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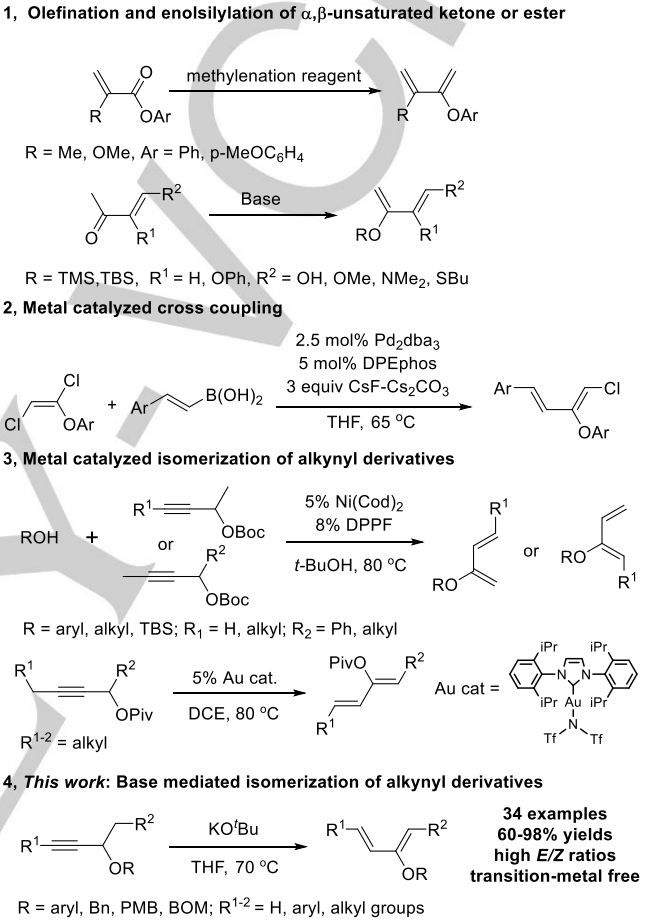
Transition-Metal-Free Synthesis of Electron Rich 1,3-Dienes via Base Promoted Isomerization of Propargylic Ethers

Chunxiang Liu,[a] Guogang Deng,[a] Xin Li,[a] Yiren Xu,[a] Kaili Yu,[a] Wen Chen,[a] Hongbin Zhang*[a] and Xiaodong Yang*[a]

Abstract: Herein, a novel and scalable synthesis of electron rich 1,3-dienes based on KO^{t}Bu mediated isomerization of propargylic ether derivatives was developed. This new process features easy handling reaction conditions, transition-metal-free isomerization, high isolated yields, and most of all, it could be used for modification of natural products at late stage functionalizations.

1,3-Dienes are important building blocks both in organic synthesis[1,2] and materials science.[3] Therefore, the construction of dienes has attracted considerable attention in synthetic community and numerous methodologies have been developed to provide access to the 1,3-dienes bearing various functionalities.[2,4] However, the approaches to electron rich 1,3-dienes, such as 2-oxygenated-1,3-butadienes, are still only a few with a remarkably restricted substrate scope.[5] Representative strategies (Scheme 1) include olefination of α,β-unsaturated esters with various reagents to form the 1,3-dienes,[4] enolization of substituted vinyl ketones to prepare Danishefsky's 1,3-dienes or surrogates,[6] palladium-catalyzed cross coupling,[7] isomerization of yne-carbonyl compounds to conjugated dienecarbonyl compounds with triphenylphosphine.[8] Recently, methods involving transition-metal catalyzed isomerization of alkyns to obtain1,3-dienes have also been reported and further enrich the arsenal of diene synthesis.[5,9] At the same time, both base-mediated isomerization of propargylic ethers to allenic ethers[10] and base-mediated allylic isomerization[11] are very well established. Our research attempts to combine these two known isomerizations. Herein, we report a useful protocol for the synthesis of electron rich 1,3-dienes based on base promoted isomerization reactions of alkynes.



Scheme 1. Selected approaches towards the synthesis of electron rich 1,3-dienes.

We selected *p*-methoxybenzyl (PMB) propargylic ether **1a** as the model substrate, which was easily synthesized using the method of Brückner[12] by reaction of propargylic alcohol with PMBCl (88% yield, see Supporting Information). At the outset, 2-PMBoxy-but-3-yn **1a** was treated with a variety of bases (3 equiv) including LiO^{t}Bu, NaO^{t}Bu, KO^{t}Bu, LiN(SiMe$_3$)$_2$ NaN(SiMe$_3$)$_2$, KN(SiMe$_3$)$_2$, NaH, Et$_3$N, imidazole, and K$_2$CO$_3$ in THF at 70 °C for 24 h (Table 1, entries 1–10). To our delight, when KO^{t}Bu was employed, the isomerization product 2-PMBoxy-1,3-diene **2a** was obtained in 94% assay yield (AY, as determined by ^{1}H NMR integration against an internal standard, entry 3). Other bases led to lower yields or no reaction. Using KO^{t}Bu, we next studied the effect of solvent. No improvement of yield was observed when switching solvents to CH_2Cl_2, DME (dimethoxyethane), ^{t}BuOH, toluene, CPME (cyclopentyl methyl ether), dioxane, or MTBE (methyl *tert*-butyl ether) all led to lower AY's (0–82%, entries 11–17). Our study of the base loading indicated that the

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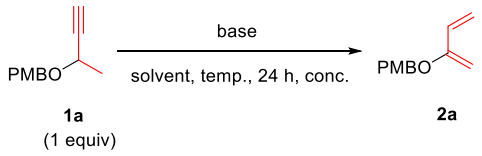
yield increased to 99% (entry 18) at 4 equiv loading, but kept 94% or dropped to 77% at 2 or 1 equiv loading (entries 19 and 20). With KO^{t}Bu as base in THF, raising the concentration from 0.05 M to 0.1 M resulted in a similar yield to the original concentration, with 99% AY and 96% isolated yield (entry 21). Conducting the reaction at 0.2 M afforded slight decrease to 96% AY (entry 22). The reaction proved to be relatively sensitive to temperature. Reducing the reaction temperature to 40 °C and room temperature resulted in decreases to 36% and 15% AY, respectively (entries 23 and 24). Based on this optimization, the standard conditions for the rearrangement reaction that will be used for the remainder of the study are those in entry 21 of Table 1.

Table 1: Optimization of isomerization of 2-PMBoxy-but-3-yn **1a**. [a]



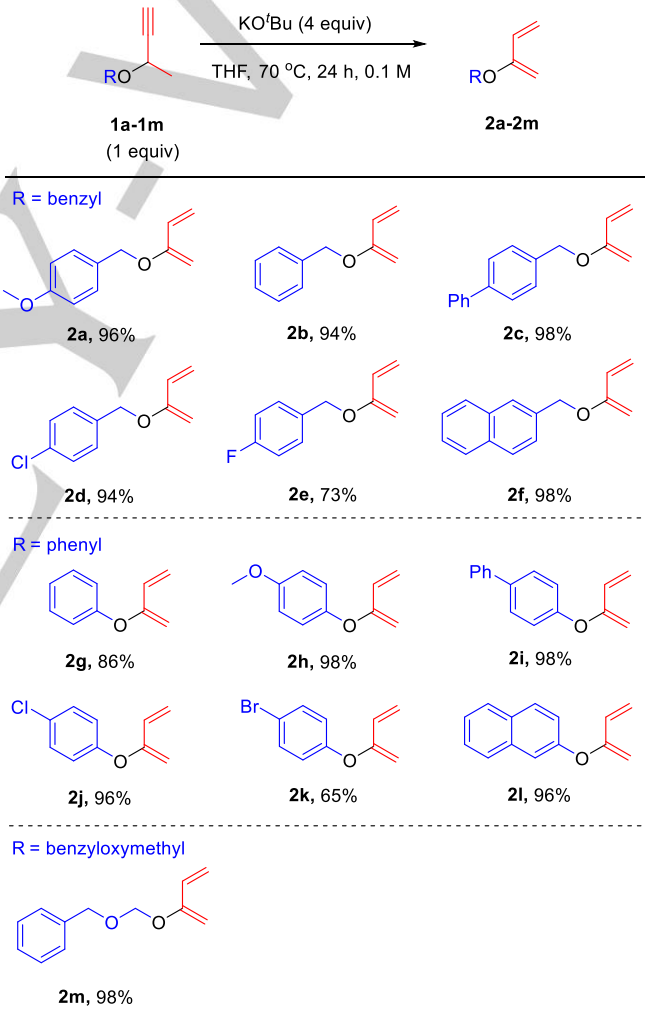
1a (1 equiv) **2a**

Entry	Base	**1a**:Base	Solvent	Conc. [M]	Temp. (°C)	Assay yield (%)
1	LiO^{t}Bu	1:3	THF	0.05	70	0
2	NaO^{t}Bu	1:3	THF	0.05	70	2
3	KO^{t}Bu	1:3	THF	0.05	70	94
4	NaN(SiMe$_3$)$_2$	1:3	THF	0.05	70	0
5	LiN(SiMe$_3$)$_2$	1:3	THF	0.05	70	0
6	KN(SiMe$_3$)$_2$	1:3	THF	0.05	70	21
7	NaH	1:3	THF	0.05	70	0
8	Et$_3$N	1:3	THF	0.05	70	0
9	imidazole	1:3	THF	0.05	70	0
10	K$_2$CO$_3$	1:3	THF	0.05	70	0
11	KO^{t}Bu	1:3	CH_2Cl_2	0.05	40	0
12	KO^{t}Bu	1:3	DME	0.05	85	42
13	KO^{t}Bu	1:3	^{t}BuOH	0.05	85	11
14	KO^{t}Bu	1:3	toluene	0.05	110	82
15	KO^{t}Bu	1:3	CPME	0.05	110	74
16	KO^{t}Bu	1:3	dioxane	0.05	110	66
17	KO^{t}Bu	1:3	MTBE	0.05	70	66
18	KO^{t}Bu	1:4	THF	0.05	70	99
19	KO^{t}Bu	1:2	THF	0.05	70	94
20	KO^{t}Bu	1:1	THF	0.05	70	77
21	KO^{t}Bu	1:4	THF	0.1	70	99(96)[b]
22	KO^{t}Bu	1:4	THF	0.2	70	96
23	KO^{t}Bu	1:4	THF	0.1	40	36
24	KO^{t}Bu	1:4	THF	0.1	rt	15

[a] Assay yields determined by ^{1}H NMR spectroscopy of the crude reaction mixtures using CH_2Br_2 as an internal standard. [b] Isolated yield after chromatographic purification.

Encouraged by the potential synthetic utility of this isomerization, we first investigated the scope of protecting groups of but-3-yn-2-ol (Table 2). A range of substituted benzyl and aryl protecting groups of but-3-yn-2-ol readily isomerized with KO^{t}Bu in good to excellent yields (65–98%) under the optimized conditions (Table 1, entry 21). In term of benzyloxy groups, for standard 2-benzyloxy-but-3-yn **1b**, the product 2-benzyloxy-1,3-diene **2b** was generated in 94% yield. Like **1a**, but-3-yn-2-ol with benzyl protecting group containing electron-rich group (**1c**, 4-Ph) afforded product **2c** in 98% yield. Benzyl groups possessing electron-withdrawing substituents, such as 4-Cl and 4-F, led to the corresponding products **2d** and **2e** in 94% and 73% yields, respectively. The sterically hindered 2-naphthylmethyl ether (**1f**) isomerized to generate the product **2f** in 98% yield. Similarly, in term of aryloxy groups, standard 2-phenyloxy-but-3-yn **1g** yielded the product 2-phenyloxy-1,3-diene **2g** in 86% yield. Interestingly, phenyl groups bearing electron-rich substituents (**1h**, 4-OMe and **1i**, 4-Ph) afforded 1,3-diene products **2h** and **2i** in the same 98% yields. For phenyl groups with electron-withdrawing groups (**1j**, 4-Cl and **1k**,4-Br), the corresponding 1,3-diene products **2j** and **2k** were obtained in 96% and 65% yields, respectively. Additionally, 2-naphthyloxy-but-3-yn **1l** furnished 1,3-diene product **2l** in 96% yield. Finally, benzyloxymethyl propargylic ether **1m** was also competent protecting group, affording the corresponding 1,3-diene product **2m** in 98% yield.

Table 2: Scope of but-3-yn-2-ol protecting groups.[a,b]



[a] Reactions were conducted on a 0.5 mmol scale using 1 equiv alkynyl ether **1** and 4 equiv KO^{t}Bu at 0.1 M. [b] Yield of isolated product after chromatographic purification.

We next explored the ability of the isomerization reaction to accommodate various alkyl or aryl substituents on the propargylic ethers (Table 3). In general, the optimized reaction conditions accommodated substituted propargylic ethers in good

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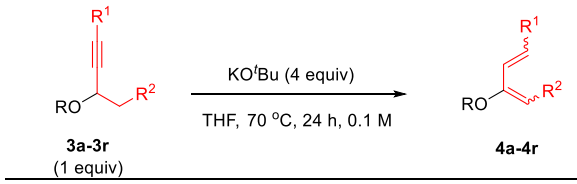
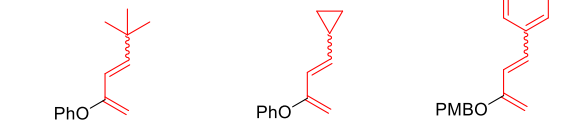
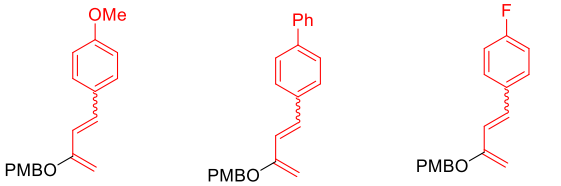
Table 3: Scope of substituted propargylic ethers.[a,b]



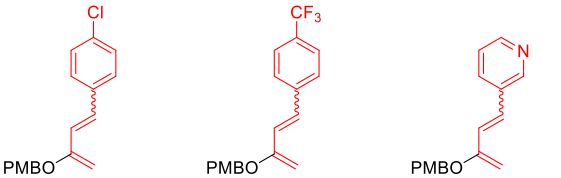
4-substituted-1,3-dienes



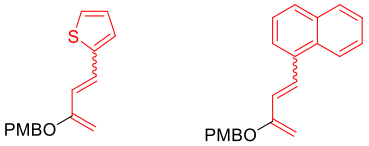
4a, 77% (*E*/*Z* = 1:0.34) **4b,** 88% (*E*/*Z* = 1:0.49) **4c,** 94% (*E*/*Z* = 1:0.57)



4d, 92% (*E*/*Z* = 1:1) **4e,** 93% (*E*/*Z* = 1:0.81) **4f,** 92% (*E*/*Z* = 1:0.80)

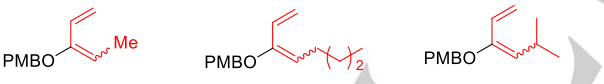


4g, 82% (*E*/*Z* = 1:1) **4h,** 60% (*E*/*Z* = 1:0.61) **4i,** 96% (*E*/*Z* = 1:0.37)

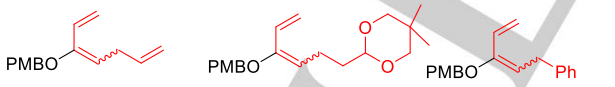


4j, 97% (*E*/*Z* = 1:0.23) **4k,** 93% (*E*/*Z* = 1:0.41)

1-substituted-1,3-dienes[c]



4l[d], 68% (*E*/*Z* = 1:0.35) **4m**[d], 65% (*E*/*Z* = 1:0.35) **4n**[d], 92% (*E*/*Z* = 1:0.26)



4o[e], 75% (*E*/*Z* = 1:0.29) **4p**[e], 67% (*E*/*Z* = 1:0.23) **4q**[e], 85% (*E*/*Z* = 1:0.31)

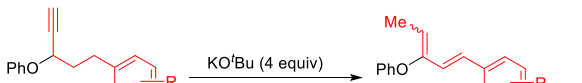
[a] Reactions were conducted on a 0.5 mmol scale using 1 equiv alkynyl ether **3** and 4 equiv KO^{t}Bu at 0.1 M. [b] Yield of isolated product after chromatographic purification, The Z/E ratio was determined by ^{1}H NMR analysis. [c] Reactions were conducted on a 0.2 mmol scale using 1 equiv alkynyl ether **3** and 4 equiv KO^{t}Bu at 0.1 M. [d] 6 h reaction time. [e] 3 h reaction time.

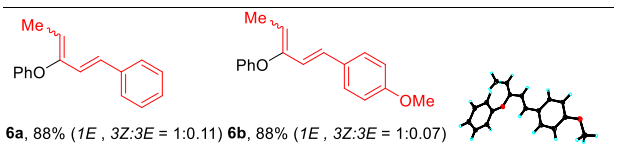
to excellent yields (60–97%). For 2-phenyloxy-but-3-yn derivatives bearing alkyl substituents at 4-position (**3a**, 4-^{t}Bu and **3b**, 4-cyclopropyl), products 2-phenyloxy-1,3-diene **4a** and **4b** were afforded in 77% (*E*/*Z* = 1:0.34) and 88% (*E*/*Z* = 1:0.49) yields, respectively. For 2-PMBoxy-but-3-yn derivatives with phenyl substituent at 4-position (**3c**), product 2-benzyloxy-1,3-diene **4c** was generated in 94% yield (*E*/*Z* = 1:0.57). The phenyl group possessing electron-donating or electron-withdrawing substituents, such as 4-OMe, 4-Ph, 4-F, 4-Cl and 4-CF_3, were also suitable substituents, leading to the corresponding 1,3-diene products **4d**, **4e**, **4f**, **4g** and **4h** in 92, 93, 92, 82, and 60% yields, respectively. We also studied heterocyclic substituted propargylic ethers possessing 3-pyridyl (**3i**) and 2-thiophenyl (**3j**), affording the 1,3-diene products **4i** and **4j** in 96 (*E*/*Z* = 1:0.37) and 97% (*E*/*Z* = 1:0.23) yields, respectively. Additionally, the sterically hindered 1-naphthyl derivative (**3k**) underwent the isomerization reaction to provide the 1,3-diene products **4k** in 93% yield (*E*/*Z* = 1:0.41).

In comparison, for 2-PMBoxy-but-3-yn derivatives with alkyl substituents at 1-position, the corresponding 1,3-diene products (**4l**–**4q**) were formed in higher *E*/*Z* ratios. When alkyl substituents at 1-position (**3l**, methyl, **3m**, n-butyl and **3n**, isopropyl) were used, the 1,3-diene products **4l**, **4m** and **4n** were obtained in 65-92% yields with *E*/*Z* ratios of 1:0.35, 1:0.35 and 1:0.26, respectively. Similarly, allyl and 5,5-dimethyl-1,3-dioxane-2-ethyl substituents at 1-position afforded 1,3-diene products **4o** and **4p** in 75% (*E*/*Z* = 1:0.29) and 67% (*E*/*Z* = 1:0.23) yields, respectively. Finally, 2-PMBoxy-but-3-yn derivative with benzyl substituent at 1-position (**3q**) successfully isomerized furnishing the 1,3-diene product **4q** in 85% yield (*E*/*Z* = 1:0.31).

Interestingly, when the PMB protecting group was replaced by phenyl group in the substrate **3q**, 2-phenyloxy-but-3-yn derivatives (**5a**–**5d**, Table 4) bearing benzyl substituent at 1-position underwent the re-isomerization to provide the 1,3-diene products in good yields (81–88%) and high *E*/*Z* ratios (up to 1:0.07). For standard benzyl group at 1-position **5a**, the re-isomerization 1,3-diene product **6a** was obtained in 88% yield (3*Z*/3*E* = 1:0.11). The benzyl group possessing electron-donating or electron-withdrawing substituents, such as 4-OMe and 4-F, were also competent substituents, generating the corresponding re-isomerization products **6b** (CCDC 1951933, see Supporting Information for details) and **6c** in 88 (3*Z*/3*E* = 1:0.07) and 85% (3*Z*/3*E* = 1:0.10) yields, respectively. When the sterically hindered 1-naphthylmethyl group replaced benzyl group at 1-position, the re-isomerization 1,3-diene product **6d** was furnished in 81% yield (3*Z*/3*E* = 1:0.10).

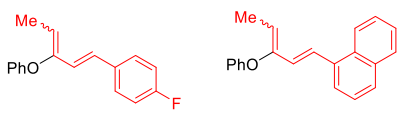
Table 4: Scope of re-isomerization.[a,b,c]





6a, 88% (*1E* , *3Z*:*3E* = 1:0.11) **6b**, 88% (*1E* , *3Z*:*3E* = 1:0.07)

X-ray structure of compound **6b**



6c, 85% (*1E* , *3Z*:*3E* = 1:0.10) **6d**[d], 81% (*1E* , *3Z*:*3E* = 1:0.10)

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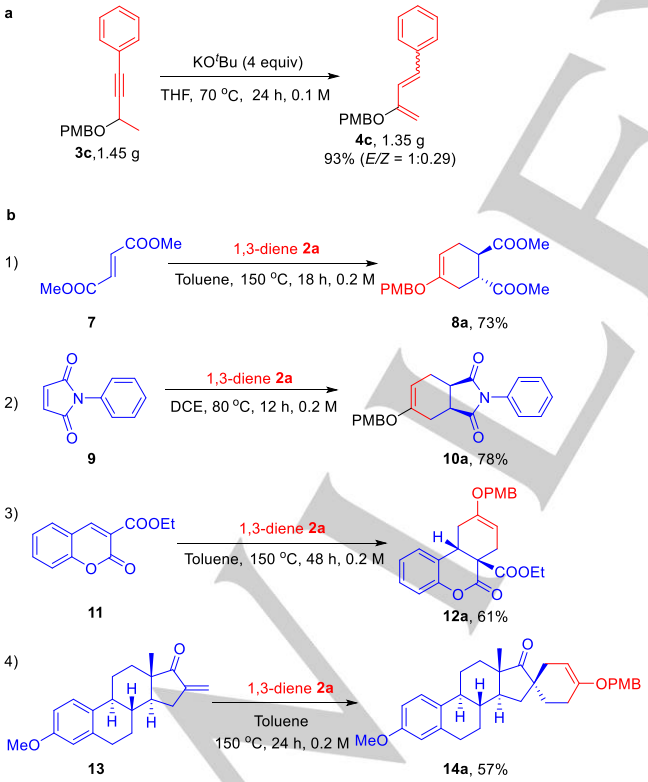
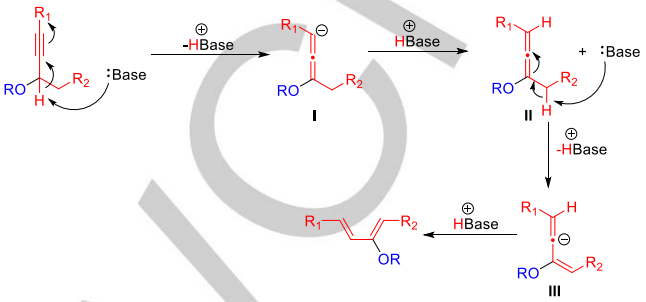
[a] Reactions were conducted on a 0.5 mmol scale using 1 equiv alkynyl ether **2** and 4 equiv KO^{t}Bu at 0.1 M. [b] Yield of isolated product after chromatographic purification. [c] The *Z*/*E* ratio was determined by ^{1}H NMR analysis. [d] 3 h reaction time.

For a synthetic strategy to be practical, it should be scalable. The scalability of our process was investigated by the gram-scale preparation. Thus, propargylic ether **3c** was conducted to form isomerization derivative on gram scale under the optimal conditions (Scheme 2a). The desired 1,3-diene product **4c** was isolated in 1.35 g (93% yield, *E*/*Z* = 1:0.29). The value of synthesized electron rich 1,3-dienes was further demonstrated by application for Diels-Alder cycloadditions (Scheme 2b). Thus, using 2-PMBoxy-1,3-diene **2a** reacted with diverse dienophiles to prepare functionalized six-membered cyclic rings. With dimethyl fumarate **7**, cycloaddition product cyclohexenyl ether **8a** was produced under heating in 73% isolated yield. *N*-phenylphthalimide **9** successfully reacted with **2a** to furnish tetrahydro-isoindole-1,3-dione **10a** in 78% yield. Notably, 1,3-diene could be used for late stage modification of natural products, which enabled the synthesis of a range of polycyclic architectures. Ethyl coumarin-3-carboxylate **11**[13] reacted with 1,3-diene **2a** leading to the tetrahydrobenzo[*c*]chromen-6-one framework 1**2a** in 61% yield. Steroid **13**[14], a derivative of natural product (+)-estrone, underwent the Diels-Alder reaction with **2a** to provide 6-member-spirocycle steroid **14a** in 57% yield.



Scheme 2. a. Gram-scale synthesis. **b.** Application for Diels-Alder reaction and modification of natural product derivatives.

The possible mechanism of this isomerization reaction was proposed (Scheme 3). Initially, α-proton of propargylic ether was deprotonated by KO^{t}Bu to generate an allenyl anion intermediate I, which captured a proton to afford the allenyl ether intermediate II. Then, β-proton of allenyl ether was deprotonated by base to provide the anion intermediate III, which further captured a proton to furnish the isomerization product 1,3-diene.



Scheme 3. Proposed mechanism.

In summary, we have developed an efficient method for constructing functionalized electron rich 1,3-dienes. In this process, simple, readily prepared propargylic ether derivatives were employed to yield a wide variety of electron rich conjugated dienes. This transformation was accomplished via a base promoted isomerization reaction of propargylic ethers. This approach enables the preparation of electron rich 1,3-diene derivatives with a diverse array of protecting groups and substituents. A gram scale electron rich 1,3-diene synthesis was conducted that showed the potential synthetic utility. A derivatization investigation demonstrated the versatility of the products in application of Diels-Alder cycloadditions and modification of natural products at late stage functionalizations. Notably, this transition-metal-free process can save the costs and avoid separation of trace transition-metal impurities, which is significant in the pharmaceutical industry.[15]

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,3-diene • propargylic ether • transition-metal-free synthesis • isomerization • Diels-Alder reaction

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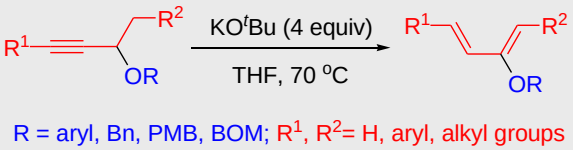

R = aryl, Bn, PMB, BOM; R^1, R^2= H, aryl, alkyl groups

34 examples
up to 98% yields
high *E/Z* ratios
transition-metal free

Chunxiang Liu, Guogang Deng, Xin Li, Yiren Xu, Kaili Yu, Wen Chen, Hongbin Zhang, Xiaodong Yang**

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Transition-Metal-Free Synthesis of Electron Rich 1,3-Dienes via Base Promoted Isomerization of Propargylic Ethers

1,3-Dienes Synthesis

An efficient and broadly applicable method for the construction of functionalized electron rich 1,3-dienes through a base promoted isomerization reaction of propargylic ethers is presented. This process features easy handling reaction conditions, transition-metal-free isomerization, high isolated yields, and most of all, it could be used for late stage modification of natural products.

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