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,ν-enynes3,4 and propargylic carboxylates5,6 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 alkylnyl 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 oximes1 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-lactams2 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 13C labeling experiment. The reaction of 1b-c, in which the 13C contents at the C1 and C2 positions were 15 and 85%, respectively, was carried out under the standard reaction conditions (eq 4):

The 13C 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, 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′ of 1 in Figure 1) specifically migrated to the nitrogen atom. Meanwhile, positional isomerism of the present reaction resulted from reorganization of the R′CH and R′CH 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...
Table 2. Copper-Catalyzed Five-Bond Cleavage Rearrangement of O-Propargyl Arylamidoximes 1c–h\(^{a}\)

| entry | catalyst | solvent | time (h) | yield of 2 (%) | recovery of 1b (%)\(^{a}\) |
|-------|----------|---------|---------|---------------|--------------------------|
| 1     | CuBr     | toluene | 24      | 96\(^{b}\)     | <1                       |
| 2     | CuCl     | toluene | 23      | 91\(^{b}\)     | <1                       |
| 3     | Cu      | toluene | 43      | 41            | 54                       |
| 4     | PtCl\(_2\) | toluene | 12      | 34            | <1                       |
| 5     | InCl\(_2\) | toluene | 33      | 42\(^{b}\)     | <1                       |
| 6     | AuCl     | toluene | 15      | trace         | <1                       |
| 7     | AgOTf    | toluene | 2       | <1            |                         |
| 8     | TiOTf    | toluene | 24      | <1            | 36                       |
| 9     | CuBr     | 1,4-dioxiane | 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.

**References**

1. (a) Activation of Unreactive Bonds and Organic Synthesis; Murai, S., Ed.; Topics in Organometallic Chemistry, Vol. 3: Springer: Berlin, 1999. (b) Jun, C.-H.; Chem. Soc. Rev. 2004, 33, 610. (c) Musaev, D. G.; Morokuma, K.; Top. Organomet. Chem. 2005, 22, 1.

2. (a) Trost, B. M.; Tandoury, G. J. Am. Chem. Soc. 1988, 110, 1636. (b) Trost, B. M.; Trost, M. K. J. Am. Chem. Soc. 1991, 113, 1850.

3. For selected reviews, see: (a) Nishiyama, J.; Tóth, L.; Tóth, L. J. Am. Chem. Soc. 2006, 128, 8986. (f) Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. J. Am. Chem. Soc. 2007, 129, 9886. (c) Ji, K.-G.; Shu, X.-Z.; Chen, J.; Zhao, S.-C.; Zheng, Z.-J.; Lu, L.; Liu, X.-Y.; Liang, Y.-M. Org. Lett. 2008, 10, 3919.

4. (a) Pujanaski, B. G.; Prasad, A. B. A.; Sarpong, R. J. Am. Chem. Soc. 2006, 128, 6766. (b) Maddirala, S. J.; Oleidra, A.; Tadari, B. P.; Liu, R.-S. Synlett 2006, 1173.

5. For a review, see: (a) Patil, N. T.; Yamamoto, Y. Chem. Rev. 2008, 108, 3395. For selected examples of copper-catalyzed skeletal rearrangement, see: (b) Fehr, C.; Farris, I.; Sommer, H. Angew. Chem., Int. Ed. 2008, 47, 3793. (c) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kelin'm, A. V.; Georgy, V. J. Am. Chem. Soc. 2007, 129, 1440.

6. For selected examples, see: (a) Rautenstrauch, V. J. Org. Chem. 1984, 49, 950. (b) Shi, X.; Gorine, D. J.; Toste, D. F. Nature 2007, 445, 395. (c) Zhang, L.; Sun, J.; Kozmin, S. A. Adv. Synth. Catal. 2006, 348, 2271. (f) Jiménez-Núñez, E.; Echavarren, A. M. Chem. Rev. 2008, 108, 3326.

7. For selected examples, see: (a) Lautenbraun, V. J. Org. Chem. 1984, 49, 950. (b) Shi, X.; Gorine, D. J.; Toste, D. F. J. Am. Chem. Soc. 2005, 127, 5802. (c) Wang, S.; Zhang, L. J. Am. Chem. Soc. 2006, 128, 8414. (d) Schwar, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Georgy, V. J. Am. Chem. Soc. 2007, 129, 9886. (e) Ji, K.-G.; Shu, X.-Z.; Chen, J.; Zhao, S.-C.; Zheng, Z.-J.; Lu, L.; Liu, X.-Y.; Liang, Y.-M. Org. Lett. 2008, 10, 3919.

8. (a) Pujanaski, B. G.; Prasad, A. B. A.; Sarpong, R. J. Am. Chem. Soc. 2006, 128, 6766. (b) Maddirala, S. J.; Oleidra, A.; Tadari, B. P.; Liu, R.-S. Synlett 2006, 1173.

9. For a review, see: (a) Patil, N. T.; Yamamoto, Y. Chem. Rev. 2008, 108, 3395. For selected examples of copper-catalyzed skeletal rearrangement, see: (b) Fehr, C.; Farris, I.; Sommer, H. Angew. Chem., Int. Ed. 2008, 47, 2271. (c) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kelin'm, A. V.; Georgy, V. J. Am. Chem. Soc. 2008, 130, 1440.

10. For selected examples, see: (a) Lee, D.-Y.; Hong, B.-S.; Cho, E.-G.; Lee, H.; Jun, C.-H. J. Am. Chem. Soc. 2003, 125, 6372. (b) Shimada, T.; Yamamoto, Y. J. Am. Chem. Soc. 2003, 125, 6646. (c) Asano, N.; Nogami, T.; Lee, S.; Yamamoto, Y. J. Am. Chem. Soc. 2003, 125, 10921.

11. For metal-catalyzed cycloisomerization via N–O bond cleavage, see: (a) Trost, B. M.; Rhee, Y. H. J. Am. Chem. Soc. 2002, 124, 2528. (b) Yeom, H.-S.; Lee, E.-S.; Shin, S. Synlett 2007, 2292. (c) Yeom, H.-S.; Lee, J.-E.; Shin, S. Angew. Chem., Int. Ed. 2008, 47, 7040.

12. Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. J. Am. Chem. Soc. 1982, 47, 2765.

13. Buynak, J. D. Curr. Med. Chem. 2004, 11, 1951.

14. (a) Ojima, I.; Delafosse, F. Chem. Rev. 1997, 26, 277. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C. Chem. Rev. 2007, 107, 4437.

15. (b) Brandi, A.; Cicchi, S.; Cordero, F. C. Chem. Rev. 2009, 108, 3988. (b) Pal, R.; Ghosh, S. C.; Chandra, K.; Basak, A. Synlett 2007, 2321.