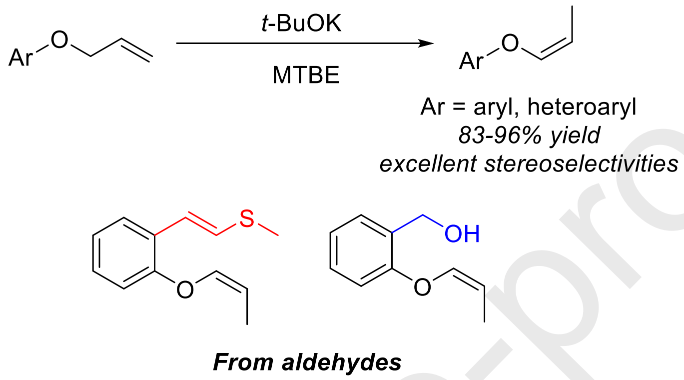

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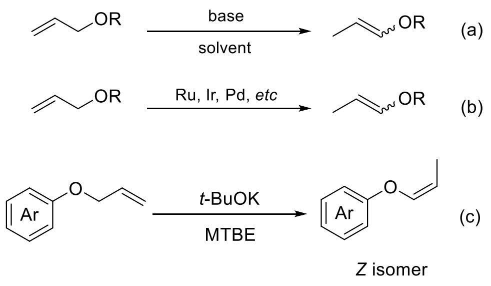
ABSTRACT

The *t*-BuOK promoted stereoselective isomerization of allyl aryl ethers has been developed. The reactions proceeded well in methyl *tert*-butyl ether (MTBE), providing the corresponding products in good to excellent yields (83–96%). Most of the substrates were isomerized predominantly to the *Z* isomers with excellent stereoselectivities. Gram-scale synthesis was also achieved on a 10 mmol scale. Moreover, the cascade Cannizzaro and isomerization reactions, and the one-pot isomerization and styryl sulfide formation reactions, were also realized, affording a potential synthetic route to access interesting compounds.

Vinyl ethers are useful synthetic intermediates in various organic transformations such as cycloaddition,[1-3] cyclization,[4] and the aldol reaction.[5] They are also utilized as monomers to produce functional polymers.[6,7] Generally, vinyl ethers can be efficiently prepared *via* the isomerization of allyl ethers in the presence of bases (Scheme 1, a)[8] or transition metal catalysts (Scheme 1, b).[9]

Among the reported procedures, transition metal catalysts are used more often than bases. For example, ruthenium[10-12] and iridium[9a] complexes efficiently catalyze the isomerization of allyl ethers. However, some isomerization reactions did not proceed well when allyl aryl ethers were used due to the strong coordinating effect between the catalyst and the substrate.[13] Moreover, the high cost of these metal catalysts is a concern for large-scale reactions. It is also worth noting that usually *E*-configuration products are thermodynamically generated as the dominant products. Thus, the development of stereoselective isomerization processes for this reaction is still a significant challenge. On the contrary, the base-promoted isomerization of allyl ethers has achieved varying degrees of success. Although these procedures are not catalytic, the bases are much cheaper and can be readily removed after the reaction. Bases such as *t*-BuOK,[9d,14,15] butyllithium[16] and lithium diisopropylamide[17] have been employed for this transformation. However, the reported methods still suffer from drawbacks such as low yields, unsatisfactory stereoselectivities, and harsh reaction conditions.

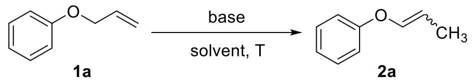
Inspired by the above-mentioned pioneering works, herein, we report the *t*-BuOK-promoted stereoselective isomerization of allyl aryl ethers in MTBE. The yields and stereoselectivities are excellent and a series of substrates are compatible with the reaction conditions (Scheme 1, c).



Scheme 1. Synthetic routes for the isomerization of allyl aryl ethers.

Initially, (allyloxy)benzene **1a** and *t*-BuOK were chosen as the model substrate and base to optimize the reaction conditions (Table 1). The solvent significantly affected the reaction. No reaction was observed when the reaction was conducted either in 1-octane, 1,2-dichlorethane (DCE), CH_2Cl_2, acetonitrile, DMF or hexafluoroisopropanol (HFIP) (Entries 1-6) at 100 °C for 6 h. DMSO was reported to be a suitable rea yield of **2a** (95% *Z* isomer) was obtained (Entry 7). Tetrahydrofuran (THF) and 1,4-dioxane were also trialled, however, lower yields and stereoselectivities were obtained (Entries 8 and 9). Pleasingly, the isomerization of **1a** in MTBE provided the desired *Z* isomer in 94% yield (Entry 10). Other bases were then examined (Entries 11-14). Among them, *t*-BuONa, NaH, $KN(SiMe_3)_2$ and $NaN(SiMe_3)_2$ did not promote the reaction at all. Only trace amounts of **2a** were observed when the reactions were performed in the presence of KOH and NaOH (Entries 15 and 16). In addition, either elevating or reducing the reaction temperature led to decreased yields while the *E*/*Z* ratios were not affected (Entries 17 and 18). Finally, the amount of *t*-BuOK was evaluated which clearly indicated that 3 equivalents of *t*-BuOK was optimum. Moreover, the reaction performed under air led to a lower yield of **2a** due to the formation of by-products (Entry 19).

Table 1. Optimization of the reaction conditions.[a]

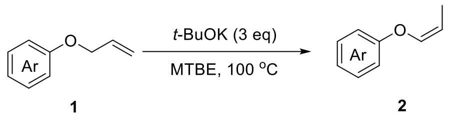


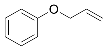
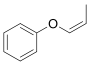
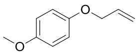
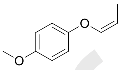
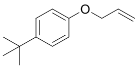
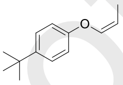
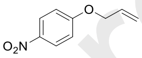
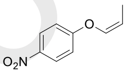
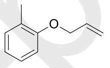
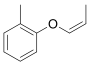
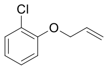
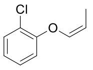
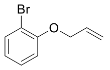
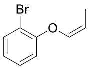
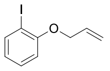
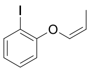
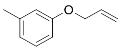
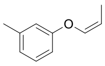
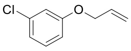
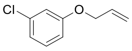
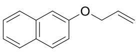
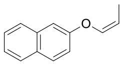
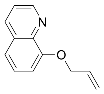
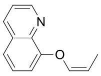
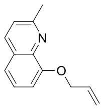
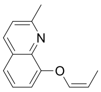
Entry	Base	Solvent	Temp. (°C)	Yield **2a** (%)[b]	*Z*:*E*[c]
1	*t*-BuOK	1-octane	100	0	–
2	*t*-BuOK	DCE	100	0	–
3	*t*-BuOK	CH_2Cl_2	100	0	–
4	*t*-BuOK	MeCN	100	0	–
5	*t*-BuOK	DMF	100	0	–
6	*t*-BuOK	HFIP	100	0	–
7	*t*-BuOK	DMSO	100	37	95:5
8	*t*-BuOK	THF	100	19	88:12
9	*t*-BuOK	1,4-dioxane	100	12	85:15
10	*t*-BuOK	MTBE	100	94	99:1
11	*t*-BuONa	MTBE	100	0	–
12	NaH	MTBE	100	0	–
13	$KN(SiMe_3)_2$	MTBE	100	0	–
14	$NaN(SiMe_3)_2$	MTBE	100	0	–
15	KOH	MTBE	100	trace	–
16	NaOH	MTBE	100	trace	–
17	*t*-BuOK	MTBE	120	75	99:1
18	*t*-BuOK	MTBE	80	41	99:1
19	*t*-BuOK	MTBE	100	81[d], 90[e], 83[f]	99:1

[a]Reagents and conditions: **1a** (0.2 mmol, 1 equiv.), base (0.6 mmol, 3 equiv.), solvent (2 mL), 6 h, N_2. [b]GC yield based on **1a**. [c]Calculated by ^1H NMR spectroscopy. [d]*t*-BuOK (2 equiv.). [e]*t*-BuOK (4 equiv.). [f]Under air.

With the optimized reaction conditions in hand, a series of allyl aryl ethers were then evaluated to probe the scope and generality of the protocol.[18] The results are summarized in Table 2.

Table 2. Isomerization of various allyl aryl ethers.[a]



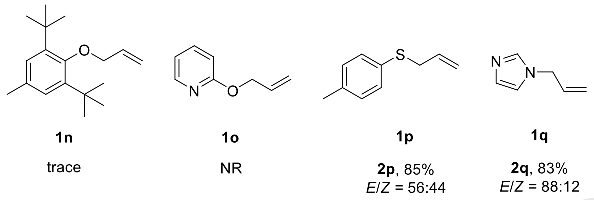
Entry	Substrate	Main product	Yield (%)[b]	*Z*:*E*[c]
1	 **1a**	 **2a**	94	99:1
2	 **1b**	 **2b**	95	98:2
3	 **1c**	 **2c**	86	>99:1
4	 **1d**	 **2d**	83	87:13
5	 **1e**	 **2e**	87	>99:1
6	 **1f**	 **2f**	91	>99:1
7	 **1g**	 **2g**	93	97:3
8	 **1h**	 **2h**	96	>99:1
9	 **1i**	 **2i**	93	>99:1
10	 **1j**	 **2j**	95	97:3
11	 **1k**	 **2k**	92	94:6
12	 **1l**	 **2l**	83	98:2
13	 **1m**	 **2m**	85	>99:1

[a]Rea

equiv.), MTBE (2 mL), 100 °C, 6 h, N_2. [b]GC yields. [c]Calculated by ^1H NMR spectroscopy.

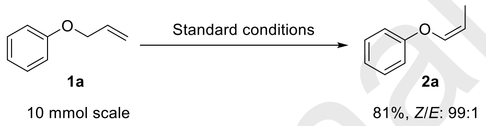
Generally, the investigated allyl aryl ethers gave the corresponding products in good to excellent yields (83–96%). Functional groups including alkyl, methoxyl, nitro and halogen were all well tolerated. The effect of steric hindrance was negligible. Both the *ortho*-and *meta*-substituted substrates provided the desired products in excellent yields. The C–Br and C–I bonds in **2g** and **2h** were not affected, enabling further manipulation of the initial products. Substrates **1k-m** were also examined, and all the reactions proceeded well. It is worth noting that nearly all the substrates were isomerized predominantly to the *Z* isomers. The nitro-substituted allyl aryl ether **1d**, however, gave lower stereoselectivity (*Z*/*E* = 87:13).

In addition, substrates with bulkier groups at the *ortho*-positions (**1n**), allyl heteroaryl ether (**1o**), allyl aryl sulfide (**1p**), and *N*-allylimidazole (**1q**) were evaluated (Scheme 2). It was observed that the reaction of **1n** led to trace amounts of the desired product. No reaction occurred when substrate **1o** was utilized. The *S*-allyl compound **1p** and *N*-allyl compound **1q**, however, were isomerized to the desired products in good yields. It was also worth noting that *E* isomers were observed as the major products in these reactions.



Scheme 2. Other substrates examined for the isomerization reaction.

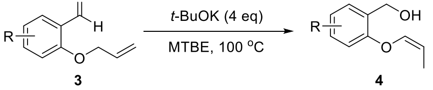
The gram-scale synthesis of **2a** was also performed. Product **2a** was obtained in 81% yield on a 10 mmol scale after 12 h (Scheme 3).



Scheme 3. Gram-scale synthesis of **2a**.

Next, we evaluated the reactivity of 2-(allyloxy)benzaldehyde derivatives **3**. Interestingly, the formyl group did not survive under the standard reaction conditions. Further studies showed that both Cannizzaro and isomerization reactions occurred in the presence of 4 equivalents of *t*-BuOK for 24 h (Table 3). Product **4a-f** were obtained with excellent stereoselectivities, although a lower stereoselectivity was observed for **4c**.

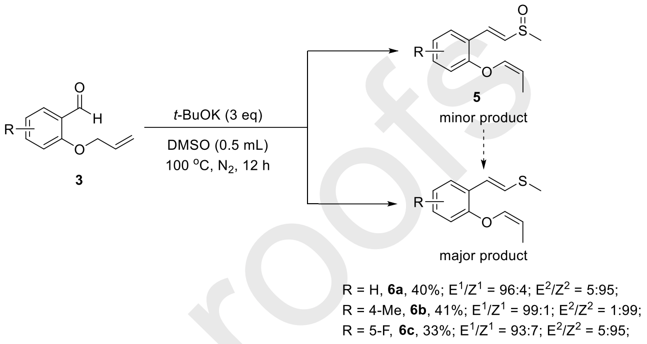
Table 3. *t*-BuOK promoted Cannizzaro and isomerization reactions.[a]



Entry	R	Product	Yield (%)[b]	Z:E[c]
1	H	**4a**	40	>99:1
2	4-CH_3	**4b**	43	>99:1
3	4-OMe	**4c**	39	89:11
4	5-CH_3	**4d**	36	>99:1
6	5-Cl	**4f**	29	>99:1

[a]Reagents and conditions: **3** (0.2 mmol), *t*-BuOK (0.8 mmol), MTBE (2 mL), 100 °C, N_2, 24 h. [b]Isolated yields based on 0.1 mmol of **3**. [c]Calculated by ^1H NMR spectroscopy.

We also examined the one-pot condensation and isomerization reaction of substrate **3** in the presence of DMSO (Scheme 3). The expected product **5** was observed as the minor product. Compound **6** was formed as the major product. Notably, the C=C bonds of the styryl sulfide are predominantly *trans*, while those of the vinyl ether are *cis*.



Scheme 3. One-pot isomerization and styryl sulfide formation reactions.

With regard to the mechanism, He and co-workers previously observed the synthesis of styryl sulfides from benzyl alcohols and DMSO in the presence of Ag/C.[19] Li and co-workers also reported the synthesis of styryl sulfides from the direct C–C coupling of benzyl alcohols and DMSO under the assistance of cobalt modified *N*-doped carbon nanotubes.[20] In their studies, benzyl alcohols were oxidized to aldehydes under basic conditions and meanwhile H_2 was generated. The vinyl sulfoxides were then reduced to form styryl sulfides. It should also be pointed out that styryl sulfides could also be directly generated from vinyl sulfoxides under strong basic reaction conditions.[21] However, the exact mechanism currently remains unclear. Efforts are underway to elucidate the mechanistic details of this reaction and the results will be reported in due course.

In summary, a *t*-BuOK promoted stereoselective isomerization of allyl aryl ethers has been developed. The desired products were obtained in good to excellent yields and excellent stereoselectivities. The gram-scale synthesis was also achieved on a 10 mmol scale. Moreover, the cascade Cannizzaro and isomerization reactions, and the one-pot isomerization and styryl sulfide formation reactions, were also realized, affording a potential synthetic route to access interesting compounds.

Acknowledgments

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Re[illegible]

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18 **General procedure for the synthesis of 2**: A sealed tube equipped with a magnetic stirrer bar was charged with substrate **1** (0.2 mmol, 1 equiv.), *t*-BuOK (0.6 mmol, 3 equiv.) and MTBE (2 mL) in a glovebox. The reaction mixture was then heated to 100 °C and stirred for 6 h. After reaction completion, water (10 mL) was added to the reaction mixture and the mixture was extracted with ether (10 mL × 3). The collected organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica [illegible]re synthesized from compound **3** using the same method.

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t-BuOK promoted stereoselective isomerization of allyl aryl ethers

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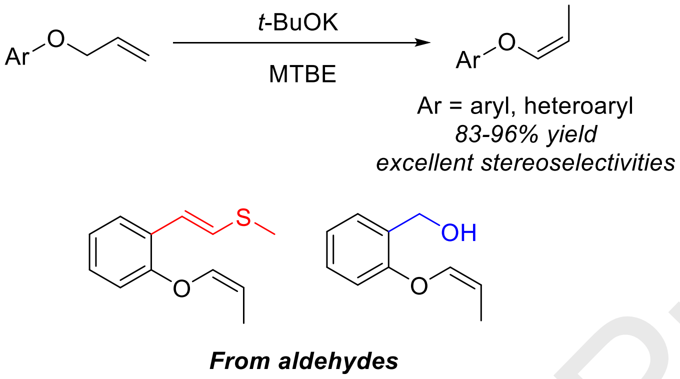

t-BuOK promoted stereoselective isomerization of allyl aryl ethers has been developed.

- Good to excellent yields and stereoselectivities.
- Good substrate scope;
- Gram-scale synthesis can be achieved.
- Cascade Cannizzaro and isomerization reactions, and the one-pot isomerization and styryl sulfide formation reactions can be realized.

The authors declared that they have no conflicts of interest to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.