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Palladium(0)-Catalyzed Ring Cleavage of Cyclobutanone Oximes Leading to Nitriles via *β*-Carbon Elimination

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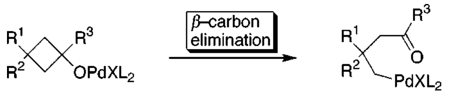
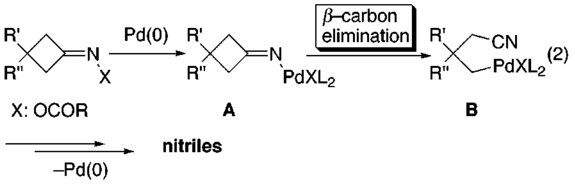
We have recently disclosed a novel Pd catalytic system involving β-carbon elimination from an intermediate palladium(II)-alcoholate to afford ketones, the driving force of which is the release of the ring strain of cyclobutane skeleton (eq 1).[1,2] To utilize this β-carbon elimination in palladium catalysis for other organic transformations, we envisaged constructing a new Pd(0) catalytic system using cyclobutanone *O*-acyloximes. As shown in eq 2, we assumed β-carbon elimination from an intermediate cyclobutaniminopalladium(II) complex (**A**) might give a γ-cyanoalkylpalladium species (**B**), since the oxidative addition of the N−O bond of ketone *O*-acyloximes to Pd(0) species giving alkaniminopalladium(II) complexes was quite recently proposed in the synthesis of five-membered nitrogen heterocycles.[3,4] In this paper we describe our successful results on the palladium(0)-catalyzed reaction of cyclobutanone *O*-acyloximes leading to various nitriles.[5,6]

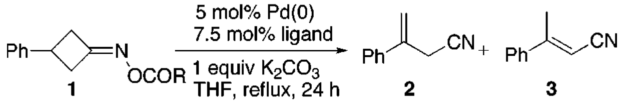


(1)



First, a tetrahydrofuran (THF) solution of 3-phenylcyclobutanone *O*-acetyloxime **1a**[7] was heated under reflux in the presence of a catalytic amount of Pd$_2$(dba)$_3$·CHCl$_3$, a base, and a bidentate phosphine ligand. The results are summarized in Table 1. As we expected, ring-opening reaction occurred to give isomeric phenylbutenenitriles **2** and **3**, the latter being the major product. As a phosphine ligand, (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)[8] was found to be most effective to give **3** in 76% yield (entry 5). In this reaction the concentration of the substrate affected the product yield which decreased using a higher concentration of **1a** (entry 6). Among various organic and inorganic bases examined, K$_2$CO$_3$ was revealed to be the base of choice. Other solvents such as toluene and *N*,*N*-dimethylformamide (DMF) were not effective. When Pd(PPh$_3$)$_4$ was used as a catalyst, the yield of the products was low (3% of **2** and 13% of **3**, respectively).[9] When the substrate having different acyl groups such as 3-phenylcyclobutanone *O*-trimethylacetyloxime (**1b**) and 3-phenylcyclobutanone *O*-benzoyloxime (**1c**) was employed, the oxime **1c** gave **3** in a higher yield than the case of **1a** and **1b** (entry 8). When **1c** was treated in the absence of Pd$_2$(dba)$_3$·CHCl$_3$, no reaction occurred and **1c** was recovered intact.[10]

Table 1. Palladium-Catalyzed Reaction of 3-Phenylcyclobutanone *O*-Acyloximes



R, **1a**: CH$_3$; **1b**: Bu^t; **1c**: Ph

entry	substrate	ligand	GLC yield (%) 2	GLC yield (%) 3
1	**1a**	dppe	3	10
2	**1a**	dppp	3	17
3	**1a**	dppb	1	8
4	**1a**	dppf	3	24
5	**1a**	(*R*)-(+)-BINAP	6	76
6[c]	**1a**	(*R*)-(+)-BINAP	3	38
7	**1b**	(*R*)-(+)-BINAP	15	66
8	**1c**	(*R*)-(+)-BINAP	4	84 (80)[d]

[a] Reaction conditions: **1** (0.50 mmol), Pd$_2$(dba)$_3$·CHCl$_3$ (0.0125 mmol), ligand (0.0375 mmol), K$_2$CO$_3$ (0.50 mmol), THF (5 mL), 90 °C (bath temp.), under N$_2$. [b] Based on **1** employed. [c] THF (2 mL). [d] Isolated yield.

The formation of the products **2** and **3** from **1c** can be explained as follows; first, the oxidative addition of the N−O bond of *O*-benzoyloxime **1c** to the Pd(0)−BINAP complex occurs to give a cyclobutaniminopalladium(II) intermediate (**A**), followed by the formation of an alkylpalladium species (**B**) via β-carbon elimination. Next, successive β-hydrogen elimination from the alkylpalladium species proceeds to give **2**, followed by the isomerization of **2** to more stable **3** and the reproduction of Pd(0) species by reductive elimination. Similarly, *O*-benzoyloxime **4** gave nitriles **5** (as an *E*/*Z* mixture), while the oxime **6** afforded nitriles **7** and **8** in 71% yield (**7**:**8** = 64:36 estimated by ^{1}H NMR,

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[1] Palladium(II)-catalyzed oxidative ring cleavage of *tert*-cyclobutanols, see: (a) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem.* Soc. **1999**, *121*, 2645. Palladium(0)-catalyzed arylation of *tert*-cyclobutanols, see: (b) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010.

[2] For examples of the dealkylation reaction of *tert*-alcoholates via β-carbon elimination catalyzed by the late transition metal, see: (a) Harayama, H.; Kuroki, T.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2352. (b) Kondo, T.; Kodoi, K.; Nishinaga, E.; Okada, T.; Morisaki, Y.; Watanabe, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **1998**, *120*, 5587. (c) Park, S.-B.; Cha, J. K. *Org. Lett.* **2000**, *2*, 147. (d) Okumoto, H.; Jinnai, T.; Shimizu, H.; Harada, Y.; Mishima, H.; Suzuki, A. *Synlett* **2000**, 629.

[3] Tsutsui, H.; Narasaka, K. *Chem. Lett.* **1999**, 45.

[4] For examples of the oxidative addition of oximes to metal, see: (a) Deeming, A. J.; Owen, D. W.; Powell, N. I. *J. Organomet. Chem.* **1990**, *398*, 299. (b) Ferreira, C. M. P.; Guedes da Silva, M. F. C.; Kukushkin, V. Y.; Fraúto da Silva, J. J. R.; Pombeiro, A. J. L. *J. Chem. Soc., Dalton Trans.* **1998**, 325.

[5] Ring opening reaction of cyclobutaniminyl radical to afford nitriles has been reported, see: (a) Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron Lett.* **1991**, *32*, 4299. (b) Boivin, J.; Fouquet, E.; Zard, S. Z. *J. Am. Chem. Soc.* **1991**, *113*, 1055. (c) Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron* **1994**, *50*, 1757. (d) Zard, S. Z. *Synlett* **1996**, 1148. (e) Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Zard S. Z. *Tetrahedron Lett.* **1997**, *38*, 2463.

[6] For examples of palladium-induced Beckmann fission of oximes to give nitriles, see: (a) Maeda, K.; Moritani, I.; Hosokawa, T.; Murahashi, S.-I. *J. Chem. Soc., Chem. Commun.* **1975**, 689. (b) Leusink, A. J.; Meerbeek, T. G.; Noltes, J. G. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 123.

[7] Cyclobutanone *O*-acyloximes were prepared by the reaction of cyclobutanone oximes with acid anhydride or acyl halide in the presence of triethylamine in CH$_2$Cl$_2$. Cyclobutanone oximes were easily prepared by the treatment of cyclobutanones with NH$_2$OH·HCl and NaOAc in an aqueous ethanol. Cyclobutanones were prepared by the reduction of α,α-dichlorocyclobutanones in the presence of Zn-powder and AcOH, which were synthesized by the reported procedure. See: Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879.

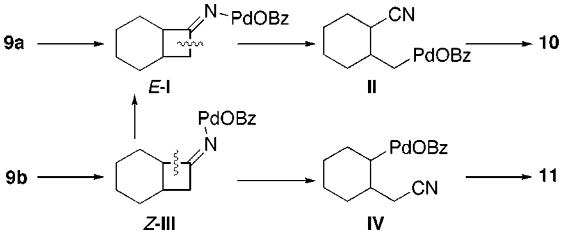
[8] dppe, dppp, dppb, and dppf stand for 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, and 1,1′-bis(diphenylphosphino)ferrocene, respectively.

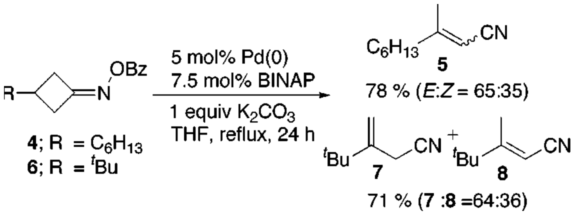
[9] The intramolecular cyclization of γ,δ-unsaturated ketone *O*-pentafluorobenzolyoximes reported by Tsutsui and Narasaka (ref 3) was successful in the presence of Pd(PPh$_3$)$_4$ and Et$_3$N in DMF. In our case, however, such combination was not effective.

[10] In the presence of Pd$_2$(dba)$_3$·CHCl$_3$, but in the absence of a phosphine ligand, the product yield was only 5%.

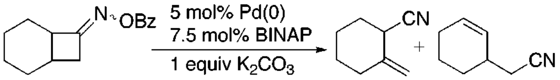
10.1021/ja005558l CCC: $19.00

Scheme 1





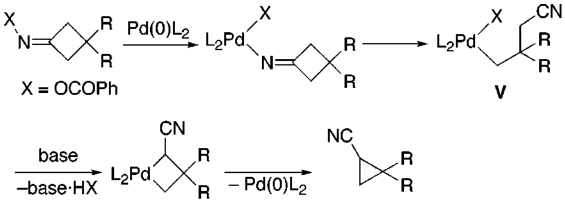
(3)



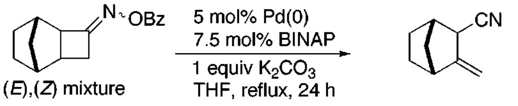
(4)

9		**10**	**11**
		GLC yield (%)	
9a (*E*)	THF, reflux, 9 h	86	8
9b (*Z*)	THF, reflux, 9 h	37	48
	ether, reflux, 72 h	83	8

Scheme 2

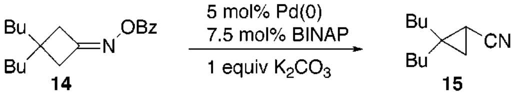


eq 3).[11] The reaction of a bicyclic compound **9a** (*E*-isomer)[12] proceeded to give the nitrile **10** preferentially in 86% yield as well as 8% of the nitrile **11** (eq 4).[13] On the other hand, **9b** (*Z*-isomer) gave **10** and **11** in 37 and 48% yield, respectively. Interestingly, when the reaction of **9b** was carried out at lower temperature (diethyl ether reflux), **10** became the main product (83%) (eq 4). We confirmed separately that **9a** or **9b** did not isomerize each other under the present conditions in the absence of $Pd_2(dba)_3{\cdot}CHCl_3$ and each was recovered completely intact after 9 h of refluxing in THF. These results indicate that *E*/*Z*-isomerization of an iminopalladium intermediate might occur during the reaction (Scheme 1). An iminopalladium species *E*-**I** may be produced from **9a** and afford **10** via the formation of an alkylpalladium species **II** formed by β-carbon elimination. The β-carbon elimination from **I** occurs by the interaction between a palladium and a sterically less hindered β-carbon in the cyclobutane ring to give a primary alkylpalladium species **II**. On the other hand, a palladium has to interact with a hindered β-carbon in *Z*-**III** to afford an alkylpalladium species **IV**. In the reaction of **9b**, the isomerization from *Z*-**III** to *E*-**I** occurs to some extent before β-carbon elimination, because the process from *Z*-**III** to **IV** may be slower due to its steric bulkiness. At lower temperature, the rate of β-carbon elimination from *Z*-**III** to **IV** may be much slower, resulting in a preferential formation of **10**. The same type of reaction of the oxime **12** underwent to give the nitrile **13** in 79% yield (eq 5).[14]



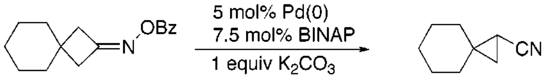
12 **13** 79 % (5)

Next, we treated 3,3-disubstituted cyclobutanone *O*-benzoyloximes under the same condition, in which there was no hydrogen available to be eliminated after the formation of an alkylpalladium intermediate (eqs 6 and 7). Interestingly, cyclopropanecarbonitriles **15** and **17** were obtained from oximes **14** and **16** respectively in 79 and 67% yields. These cyclopropanes might be produced via an intramolecular attack of an active methylene carbon of an intermediate alkylpalladium benzoate species **V** to the palladium in the presence of a base to afford a palladacyclobutane **VI**, followed by the reductive elimination to give the product and Pd(0) species (Scheme 2).



14 **15** (6)

THF, reflux, 48 h 71 %
1,4-dioxane, 100 °C, 15 h 79 %



16 **17** 67 % (7)

Supporting Information Available: Experimental procedures and analytical and spectroscopic data of compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] The isomerization of an *exo*-methylene compound to α,β-unsaturated nitrile might occur by Pd(II)-H species. In the case of **6**, the recombination of Pd(II)-H species with **7** leading to its isomerization to **8** might be slow because of a sterically hindered substituent (*t*-Bu).

[12] *E*- and *Z*-configurations were estimated by ^{13}C NMR. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 5th ed.; Wiley: New York, 1991; Chapter 5, p 245.

[13] Each product was isolated respectively by column chromatography and fully characterized by ^{1}H and ^{13}C NMR, IR, and C, H, N combustion analysis. The isomerization of an *exo*-methylene compound **10** to an internal alkene was not observed. It is probably due to spatial restrictions of the cyclohexane ring.

[14] Even in the reactions using each separated isomer of **12**, a significant difference of the yield of **13** was not observed.