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Five-Bond Cleavage in Copper-Catalyzed Skeletal Rearrangement of *O*-Propargyl Arylaldoximes to β-Lactams

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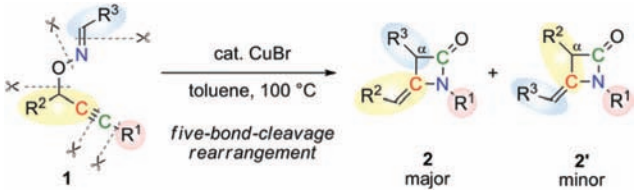
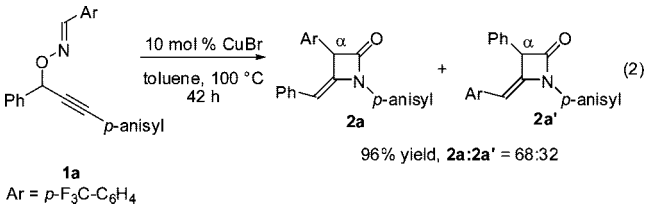
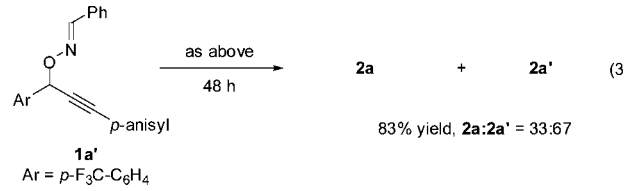
Catalytic skeletal rearrangement, which involves cleavage and formation of several covalent bonds and results in a rapid increase of molecular complexity, has been an area of intense research.[1] Since the pioneering studies by Trost and co-workers,[2] a range of transition-metal complexes have served as excellent catalysts for a wide variety of remarkable skeletal rearrangements. These investigations have mainly focused on the use of 1,*n*-enynes[3,4] and propargylic carboxylates[5,6] as substrates to demonstrate diversity of the skeletal rearrangement involving cleavage of two or three covalent bonds. Recently, it has been reported that catalytic rearrangement of alkynyl epoxides proceeds through cleavage of four bonds, including highly strained oxirane C—O bonds.[7] Herein, we report an unprecedented skeletal rearrangement of *O*-propargyl oximes **1** catalyzed by copper complexes that involves cleavage of five different covalent bonds (C═N, N—O, C—O, C—C, and C≡C) and leads to reorganization into the corresponding β-lactams **2** in good to excellent yields (eq 1).[8]



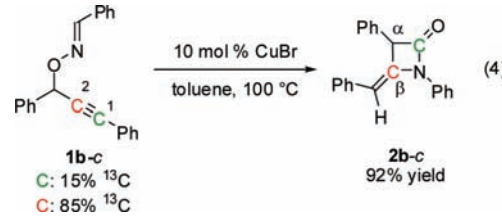
This unexpected transformation was discovered when we conducted the reaction of the propargyl arylaldoxime **1a** under the influence of copper catalysts. That is, the reaction of **1a** in the presence of 10 mol % CuBr in toluene at 100 °C for 42 h afforded a 68:32 mixture of the β-lactam derivative **2a** and its regioisomer **2a′** in 96% yield (eq 2):



The structures of the products **2a** and **2a′** were fully characterized by spectroscopic methods. In addition, the structure of **2a** was unambiguously determined by X-ray crystallography, as shown in Figure 1. The reaction of **1a′**, in which the substituents at the propargyl moiety and the oxime group were switched in comparison with **1a**, afforded a 33:67 mixture of **2a** and **2a′** in 83% yield (eq 3). These results suggest that the regioselectivity between **2** and **2′** is primarily attributed to the structure of the starting material **1** rather than the electronic character of the substituents.



Cleavage of five chemical bonds was rigorously proved by a ^{13}C labeling experiment. The reaction of **1b**-*c*, in which the ^{13}C contents at the C1 and C2 positions were 15 and 85%, respectively, was carried out under the standard reaction conditions (eq 4):



The ^{13}C contents in the resulting product **2b**-*c* were 15 and 85% at the carbonyl carbon and the β-position of the azetidinone ring, respectively. Thus, it is clearly evident that cleavage of the C≡C bond occurred in this reaction.[3b,9] Consequently, we concluded that the present transformation proceeds via cleavage of five bonds (C═N, N—O,[10] C—O, C—C, and C≡C) and formation of six new covalent bonds [three C—N, two C—C (or C═C), and one C═O]. Accordingly, a substituent at the alkynyl terminus of the substrate (R^1 of **1** in Figure 1) specifically migrated to the nitrogen atom. Meanwhile, positional isomerism of the present reaction resulted from reorganization of the R^2CH and R^3CH units of the starting material into either the arylidene moiety or the α-carbon unit of the products, as illustrated in Figure 1. It should be noted that all of the covalent bonds on three atoms, namely, the nitrogen and

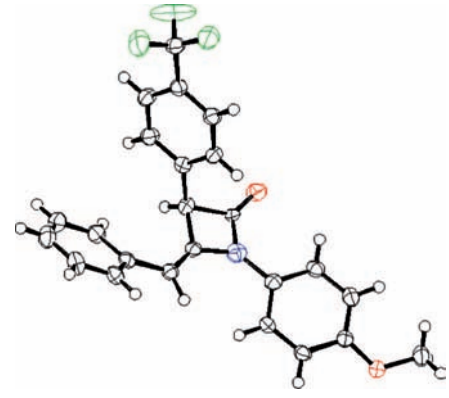
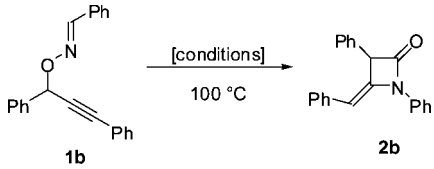


Figure 1. ORTEP drawing of **2a** (shown with 50% probability ellipsoids).

10.1021/ja900133m CCC: $40.75

Table 1. Reaction Development

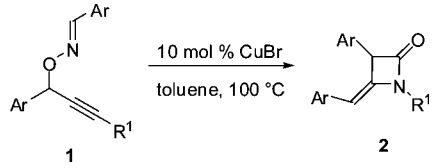


1b **2b**

entry	catalyst	solvent	time (h)	yield of **2b** (%)[a]	recovery of **1b** (%)[a]
1	CuBr	toluene	24	96[b]	<1
2	CuCl	toluene	23	91[b]	<1
3	CuI	toluene	43	41	54
4	$PtCl_2$	toluene	12	34[b]	<1
5	InCl	toluene	33	42[b]	<15
6	AuCl	toluene	15	trace	<1
7	AgOTf	toluene	2	<1	<1
8	TfOH	toluene	24	<1	36
9	CuBr	1,4-dioxane	11	93	<1
10	CuBr	THF	11	93	<1
11	CuBr	MeCN	3.5	82	<1
12	CuBr	hexane	26	75	16
13	CuBr	DMF	2.5	62	<1

[a] Determined by ^{1}H NMR using 1,3-benzodioxole as an internal standard. [b] Isolated yield.

Table 2. Copper-Catalyzed Five-Bond Cleavage Rearrangement of *O*-Propargyl Arylaldoximes **1c**−**h**[a]



1 **2**

entry	**1**	R^1	Ar	time (h)	**2**	yield (%)[b]
1	**1c**	*p*-$F_3C-C_6H_4$	Ph	16	**2c**	92
2	**1d**	*p*-Cl−C_6H_4	Ph	24	**2d**	85
3	**1e**	*p*-MeO−C_6H_4	Ph	39	**2e**	83
4	**1f**	*n*-Pr	Ph	10	**2f**	80[c]
5	**1g**	Cy	Ph	18	**2g**	80[d]
6	**1h**	Ph	*p*-$F_3C-C_6H_4$	67	**2h**	61[e]

[a] The reaction of **1** (0.4 mmol) was carried out in the presence of 10 mol % CuBr in 0.8 mL of toluene at 100 °C. [b] Isolated yield. [c] An 81:19 mixture of the E and Z isomers was obtained. [d] A 93:7 mixture of the E and Z isomers was obtained. [e] The amount of **1h** recovered was 26%.

oxygen atoms of the oxime group and the carbon atom at the C1 position, were disconnected and rebuilt during the skeletal rearrangement.

Results of optimization of the reaction of **1b** are summarized in Table 1. The reaction in the presence of 10 mol % CuBr in toluene at 100 °C afforded **2b** in 96% yield (entry 1). CuCl also acted as an efficient catalyst for the reaction of **1b**, whereas reactions using CuI, $PtCl_2$, or InCl as the catalyst instead of CuBr gave **2b** in lower yields (entries 2−5). The use of gold or silver salts (e.g., AuCl or AgOTf) instead of CuBr led to quick decompoisiton of the starting material (entries 6 and 7). Brønsted acids, such as TfOH, did not promote the reaction at all (entry 8). The reactions using 1,4-dioxane or THF as the solvent instead of toluene gave **2b** in good yields, while using of acetonitrile, hexane, or DMF was less effective (entries 9−13).

The scope of the present reaction is summarized in Table 2. The reaction of the *O*-propargyl arylaldoximes **1c**−**h**, which bear identical substituents at the oxime moiety and the propargyl position, afforded the β-lactam derivatives (4-arylideneazetidin-2-ones) **2c**−**h** in good to excellent yields without formation of any regioisomers. β-Lactam **2e** bearing a *p*-methoxyphenylmethyl group, which is an easily removable protecting group,[11] on the nitrogen atom was obtained in good yield (entry 3), indicating that the present methodology is potentially applicable for the synthesis of *N*-unsubstituted β-lactams. The arylaldoximes **1f** and **1g**, each of which has an alkyl substituent at the alkynyl terminus, were smoothly converted to the corresponding *N*-alkylazetidinones in good yields, although small amounts of the Z isomers were obtained as byproducts (entries 4 and 5). Further investigations, including mechanistic studies, are ongoing in our laboratory.

In conclusion, we have revealed a drastic skeletal rearrangement of readily accessible and fairly stable *O*-propargyl oximes to β-lactam derivatives. β-Lactams have gathered great interest for their key roles in antibacterial activity[12] and have been widely utilized as building blocks for the β-lactam synthon method.[13] Therefore, the present skeletal rearrangement is highly useful as an entirely new approach for synthesizing β-lactam derivatives in an efficient manner.[14]

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Supporting Information Available: Experimental procedures and characterization of the products **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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