HETEROCYCLES, Vol. 74, 2007, pp. 233 - 237. © The Japan Institute of Heterocyclic Chemistry
Received, 7th September, 2007, Accepted, 4th October, 2007, Published online, 5th October, 2007. COM-07-S(W)68

SUZUKI-MIYAURA COUPLING OF BENZYLIC CARBONATES WITH HETEROARYLBORONIC ACIDS

Ryoichi Kuwano* and Jung-Yi Yu

Department of Chemistry, Graduate School of Sciences, Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka, 812-8581, Japan; e-mail: rkuwascc@mbox.nc.kyushu-u.ac.jp

Abstract – Cross-coupling of benzylic carbonates with heteroarylboronic acids successfully proceeded in the presence of the palladium catalyst that was generated *in situ* from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and a chelate bisphosphine DPPPent. Various heteroarylboronic acids were applicable to the catalytic cross-coupling, giving the desired benzylated heteroaromatics in high yields.

Palladium-catalyzed cross-coupling of organohalides with organoboron compounds, *i.e.* Suzuki-Miyaura coupling, is regarded as a basic method for carbon-carbon bond formation in organic synthesis.[1] Halo or sulfonate functionality has usually been utilized as a leaving group of electrophilic substrates for the catalytic reaction. Recently, we have directed our attention to an activation of the benzylic C–O bond in benzylic carbonates and acetates with homogeneous palladium catalysis. The C–O bond activation has applied to some palladium-catalyzed nucleophilic substitutions of benzylic esters[2] and the related reactions.[3] As a part of the research program, we reported that the cross-coupling of arylboronic acids with benzylic carbonates[4] or acetates[5] proceeded in the presence of a palladium catalyst to give various diarylmethane skeletons in high yields.[6,7]

Meanwhile, useful biologically active compounds, *e.g.* antispasmodic agent papaverine, often contain (aryl)(heteroaryl)methane skeletons.[8] We envisioned that such skeletons would readily be prepared through the above benzylic cross-coupling when a heteroarylboronic acid was employed in place of the arylboronic acid. Heteroarylboronic acids have worked as nucleophilic substrates in Suzuki-Miyaura biaryl synthesis.[9] However, application of the heteroaromatic substrates to catalytic cross-coupling has sometimes faced the hurdles caused by their electronic properties[10] and/or by the interaction of their

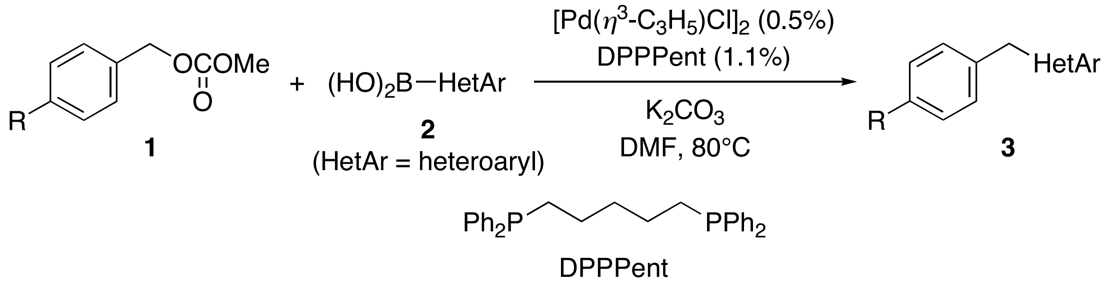
---

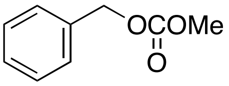
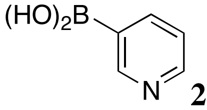
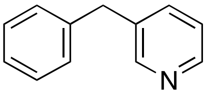
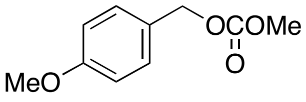
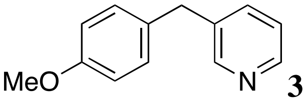
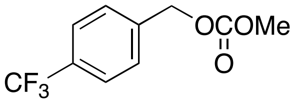
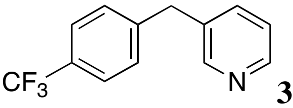
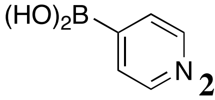
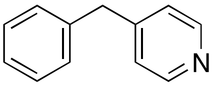
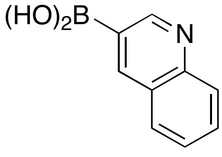
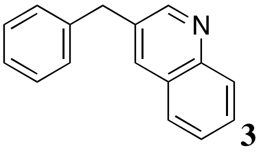
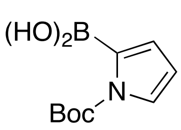
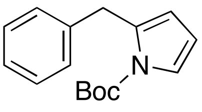
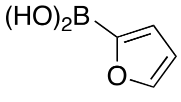
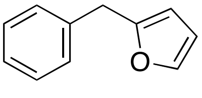
This paper is dedicated to Professor Ekkehard Winterfeldt on the occasion of his 75th birthday.

heteroatom with the catalyst.[11] In this paper, we describes the cross-coupling of benzylic carbonates with heteroarylboronic acids by using a palladium complex as a catalyst.[12]

The reactions of benzylic carbonates **1** with heteroarylboronic acids **2** were carried out in DMF at 80 °C in the presence of 1% palladium catalyst generated *in-situ* from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and a chelate bisphosphine, 1,5-bis(diphenylphosphino)pentane (DPPPent).[4] As with arylboronic acids, 3-pyridylboronic acid (**2a**)

Table 1. Cross-couplings of benzylic carbonates **1** with heteroarylboronic acids **2**[a]



Entry	1	2	Time (h)	Product (3)	Yield[b]
1	 **1a**	 **2a**	24	 **3a**	93
2[c]	 **1b**	**2a**	3	 **3b**	96
3	 **1c**	**2a**	48	 **3c**	79
4	**1a**	 **2b**	24	 **3d**	83
5	**1a**	 **2c**	45	 **3e**	96
6	**1a**	 **2d**	24	 **3f**	75
7[c,d]	**1a**	 **2e**	24	 **3g**	91

[a] Reactions were conducted on 1.0 mmol scale in DMF (1 ml) at 80 °C unless otherwise noted. The ratio of **1**:**2**:K_2CO_3:$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$:DPPPent was 1:1.1:2.2:0.005:0.011.

[b] Isolated yield.

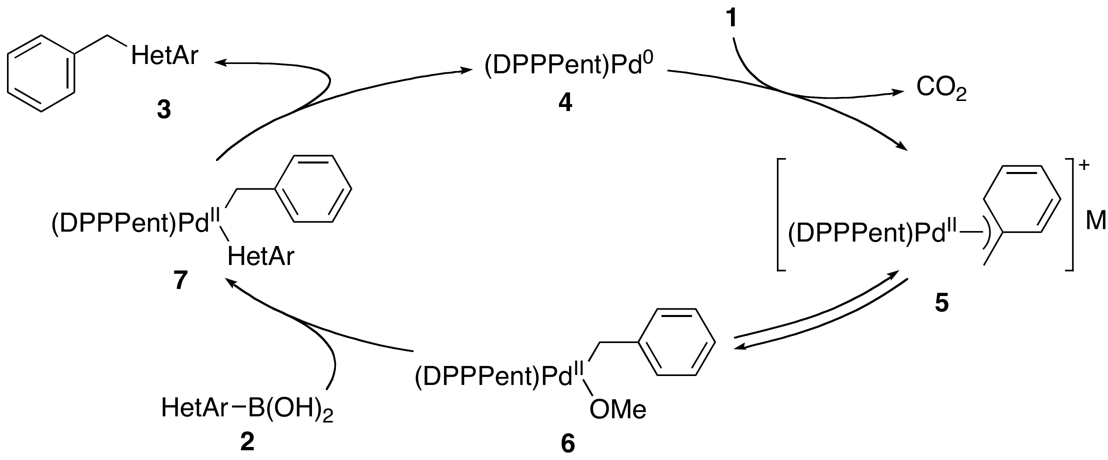
[c] The reactions were conducted at 100 °C.

[d] The reaction was conducted in *tert*-amyl alcohol.

reacted with benzyl methyl carbonate (**1a**) to give the desired cross-coupling product **3a** in 93% yield (Table 1, entry 1).[13] Large excess of pyridines to a phosphine-palladium catalyst are possible to causethe dissociation of chelating bisphosphine ligands because *sp*^{2}-nitrogen of pyridines can tightly interact with palladium(II).[11] Fortunately, the displacement of DPPPent by pyridines negligibly occurred during the catalytic process or scarcely affected the palladium catalysis. Electron-donating methoxy group of **1b** brought about significant decrease in the reaction rate. Higher reaction temperature was required for the efficient cross coupling with **2a** (entry 2). Similarly, electron-poor **1c** reacted slowly with **2a** at 80 °C (entry 3). Appreciable decomposition of **1c** to *p*-trifluoromethylbenzyl alcohol occurred at 100 °C, obstructing the improvement in the production of **3c**. 4-Pyridylboronic acid (**2b**) as well as **2a** was converted into 4-benzylpyridine (**3d**) in high yield (entry 4). $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$–DPPPent failed to catalyze the cross-coupling when acetate was used as a leaving group in the benzylic substrate. Benzyl acetate was possible to couple with **2b** by using DPEphos ligand,[14] but the reaction produced **3d** at 72 h in only 24% yield.

Other heteroarylboronic acids also worked as nucleophilic substrates for the cross-coupling with benzylic carbonates. The reaction of benz-fused substrate **2c** with **1a** gave 3-benzylquinoline (**3e**) in high yield (entry 5). Five-membered heteroarylboronic acids **2d** and **2e** could be used as substrates for the present catalytic reaction, but they showed lower reactivity than pyridylboronic acids (entries 6 and 7). 2-Thienylboronic acid failed to react with **1a** by the DPPPent-palladium catalysis.

The present catalytic reaction would proceed through the catalytic cycle in Scheme 1, which followed a typical mechanism of the palladium-catalyzed cross-couplings. Benzyl carbonate **1** underwent the S_N2'-like nucleophilic attack of DPPPent-ligated palladium(0) **4**, forming a cationic (η^3-benzyl)palladium(II) **5**. The η^3-complex **5** readily reached to the equilibrium with η^1-benzyl complex **6**. The methoxide ligand of **6** was replaced by heteroaryl through the transmetalation with



Scheme 1. A possible mechanism of the cross-coupling of **1** with **2**

heteroarylboronic acid **2**. The resulting (benzyl)(heteroaryl)palladium **7** yielded the desired benzylheteroarene **3** and regenerated **4** through the reductive elimination.

We have demonstrated that a variety of heteroarylboronic acids **2** were usable for the Suzuki-Miyaura coupling with benzylic carbonates **1**. The cross-coupling readily proceeded in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$–DPPPent catalyst, producing the desired products in good to high yields. The results shown in this paper will offer a fruitful and general access to various (aryl)(heteroaryl)methanes.

ACKNOWLEDGEMENTS

This work was supported by Iketani Science and Technology Foundation and KAKENHI (No. 16685011 and 19020051) from MEXT.

REFERENCES AND NOTES

1. Representative reviews: N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; N. Miyaura, *Top. Curr. Chem.*, 2002, **219**, 11; F. Bellina, A. Carpita, and R. Rossi, *Synthesis* **2004**, 2419.
2. R. Kuwano, Y. Kondo, and Y. Matsuyama, *J. Am. Chem. Soc.*, 2003, **125**, 12104; R. Kuwano and Y. Kondo, *Org. Lett.*, 2004, **6**, 3545; R. Kuwano, Y. Kondo, and T. Shirahama, *Org. Lett.*, 2005, **7**, 2973; R. Kuwano and H. Kusano, *Chem. Lett.*, 2007, **36**, 528; M. Yokogi and R. Kuwano, *Tetrahedron Lett.*, 2007, **48**, 6109.
3. R. Kuwano and T. Shige, *J. Am. Chem. Soc.*, 2007, **129**, 3802.
4. R. Kuwano and M. Yokogi, *Org. Lett.,* 2005, **7**, 945.
5. R. Kuwano and M. Yokogi, *Chem. Commun.*, 2005, 5899.
6. Recent examples of the cross-coupling of benzylic halides with organoboron compounds, see: S. M. Nobre and A. L. Monteiro, *Tetrahedron Lett.*, 2004, **45**, 8225; G. A. Molander and M. D. Elia, *J. Org. Chem.*, 2006, **71**, 9198.
7. The cross-coupling of benzylic phosphates with organometallic compounds, see: M. McLaughlin, *Org. Lett.*, 2005, **7**, 4875; C. C. Kofink and P. Knochel, *Org. Lett.*, 2006, **8**, 4121.
8. K. L. McPhail, D. E. A. Rivett, D. E. Lack, and M. T. Davies-Coleman, *Tetrahedron*, 2000, **56**, 9391; A. Rosowsky, H. Chen, H. Fu, and S. F. Queener, *Bioorg. Med. Chem.*, 2003, **11**, 59; R. A. Forsch, S. F. Queener, and A. Rosowsky, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1811; Y.-Q. Long, X.-H. Jiang, R. Dayam, T. Sanchez, R. Shoemaker, S. Sei, and N. Neamati, *J. Med. Chem.*, 2004, **47**, 2561.
9. K. L. Billingsley, K. W. Anderson, and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2006, **45**, 3484; K. Billingsley and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 3358; A. S. Guram, X. Wang, E. E. Bunel, M. M. Faul, R. D. Larsen, and M. J. Martinelli, *J. Org. Chem.*, 2007, **72**, 5104.

10. G. A. Molander and B. Biolatto, *J. Org. Chem.*, 2003, **68**, 4302; T. E. Barder, S. D. Walker, J. R. Martinelli, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685.
11. Q. Shen, S. Shekhar, J. P. Stambuli, and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2005, **44**, 1371.
12. Several (aryl)(heteroaryl)methanes have been prepared by the cross-coupling of benzylic carbonates with organometallic compounds, see: C. C. Lindsey, B. M. O'Boyle, S. J. Mercede, and T. R. R. Pettus, *Tetrahedron Lett.*, 2004, **45**, 867; Y. Nakao, S. Ebata, J. Chen, H. Imanaka, and T. Hiyama, *Chem. Lett.*, 2007, **36**, 606.
13. Typical procedure for palladium-catalyzed cross-coupling of **1** with **2**: Under nitrogen atmosphere, a benzylic carbonate **1** (1.0 mmol) was added to a mixture of a heteroarylboronic acid (1.1 mmol), potassium carbonate (303 mg, 2.2 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1.8 mg, 5.0 μmol), and DPPPent (4.8 mg, 11 μmol) in DMF (1.0 ml). The mixture was stirred until **1** disappeared in GC analysis. On cooling the reaction vessel, water was added to the resulting mixture and then it was extracted several times with EtOAc. The combined organic layer was washed with brine, dried with Na_2SO_4, and evaporated under reduced pressure. The residue was purified with a flash column chromatography on silica gel (EtOAc/hexane).
14. DPEphos = bis[2-(diphenylphosphino)phenyl] ether, see: M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, and J. Fraanje, *Organometallics*, 1995, **14**, 3081.