ORGANIC
LETTERS

2005
Vol. 7, No. 12
2425–2427

Iridium-Catalyzed Ring Cleavage Reaction of Cyclobutanone *O*-Benzoyloximes Providing Nitriles

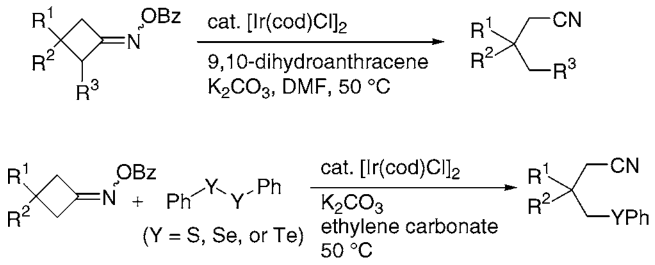
**Takahiro Nishimura,* Tomoaki Yoshinaka, Yoshiki Nishiguchi,
Yasunari Maeda, and Sakae Uemura***

*Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering,
Kyoto University, Nishikyo-ku, Kyoto 606-8510, Japan*

takahiro@scl.kyoto-u.ac.jp

Received April 4, 2005

ABSTRACT



Iridium-catalyzed ring cleavage reaction of cyclobutanone *O*-benzoyloximes in the presence of 9,10-dihydroanthracene and potassium carbonate proceeds to give saturated nitriles via C–C bond fission at the sterically more hindered site.

The cleavage of C−C bonds by transition metal complexes is a very attractive field in organometallic chemistry.[1] Its catalytic reaction is of interest particularly due to its ability to provide useful synthetic tools for various unique transformations.[2]

Recently, we have disclosed some transition metal-catalyzed C−C bond cleavage reactions[3−5] such as oxidative transformation[3] and arylation[4] of *tert*-cyclobutanols via β-carbon elimination of a palladium−alcoholate intermediate. Furthermore, it was found that the Pd-catalyzed C−C bond cleavage of cyclobutanone *O*-acyloximes afforded *unsaturated* nitriles where C−C bond fission occurred at the sterically less hindered site (Scheme 1).[5,6] In sharp contrast, we have now found that the use of an iridium complex in place of a palladium complex resulted in a formation of *saturated* nitriles where the bond fission occurred at the sterically more hindered site.

---

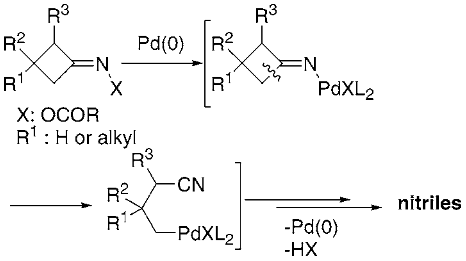
(1) For reviews of C−C bond cleavage reactions, see: (a) Bishop, K. C., III. *Chem. Rev.* **1976**, *76*, 461. (b) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (c) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241. (d) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870. (e) Murakami, M.; Ito, Y. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: New York, 1999; pp 97−129.

(2) See for examples: Rhodium-catalyzed reactions: (a) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815. (b) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976. Ruthenium-catalyzed reactions: (c) Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 2379. Nickel-catalyzed reaction: (d) Miller, J. A. *Tetrahedron Lett.* **2001**, *42*, 6991. (e) Kondo, T.; Kaneko, Y.; Taguchi, Y.; Nakamura, A.; Okada, T.; Shiotsuki, M.; Ura, Y.; Wada, K.; Mitsudo, T. *J. Am. Chem. Soc.* **2002**, *124*, 6824. Palladium-catalyzed reactions: (f) Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 2661. (g) Suginome, M.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11015. (h) Lautens, M.; Piguel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045. (i) Park, S.-B.; Cha, J. K. *Org. Lett.* **2000**, *2*, 147. (j) Okumoto, H.; Jinnai, T.; Shimizu, H.; Harada, Y.; Mishima, H.; Suzuki, A. *Synlett* **2000**, 629. (k) Satoh, T.; Jones, W. D. *Organometallics* **2001**, *20*, 2916. (l) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 270 (m) Nüske, H.; Noltemeyer, M.; de Meijere, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3411. (n) Trost, B. M.; Yasukata, T. *J. Am. Chem. Soc.* **2001**, *123*, 7162. (o) Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407. (p) Knoke, M.; de Meijere, A. *Synlett* **2003**, 195. (q) Ma, S.; Zhang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 184. (r) Chiba, S.; Kitamura, M.; Saku, O.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 785.

(3) (a) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645. (b) Nishimura, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 1455.

10.1021/ol0507120 CCC: $30.25

Scheme 1. Palladium-Catalyzed Ring-Opening Reaction of Cyclobutanone *O*-Benzoyloximes



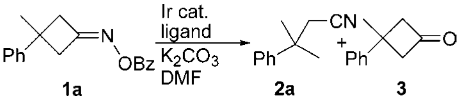
Treatment of 3-methyl-3-phenylcyclobutanone *O*-benzoyloxime (**1a**) in DMF (*N*,*N*-dimethylformamide) in the presence of $[Ir(cod)Cl]_2$ at 100 °C for 3 h under nitrogen gave the ring-opening product **2a** (a saturated nitrile) as well as cyclobutanone **3**, where the process for **2a** should involve the reduction step (Table 1, entry 1).[7] The reaction in DMF-d_6 showed the deuterium incorporation at the newly formed methyl group of **2a**. The addition of 9,10-dihydroanthracene as a hydrogen donor increased the yield of **2a** (entry 2). Hoping to improve the yield of the product, we added several ligands[8] to the reaction, but a signifcant effect was not observed (entries 3−7). The presence of 9,10-dihydroanthracene was important for the efficient reaction even in the reaction in the presence of ligand (entry 8). $IrCl(CO)(PPh_3)_2$ also worked well as a catalyst (entry 9). At a lower temperature (50 °C), the yield of **2a** was much improved (entries 10−13), where the addition of BnBPA[9] as a ligand was slightly effective, giving **2a** in 91% yield (entry 10). Certainly, no reaction occurred in the absence of the catalyst.

Table 1. Iridium-Catalyzed Ring-Opening Reaction of **1a**[a]

				GLC yield (%)	
entry	ligand (mol %)	temp (°C)	time (h)	**2a**	**3**
1[b]		100	3	39	29
2		100	3	58	4
3	(*R*)-(+)-BINAP (5)	100	3	60	3
4	PPh_3 (10)	100	3	55	6
5	bpy (5)	100	3	55	29
6	TPA (5)	100	3	62	4
7	BnBPA (5)	100	3	62	4
8[b]	BnBPA (5)	100	3	44	33
9	*c*	100	3	62	4
10	BnBPA (5)	50	48	91	3
11	(*R*)-(+)-BINAP (5)	50	48	89	3
12	TPA (5)	50	48	85	4
13	*c*	50	48	84	4

[a] Reaction conditions: **1a** (0.1 mmol), $[Ir(cod)Cl]_2$ (2.5 mol %), ligand, 9,10-dihydroanthracene (1.2 equiv.), K_2CO_3 (1.0 equiv), DMF (1.0 mL) at 100 °C for 3 h. [b] In the absence of 9,10-dihydroanthracene. [c] $IrCl(CO)(PPh_3)_2$ (5 mol %) was used.

Scheme 2

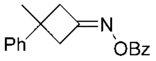
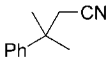
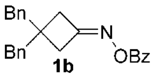
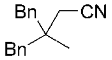
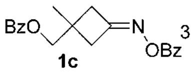
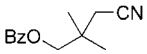
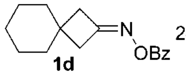
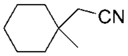
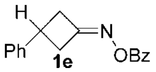
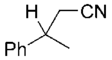


1a **2a** **3**

Among the solvents examined such as toluene, NMP (*N*-methyl-2-pyrrolidone), DMAc (dimethylacetamide), ethylene carbonate, and benzene, DMF was revealed to be the solvent of choice.

The presence of a base was also essential for efficient reaction, where K_2CO_3 was more effective than other bases such as Na_2CO_3, Cs_2CO_3, KOAc, and organic bases. When the reaction was carried out under air, it did not proceed at all. On the other hand, the reaction under an inert atmosphere occurred smoothly even in the dark.

Table 2. Reactions of Various Cyclobutanone *O*-Benzoyloximes[a]

entry	substrate	time (h)	product	isolated yield (%)
1	 **1a**	16	 **2a**	78
2	 **1b**	24	 **1b**	78
3[b]	 **1c**	36	 **1c**	85
4[b]	 **1d**	24	 **1d**	61
5	 **1e**	48	 **1e**	50

[a] Reaction conditions: **1** (0.50 mmol), $[Ir(cod)Cl]_2$ (2.5 mol %), BnBPA (5.0 mol %), K_2CO_3 (1.0 equiv), 9,10-dihydroanthracene (1.2 equiv), DMF (1.0 mL, 0.5 M) at 50 °C. [b] **1** (0.3 mmol).

---

(4) (a) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010. (b) Nishimura, T.; Matsumura, S.; Maeda, Y.; Uemura, S. *Tetrahedron Lett.* **2002**, *43*, 3037. (c) Nishimura, T.; Matsumura, S.; Maeda, Y.; Uemura, S. *Chem. Commun.* **2002**, 50. (d) Nishimura, T.; Matsumura, S.; Maeda, Y.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 8862.

(5) (a) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2000**, *122*, 12049. (b) Nishimura, T.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 5342.

(6) An alkylideneaminopalladium species was suggested, see: (a) Tsutsui, H.; Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1451. (b) Zaman, S.; Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1055.

(7) Reaction of cyclobutanone oximes with tributyltin hydride or under photolysis was reported by Zard et al.; see for example: (a) Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron* **1994**, *50*, 1757. (b) Boivin, J.; Fouquet, E.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1994**, *50*, 1769. (c) Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 2463.

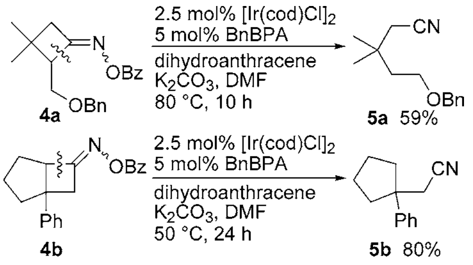
(8) Abbreviations for the ligands are as follows: (*R*)-(+)-2,2′-bis-(diphenylphosphino)-1,1-binaphthyl ((*R*)-(+)-BINAP), triphenylphosphine (PPh_3), 2,2′-bipyridine (bpy), *N*,*N*,*N*-tris(2-pyridylmethyl)amine (TPA), *N*-benzyl-*N*,*N*-bis(2-pyridylmethyl)amine (BnBPA).

(9) de Bruin, B.; Brands, J. A.; Donners, J. J. J. M.; Donners, M. P. J.; de Gelder, R.; Smits, J. M. M.; Gal, A. W.; Spek, A. L. *Chem. Eur. J.* **1999**, *5*, 2921.

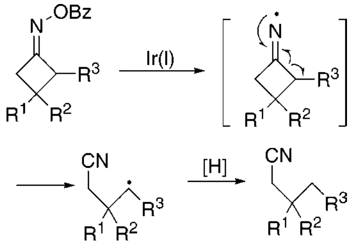
The results of the reactions of several cyclobutanone *O*-benzoyloximes are shown in Table 2. The reaction of 3,3-disubstituted cyclobutanone *O*-benzoyloximes (**1a**−**d**) gave the corresponding nitriles in good yields (Table 2, entries 1−4). 3-Monosubstituted cyclobutanone *O*-benzoyloxime such as **1e** also gave the corresponding nitrile in a moderate yield (entry 5).

Next, the reaction of 2,3,3-trisubstituted cyclobutanone *O*-benzoyloximes was carried out (Scheme 3). The reaction of **4a** gave the corresponding saturated nitrile **5a**. Similarly, bicyclic **4b** afforded **5b** in a good yield. It is noteworthy that the C−C bond at the sterically more hindered site was selectively cleaved in this iridium-catalyzed reaction in contrast to the palladium-catalyzed system. Considering the known C−C bond fission of a cyclobutane ring via a cyclobutylideneaminyl radical initiated by tributyltin hydride or photolysis,[7] we propose a similar radical pathway for this reaction, which affords a more stable secondary carbon radical via a homolytic cleavage of the C−C bond (Scheme 4). Contrary to the palladium case, there is no evidence for intervention of an organoiridium intermediate.

Scheme 3

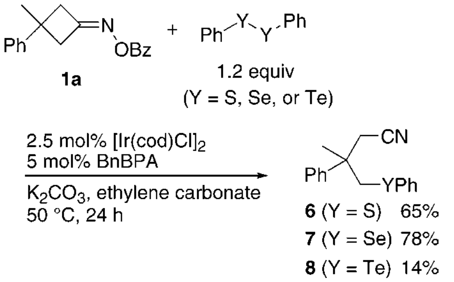


Scheme 4. Ring Opening via a Cyclobutylideneaminyl Radical



To obtain more information about the reaction pathway, the effect of radical inhibitors such as galvinoxyl and BHT (2,6-di-*tert*-butyl-4-methylphenol) was investigated, but they did not show any significant effects on the reaction.[10] On the other hand, when the reaction was carried out in the presence of several diphenyl dichalcogenides, which are known to react with a carbon radical forming a carbon−chalcogen bond,[11] a saturated nitrile containing a benzenechalogeno moiety was produced (Scheme 5). Thus, treatment of **1a** with diphenyl disulfide in DMF in the absence of 9,10-dihydroanthracene gave **2a** and **6** in 19 and 59% yield, respectively. To avoid hydrogen transfer from the solvent, the same reaction was tested in several solvents. As a result, the reaction in ethylene carbonate instead of DMF improved the yield of **6** to 65% without any formation of **2a**. The reaction of **1a** with diphenyl diselenide afforded **7** in much higher yield. On the other hand, the yield of the corresponding telluride **8** was lower in the reaction with diphenyl ditelluride. These results suggest the presence of a carbon radical in this catalytic reaction system as shown in Scheme 4.

Scheme 5. Reaction of **1a** with Diphenyl Dichalcogenides



In summary, we demonstrated that the iridium-catalyzed ring cleavage reaction of cyclobutanone *O*-benzoyloximes proceeded via an iminyl radical to afford the saturated nitriles. The carbon radical, which may be formed from the aminyl radical, can be trapped by diphenyl dichalcogenides to produce nitriles containing a benzenechalcogeno moiety.

Note Added after ASAP Publication. Errors were found in the TOC and Abstract graphics in the version published ASAP May 13, 2005; the corrected version was published ASAP May 20, 2005.

Supporting Information Available: Standard experimental procedure and characterization data for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0507120

---

(10) The smaller influence of radical inhibitors in this reaction system is probably due to the large cage effect of the solvent, which can prevent the trap of the radical species by the inhibitors, especially when the solvent has a high viscosity.

(11) For an example, see: Ogawa, A.; Obayashi, R.; Ine, H.; Tsuboi, Y.; Sonoda, N.; Hirao, T. *J. Org. Chem.* **1998**, *63*, 881.