Palladium-Catalyzed Arylation of *tert*-Cyclobutanols with Aryl Bromide via C−C Bond Cleavage: New Approach for the γ-Arylated Ketones

Takahiro Nishimura and Sakae Uemura*

Department of Energy and Hydrocarbon Chemistry
Graduate School of Engineering, Kyoto University
Sakyo-ku, Kyoto 606-8501, Japan

Received August 20, 1999

Palladium-catalyzed arylation of a wide variety of compounds with aryl halide has been developed in recent years as a powerful method to create an aromatic carbon−carbon bond[1] as well as an aromatic carbon−heteroatom bond.[2]

Recently, we have reported the palladium(II)-catalyzed oxidative ring cleavage of *tert*-cyclobutanols using oxygen as a reoxidant (Scheme 1),[3] in which we postulated that the C−C bond of *tert*-cyclobutanols was easily cleaved via β-carbon elimination from a Pd(II) alcoholate formed in situ to give a less hindered primary alkylpalladium intermediate. In this reaction, we suggested that divalent palladium works as an active species throughout the reaction using oxygen as a reoxidant. On the other hand, aryl halide is a well-known reagent for the oxidative reaction of Pd(0) to Pd(II).[1] Thus, our attention turned to the combination of Pd(0) and aryl halide in the reaction of *tert*-cyclobutanols, in which it is expected that arylation via β-carbon elimination from a Pd(II) alcoholate can proceed. Now we report a novel palladium-catalyzed arylation of *tert*-cyclobutanols involving selective β-carbon elimination from an arylpalladium alcoholate.

Recent advances in palladium-catalyzed arylation of alcohols with aryl halide for diaryl ether or aryl alkyl ether synthesis have been reported by Hartwig et al. and Buchwald et al.[4] They showed that a Pd(II) alcoholate is a key intermediate in which reductive elimination of C−O bond gives a product ether and also that a bulky or a chelating ligand can accelerate the reductive elimination step and retard β-hydrogen elimination relative to reductive elimination.[4a,c,5] Thus, our initial attempt to find the efficient catalyst system was done with 3-*tert*-butyl-1-phenyl-1-cyclobutanol (**1a**) as a substrate, using a palladium catalyst and various kinds of chelating phosphine ligands. The choice of ligands seems to be a crucial factor because an alkylpalladium intermediate formed by β-carbon elimination from a Pd(II) alcoholate could undergo both reductive elimination and β-hydrogen elimination. Treatment of **1a**[6] with 1.1 equiv of both bromobenzene and K_2CO_3 in the presence of 1 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ and 2 mol % phosphine ligand in 1,4-dioxane at 100 °C for 12 h under N_2 atmosphere afforded 4,4-dimethyl-1-phenyl-3-(phenylmethyl)-1-pentanone (**1b**) (Table 1). Among the ligands examined, (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)[7] was revealed to be the most efficient for the arylation of *tert*-cyclobutanol **1a** (71% GLC yield, entry 5).[8] Although a produced ketone **1b** has a chiral carbon center, no asymmetric induction occurred under these conditions.[9] As a solvent for this reaction, 1,4-dioxane was revealed to be more efficient than 1,2-dimethoxyethane, *N*,*N*-dimethylformamide, and toluene. Potassium carbonate (K_2CO_3) was a base of choice, and other bases, such as Na_2CO_3, NaOAc, Cs_2CO_3, and Et_3N, were less effective.

The arylation of siloxycyclopropanes in hexamethylphosphoric triamide (HMPA) was explored by Nakamura and Kuwajima et al. in 1988, in which a C−C bond of cyclopropane ring is cleaved catalytically by an arylpalladium complex to create an aryl carbon−alkyl carbon bond.[10] This reaction is suggested to occur by direct electrophilic attack of the arylpalladium cationic complex to an electron-rich β-carbon atom of siloxycyclopropanes to give an alkylpalladium intermediate, from which reductive elimination occurs to afford a β-arylated ketone. Their reaction requires a cationic complex produced from $[PdCl(C_3H_5)]_2$, triphenylphosphine, and aryl triflate, while aryl halide failed to react with

Scheme 1

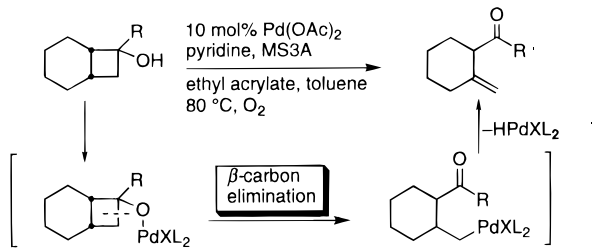
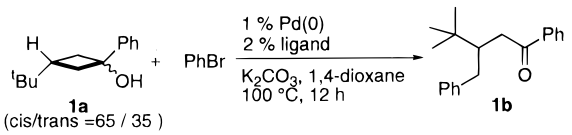


Table 1. Palladium-Catalyzed Arylation of *tert*-Cyclobutanols[a]



entry	ligand	GLC yield (%)
1	dppe	63
2	dppp	35
3	dppb	23
4	dppf	59
5	(*R*)-(+)-BINAP	71

[a] Reaction conditions: alcohol (0.20 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.001 mmol), ligand (0.004 mmol), bromobenzene (0.22 mmol), K_2CO_3 (0.22 mmol), 1,4-dioxane (1 mL), 100 °C, 12 h, under N_2.

(1) Tsuji, J. In *Palladium Reagents and Catalysis*; John Wiley: New York, 1995.

(2) For reviews, see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (c) Hartwig, J. F. *Synlett* **1997**, 329. (d) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (e) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.

(3) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645.

(4) For recent advances in palladium-catalyzed arylation of alcohols with aryl halide to produce aryl ethers, see: (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333. (b) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109. (c) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395. (d) Widenhoefer R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787. (e) Mann, G.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 5413. (f) Mann, G.; Hartwig, J. F. *Tetrahedron Lett.* **1997**, *38*, 8005. (g) Widenhoefer R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504. (h) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224. (i) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.

(5) For examples of C−C reductive elimination, which is much faster than β-hydrogen elimination in palladium-catalyzed arylation of ketones, see: (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (b) Hammann, B. C.; Hartwig J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382. (c) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (d) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

(6) Cyclobutanols are readily accessible from the corresponding cyclobutanones and Grignard reagent. For typical methods for preparing cyclobutanones, see: (a) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879. (b) Greene, A. E.; Luche, M.-J.; Serra, A. A. *J. Org. Chem.* **1985**, *50*, 3957.

(7) Racemic BINAP can also be used as a ligand. For the other ligands, 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.

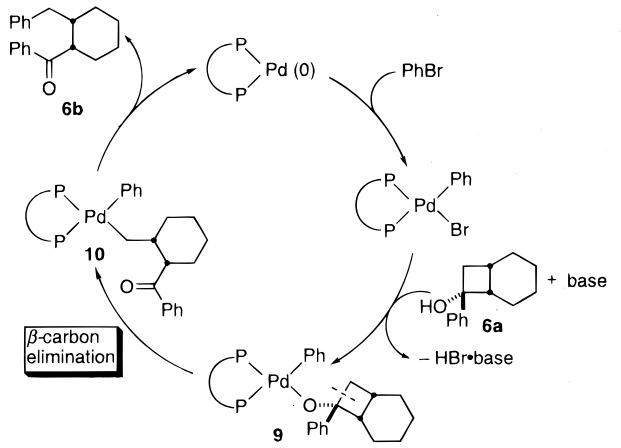
(8) Although $Pd(OAc)_2$ can also be used for the arylation of **1a**, the yield of **1b** decreased (58% GLC yield). The reaction can also proceed with $Pd(PPh_3)_4$ (65% GLC yield of **1b**).

(9) The enantiomeric excess was measured by HPLC.

(10) Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1988**, *110*, 3296.

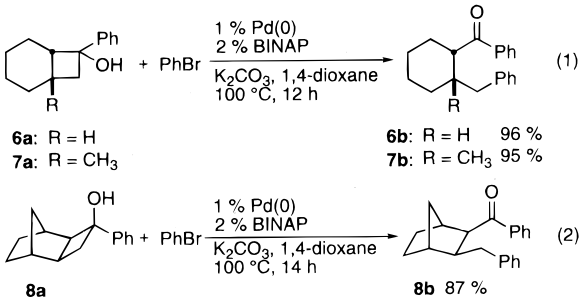
10.1021/ja993023q CCC: $18.00
Published on Web 11/12/1999

Scheme 2. Plausible Reaction Pathway



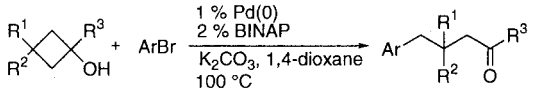
siloxycyclopropanes. In contrast, in our reaction, the arylation of *tert*-cyclobutanols proceeds with aryl bromide, because the formation of a Pd(II) alcoholate between a neutral palladium species and an alcohol is a crucial step which is followed by β-carbon elimination (vide infra).

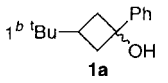
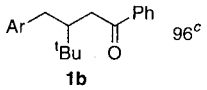
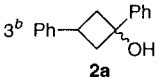
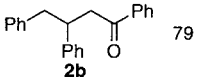
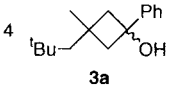
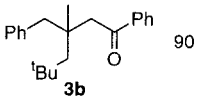
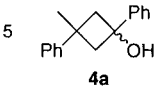
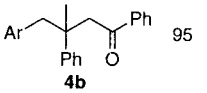
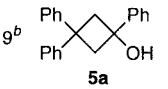
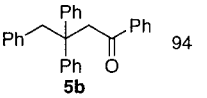
The results of arylation of several monocyclic *tert*-cyclobutanols leading to γ-arylated ketone under the optimized conditions described above are listed in Table 2. Using bromobenzene as an arylating reagent, 3-substituted cyclobutanols **1a** and **2a** gave the corresponding γ-arylated ketones **1b** and **2b** in good yields (entries 1 and 3).[11] 3,3-Disubstituted cyclobutanols **3a**−**5a** also afforded the corresponding ketones **3b**, **4b**, and **5b** in high yields. The arylation of **1a** and **4a** with 2-bromonaphthalene could also proceed to afford ketones **1c** and **4c** in good yields (entries 2 and 6). Similarly, the reaction of **4a** with *p*-bromotoluene smoothly occurred to give **4d** in high yield (entry 7). *p*-Bromochlorobenzene afforded **4e** selectively without affecting the chloro substituent (entry 8). The reaction could also be applied to bicyclic cyclobutanols **6a**−**8a** (eqs 1 and 2). In contrast to monocyclic cyclobu-



tanols, bicyclic ones have two C−C bonds in the ring that may be cleaved. In these cases, a selective C−C bond cleavage of cyclobutanol, giving a less hindered primary alkylpalladium complex, occurred to give arylated ketones **6b**−**8b** in high yields, in which an initial configuration (*cis*-configuration at bridgehead carbons in a substrate) was kept during the reaction.[12]

Table 2. Palladium-Catalyzed Arylation of *tert*-Cyclobutanols[a]



entry	substrate	Ar	time (h)	product and isolated yield (%)	
1[b]	 **1a**	Ph	24	 **1b**	96[c]
2[b]		2-naphthyl	24	**1c**	82
3[b]	 **2a**	Ph	24	 **2b**	79
4	 **3a**	Ph	12	 **3b**	90
5	 **4a**	Ph	9	 **4b**	95
6		2-naphthyl	12	**4c**	85
7		*p*-MeC$_6$H$_4$	12	**4d**	93
8		*p*-ClC$_6$H$_4$	19	**4e**	94
9[b]	 **5a**	Ph	24	 **5b**	94

[a] Reaction conditions: alcohol (0.4 mmol), $Pd_2(dba)_3$·$CHCl_3$ (0.002 mmol), (*R*)-(+)-BINAP (0.008 mmol), aryl bromide (0.44 mmol), K_2CO_3 (0.44 mmol), 1,4-dioxane (2 mL), 100 °C, 12 h, under N_2. [b] 1.2 equiv of both aryl bromide and K_2CO_3 to alcohol were used. [c] GLC yield.

The formation of a ring-opening arylated ketone can be explained by assuming the reaction sequence shown in Scheme 2. An arylpalladium intermediate, formed by oxidative addition of aryl bromide to a palladium(0) phosphine complex, undergoes a ligand exchange with *tert*-cyclobutanol to afford a palladium alcoholate **9**, which gives an alkylpalladium intermediate **10** by β-carbon elimination. The species **10** is prone to eliminate a palladium(0) phosphine complex reductively to give γ-arylated ketones. The fact that no aryl ether formation was observed suggests that β-carbon elimination is much faster than reductive elimination of an aryl C−O bond. Furthermore, the results of the reactions of **1a**, **2a**, **6a**, and **8a** clearly show that reductive elimination from **10** is much faster than β-hydrogen elimination to give an alkene.

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. See any current masthead page for ordering information and Web access instructions.

JA993023Q

(11) In the case of **1a**, the formation of a small amount of 3,4,4-trimethyl-1-phenyl-2-penten-1-one (<3%) was detected by ^{1}H NMR analysis of the crude reaction mixture. It may be formed by isomerization from an initially formed β,γ-unsaturated ketone via β-hydrogen elimination from an alkylpalladium intermediate. Similarly, from the reaction of **2a**, 3-methyl-1,3-diphenyl-2-buten-1-one was isolated in 6% yield.

(12) The stereochemistry of **6b**, **7b**, and **8b** was confirmed by the observation of the different NOE spectra (methine protons for **6b** and **8b**, methyl and methine protons for **7b**, respectively, in these NMR spectra).