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Homogeneous Catalysis

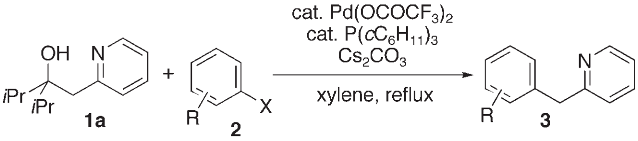
Palladium-Catalyzed 2-Pyridylmethyl Transfer from 2-(2-Pyridyl)ethanol Derivatives to Organic Halides by Chelation-Assisted Cleavage of Unstrained C_{sp^3}–C_{sp^3} Bonds**

Takashi Niwa, Hideki Yorimitsu, and Koichiro Oshima**

Transition-metal-catalyzed cleavage of carbon–carbon bonds is not only scientifically challenging but also potentially useful in organic synthesis.[1] Among the bond-breaking reactions, the cleavage of unstrained carbon–carbon bonds ranks as one of the most difficult processes because of the lack of sufficient strain energy as a driving force. Assistance by chelation is promising for the metal-mediated cleavage of such unstrained carbon–carbon bonds.[1d,f,2] However, it is always C_{sp^3}–C_{sp^2}[1d,f,2b,c] or C_{sp^2}–C_{sp^2}[2d] bonds that are cleaved. The kinetic as well as thermodynamic stability[1a–d] of C_{sp^3}–C_{sp^3} bonds has resulted in little being known about their chelation-assisted cleavage under catalytic conditions.[3] Here we report such an example: the palladium-catalyzed reactions of aryl and alkenyl chlorides with 2-(2-pyridyl)ethanol derivatives that result in the substitution of the chloro moieties with a 2-pyridylmethyl group.

Treatment of chlorobenzene (**2a**) with pyridyl alcohol **1a** in the presence of cesium carbonate and a palladium catalyst in refluxing xylene provided 2-benzylpyridine (**3a**) in good yield (Table 1, entry 1). A variety of aryl chlorides underwent the reaction and the presence of either an electron-withdrawing or electron-donating group on the aryl chlorides did not hinder the reaction (Table 1, entries 2–5). Aryl chloride **2f** with a methyl group at the 2-position also participated in the reaction (Table 1, entry 6). It is worth noting that the reaction of 4-chlorostyrene (**2g**) provided the desired product **3g** selectively (Table 1, entry 7), even though **2g** can competitively undergo repetitious Mizoroki–Heck reactions which lead to oligo(4-phenylenevinylene) through self-oligomerization.[4] The synthesis of di(2-pyridyl)methane (**3h**) was also successful (Table 1, entry 8). The yield of **3a** was slightly lower when the reaction with **2a** was performed at a lower temperature (Table 1, entry 9). Aryl bromides and iodides also underwent the pyridylmethylation (Table 1, entries 10 and 11).

Table 1: Palladium-catalyzed 2-pyridylmethyl transfer to aryl halides **2** from alcohol **1a**.[a]

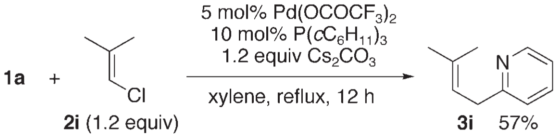


Entry	R	X	2	3	Yield[b] [%]
1	H	Cl	**2a**	**3a**	88
2	4-CF_3	Cl	**2b**	**3b**	89
3	4-COOEt	Cl	**2c**	**3c**	80
4	4-CN	Cl	**2d**	**3d**	70
5	4-OMe	Cl	**2e**	**3e**	90
6	2-Me	Cl	**2f**	**3f**	79
7	4-CH_2=CH	Cl	**2g**	**3g**	81
8	2-chloropyridine		**2h**	**3h**	50 (63)
9	H	Cl	**2a**	**3a**	85[c]
10	H	Br	**2a-Br**	**3a**	80[c]
11	H	I	**2a-I**	**3a**	88[c]
12	H	I	**2a-I**	**3a**	80[c,d]

[a] A mixture of **1a** (0.8 mmol), **2** (1.2 equiv), $Pd(OCOCF_3)_2$ (5 mol%), $P(cC_6H_{11})_3$ (10 mol%), and Cs_2CO_3 (1.2 equiv) was heated at reflux in xylene (0.5 M) for 1.5–10 h. [b] Yield of isolated product. The yield determined by ^1H NMR spectroscopy is given in parentheses. [c] Performed in refluxing toluene. [d] PPh_3 was used instead of $P(cC_6H_{11})_3$.

Triphenylphosphine functioned as well as tricyclohexylphosphine as the catalyst in the reaction of iodobenzene in refluxing toluene, and resulted in **3a** in being formed in 80% yield (Table 1, entry 12). The choice of palladium salt is crucial. Palladium trifluoroacetate proved to be the best precursor. The use of $Pd(OAc)_2$, $[Pd(acac)_2]$, $PdCl_2$, $[PdCl_2(CH_3CN)_2]$, $[PdCl(\pi\text{-allyl})]_2$, $[Pd(PPh_3)_4]$ (with no additional ligand), and $[Pd_2(dba)_3]$ (acac = acetylacetanoate, dba = *trans,trans*-dibenzylideneacetone) resulted in significantly lower yields of 73, 33, 15, 14, 20, 26, and 73%, respectively, relative to that obtained with $P(cC_6H_{11})_3$ (Table 1, entry 11). We have no clear reason for the difference. Unfortunately, the reactions of alkyl chlorides failed to yield the corresponding products, and **1a** was completely recovered. The reactions of benzyl chloride and allyl chloride afforded complex mixtures.

The reaction of alkenyl chloride **2i** yielded 2-prenylpyridine (**3i**) in reasonable yield [Eq. (1)]. The high efficiency of



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[*] T. Niwa, Dr. H. Yorimitsu, Prof. Dr. K. Oshima
Department of Material Chemistry
Graduate School of Engineering
Kyoto University
Kyoto-daigaku Katsura, Nishikyo-ku, Kyoto 615-8510 (Japan)
Fax: (+81) 75-383-2438
E-mail: yori@orgrxn.mbox.media.kyoto-u.ac.jp
oshima@orgrxn.mbox.media.kyoto-u.ac.jp

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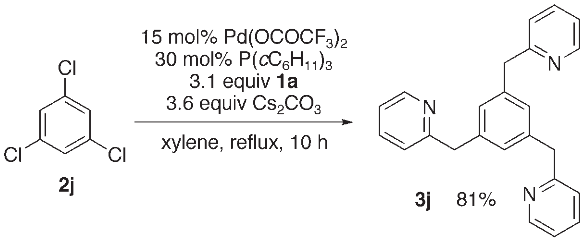
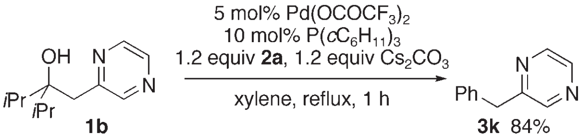
the pyridylmethyl transfer resulted in the reaction of 1,3,5-trichlorobenzene (**2j**) providing the new scaffold **3j** which is potentially applicable for use in supramolecular chemistry [Eq. (2)].



(2)

Pyrazinyl alcohol **1b** transferred the pyrazinylmethyl moiety efficiently under the same reaction conditions [Eq. (3)]. Disubstituted pyridines such as **3l** and **3m** were also readily synthesized [Eqs. (4) and (5)].[5] Notably, a number of attempts to effect benzyl group transfer reactions with **1e** and related 2-phenylethanol derivatives resulted in recovery of the starting alcohols [Eq. (6)]. Furthermore, alcohol **1f** (the 4-pyridyl analogue of **1a**) also resisted bond cleavage [Eq. (7)]. These results clearly suggest that the coordination of the basic nitrogen atom is essential for the success of the transfer reactions, and that the hydroxy group by itself is not sufficient to result in cleavage of the $C_{sp^3}-C_{sp^3}$ bond.[6]



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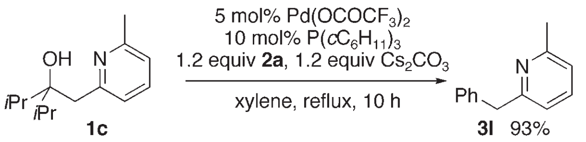

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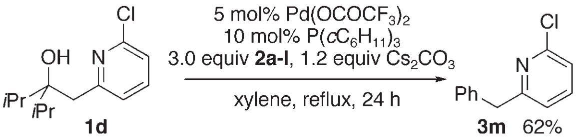

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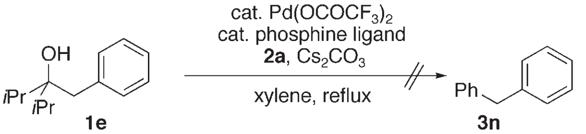

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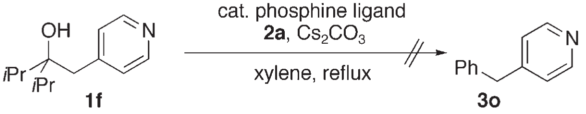
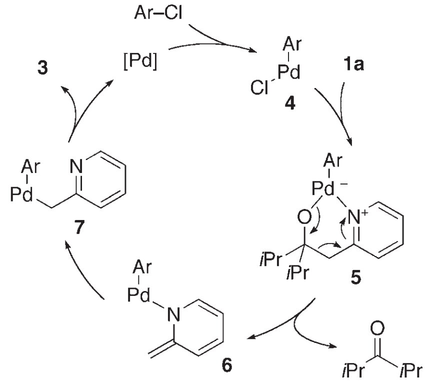


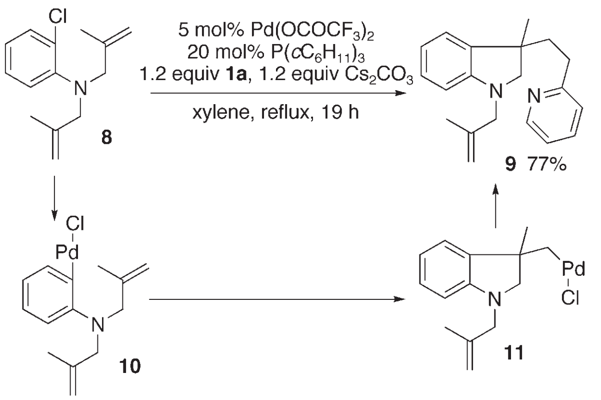
(7)

We tentatively postulate that the reaction mechanism is as follows (Scheme 1): After the oxidative addition,[7] ligand exchange takes place to afford aryl palladium alkoxide **5** through intramolecular coordination of the basic nitrogen atom to the palladium center. With the aid of the coordination, the intermediate **5** is likely to undergo cleavage of the $C_{sp^3}-C_{sp^3}$ bond to yield palladium amide **6**.[8,9] This amide would immediately isomerize to aryl(2-pyridylmethyl)palladium **7** to recover aromaticity. Reductive elimination then regenerates the initial low-valent palladium species as well as the product **3**.



Scheme 1. Plausible reaction mechanism. [Pd] = palladium catalyst.

Following cleavage of the $C_{sp^3}-C_{sp^3}$ bond, formation not only of the $C_{sp^2}-C_{sp^3}$ bond but also of the $C_{sp^3}-C_{sp^3}$ bond proceeds smoothly. The reaction of **8** with **1a** furnished the pyridylethyl-substituted dihydroindole **9** in good yield (Scheme 2). The reaction involves the conversion of the initial oxidative adduct **10** with an C_{sp^2}–Pd bond into a dihydroindolylmethylpalladium intermediate **11** with an C_{sp^3}–Pd bond by intramolecular carbopalladation.



Scheme 2. Tandem reaction to form dihydroindole.

Pyridine and related azaarenes are interesting cores of biologically active molecules and functional materials. We have found a new method to install such azaarenes by taking advantage of chelation-assisted cleavage of a C_{sp^3}–C_{sp^3} bond.

Experimental Section

Cesium carbonate (0.32 g, 0.97 mmol) was placed in a 30-mL two-necked reaction flask equipped with a Dimroth condenser. The cesium carbonate was dried in vacuo by heating (with a hair dryer for 2 min). The flask was then filled with argon by using the standard Schlenk technique. Palladium trifluoroacetate (13.4 mg, 0.040 mmol), tricyclohexylphosphine (0.5 M in toluene, 0.16 mL, 0.080 mmol), xylene (1.6 mL), pyridyl alcohol **1a** (0.17 g, 0.81 mmol), and chlorobenzene (**2a**, 0.11 g, 0.97 mmol) were added sequentially at room temperature. The resulting mixture was then heated at reflux for 6 h. After the mixture had cooled to room temperature, water (10 mL) was added and the product extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried over sodium sulfate, and concentrated in vacuo. Purification by column chromatography on silica gel (hexane:ethyl acetate 5:1) gave 2-benzylpyridine (**3a**, 0.12 g, 0.71 mmol) in 88% yield.

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[1] For reviews, see: a) M. Murakami, Y. Ito in *Activation of Unreactive Bonds and Organic Synthesis* (Ed.: S. Murai), Springer, Berlin, **1999**, pp. 97–129; b) K. C. Bishop III, *Chem. Rev.* **1976**, *76*, 461–486; c) R. H. Crabtree, *Chem. Rev.* **1985**, *85*, 245–269; d) B. Rybtchinski, D. Milstein, *Angew. Chem.* **1999**, *111*, 918–932; *Angew. Chem. Int. Ed.* **1999**, *38*, 870–883; e) T. Kondo, T. Mitsudo, *Chem. Lett.* **2005**, *34*, 1462–1467; f) C. H. Jun, *Chem. Soc. Rev.* **2004**, *33*, 610–618; g) T. Nishimura, S. Uemura, *Synlett* **2004**, 201–216; h) M. Catellani, *Synlett* **2003**, 298–313; i) P. W. Jennings, L. L. Johnson, *Chem. Rev.* **1994**, *94*, 2241–2290.

[2] a) K. Kaneda, H. Azuma, M. Wayaku, S. Teranishi, *Chem. Lett.* **1974**, 215–216; b) J. W. Suggs, C.-H. Jun, *J. Am. Chem. Soc.* **1984**, *106*, 3054–3056; c) C.-H. Jun, H. Lee, *J. Am. Chem. Soc.* **1999**, *121*, 880–881; d) N. Chatani, Y. Ie, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **1999**, *121*, 8645–8646.

[3] a) H. Harayama, T. Kuroki, M. Kimura, S. Tanaka, Y. Tamaru, *Angew. Chem.* **1997**, *109*, 2449–2451; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2352–2354; b) H. Wakui, S. Kawasaki, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2004**, *126*, 8658–8659.

[4] W. Heitz, W. Brugging, L. Freund, M. Gailberger, A. Greiner, H. Jung, U. Kampschulte, N. Niessner, F. Osan, H. W. Schmidt, M. Wicker, *Makromol. Chem.* **1988**, *189*, 119–127.

[5] The pyridyl alcohol $C(OH)(iPr)_2CHMe$(2-pyridyl) underwent a similar cleavage of a carbon–carbon bond, but unfortunately we only obtained vinylpyridine and other by-products.

[6] For examples of catalytic C_{sp^3}–C_{sp^3} bond cleavage assisted by coordination of a single oxygen atom, see a) T. Kondo, K. Kodoi, E. Nishinaga, T. Okada, Y. Morisaki, Y. Watanabe, T. Mitsudo, *J. Am. Chem. Soc.* **1998**, *120*, 5587–5588; b) P. Shukla, C. H. Cheng, *Org. Lett.* **2006**, *8*, 2867–2869; c) S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2006**, *128*, 2210–2211; d) Y. Takada, S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2006**, *8*, 2515–2517; e) A. Yanagisawa, T. Aoki, T. Arai, *Synlett* **2006**, 2071–2074.

[7] We prepared the palladium complex $[PdBr(Ph)(PPh_3)_2]$ and performed the stoichiometric reaction of the aryl palladium complex with **1a** in the presence of an equimolar (1.2 equiv) amount of cesium carbonate in refluxing xylene for 12 h. The reaction afforded **3a** in 50% yield.

[8] The X-ray structures of similar metal amides have been reported, see a) U. Pieper, D. Stalke, *Organometallics* **1993**, *12*, 1201–1206; b) W.-P. Leung, H. K. Lee, L.-H. Weng, B.-S. Luo, Z.-Y. Zhou, T. C. W. Mak, *Organometallics* **1996**, *15*, 1785–1792; c) P. C. Andrews, D. R. Armstrong, C. L. Raston, B. A. Roberts, B. W. Skelton, A. H. White, *J. Chem. Soc. Dalton Trans.* **2001**, 996–1006; d) D. Thomas, W. Baumann, A. Spannenberg, R. Kempe, U. Rosenthal, *Organometallics* **1998**, *17*, 2096–2102.

[9] Alternatively, a β-carbon elimination process would produce **7**, see: a) Y. Terao, H. Wakui, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2001**, *123*, 10407–10408; b) H.-F. Chow, C.-W. Wan, K.-H. Low, Y.-Y. Yeung, *J. Org. Chem.* **2001**, *66*, 1910–1913; c) T. Ooi, T. Miura, K. Maruoka, *J. Am. Chem. Soc.* **1998**, *120*, 10790–10791; d) T. Nishimura, H. Araki, Y. Maeda, S. Uemura, *Org. Lett.* **2003**, *5*, 2997–2999.