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Cross-coupling of benzylic acetates with arylboronic acids: one-pot transformation of benzylic alcohols to diarylmethanes†

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Received (in Cambridge, UK) 21st September 2005, Accepted 11th October 2005
First published as an Advance Article on the web 26th October 2005
DOI: 10.1039/b513372f

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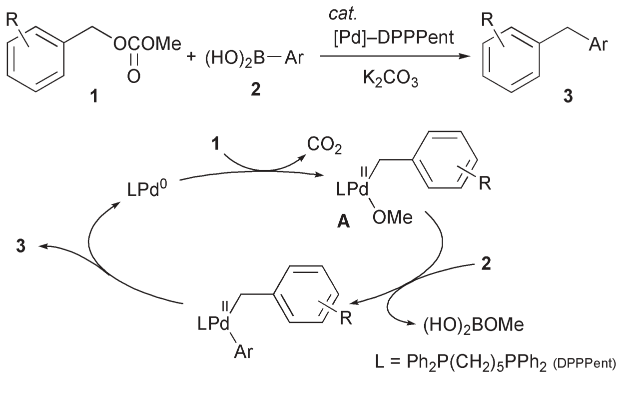
Published on 26 October 2005 on http://pubs.rsc.org | doi:10.1039/B513372F

Benzylic acetates reacted with arylboronic acids in the presence of a DPEphos–[Pd(η^3-C_3H_5)Cl]$_2$ catalyst when *tert*-amyl alcohol was used as a solvent, and the catalytic cross-couplings produced diarylmethanes in high yields (up to 94% isolated yield).

In organic synthesis, a basic method of C–C bond formation is the palladium-catalysed cross-couplings of organohalides with organometallic compounds.[1,2] The cross-coupling of benzylic halides with aryl metal compounds yields diarylmethane skeletons,[3–5] which are often found in pharmacologically interesting compounds[6] and supramolecules.[7] However, the use of benzylic cross-coupling has been limited in organic synthesis because benzylic halides are sometimes lachrymatory and are not always stable.

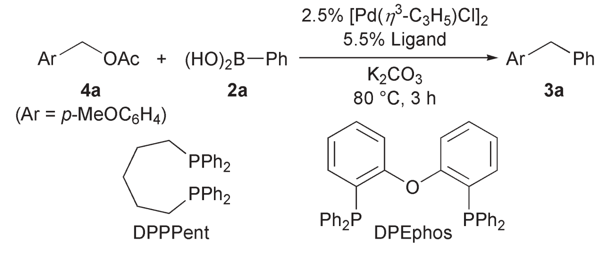
Recently, we reported the cross-coupling of benzylic carbonates **1** with arylboronic acids **2** (Scheme 1).[8] The reaction proceeded successfully in DMF with a DPPPent–palladium catalyst. However, the optimal reaction conditions failed to trigger the reaction of benzylic acetates **4**, which were more accessible than carbonates **1**. The mechanism shown in Scheme 1 had been proposed for the catalytic reaction. We assumed that the alkoxide in intermediate **A** was advantageous for successive transmetalation with arylboronic acids[9] and that (acetato)(benzyl)palladium generated from benzyl acetate was inactive in the transmetalation. However, if the acetate ligand on palladium can be replaced with an alkoxide, benzylic acetates may be employed as an electrophilic substrate. Based on this hypothesis, we attempted the reaction of benzylic acetates with phenylboronic acid in alcoholic solvents. A large amount of alcohol was expected to allow ligand exchange between the acetate and the alkoxide on the palladium catalyst.



Scheme 1 Cross-coupling of benzylic carbonates (**1**) with arylboronic acids (**2**) and its proposed mechanism.

Various organic solvents were evaluated for the reaction of anisyl acetate (**4a**) with phenylboronic acid (**2a**) at 80 °C in the presence of 5 mol% DPPPent–palladium (Table 1). The consumption of **4a** was scarcely observed in either aprotic DMF or dioxane solvent (entries 1 and 2). The use of methanol resulted in the solvolysis of **4a** and did not yield diarylmethane **3a** (entry 3). Isopropyl alcohol caused the palladium catalyst to decompose into a black suspension (entry 4). Cross-coupling product **3a** was obtained successfully from the reaction using a tertiary alcohol without the undesired solvolysis. *tert*-Amyl alcohol was the solvent of our choice because it is liquid at room temperature (entry 5). In a further evaluation of various palladium catalyst precursors, ligands, and bases, the cross-coupling of **4a** with **2a** was found to produce **3a** in high yield when DPEphos[10]–[Pd(η^3-C_3H_5)Cl]$_2$ was used as a catalyst (entry 6).‡ Catalyst loading can be reduced to 2 mol% under optimal conditions. Moreover, **3a** was obtained in 94% isolated yield (entry 7).§

Table 1 Cross-coupling of **4a** with **2a**: optimization of reaction conditions[a]



Entry	Solvent	Ligand	Yield (%)[b]
1	DMF	DPPPent	2 (2)
2	Dioxane	DPPPent	1
3	MeOH	DPPPent	0
4	*i*-PrOH	DPPPent	0
5	*tert*-Amyl alcohol	DPPPent	19 (65)
6	*tert*-Amyl alcohol	DPEphos	32 (95)
7[c]	*tert*-Amyl alcohol	DPEphos	94[d]

[a] Reactions were conducted on a 0.2 mmol scale in 1.0 cm^3 of a solvent unless otherwise noted. The ratio of **4a** : **2a** : K$_2$CO$_3$: [Pd(η^3-C$_3$H$_5$)Cl] : ligand was 100 : 150 : 300 : 2.5 : 5.5. [b] GC yield after 3 h (average of two runs). GC yields after 24 h are given in parentheses. [c] The reaction was conducted on a 1 mmol scale (1.0 M) for 72 h with 2 mol% palladium. [d] Isolated yield.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures and characterization data for products **3**. See DOI: 10.1039/b513372f

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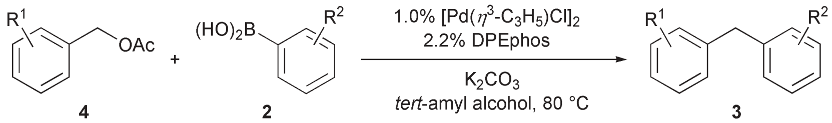
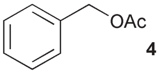
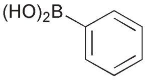
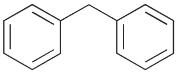
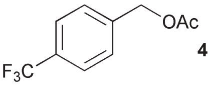
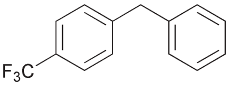
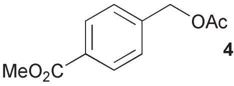
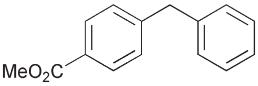
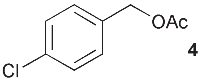
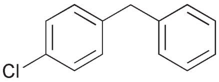
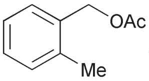
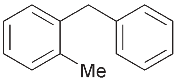
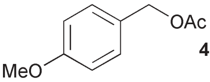
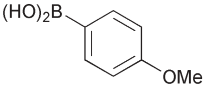
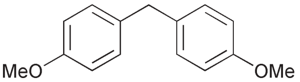
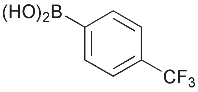
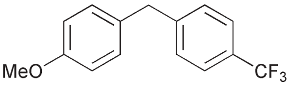
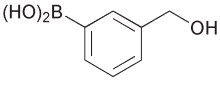
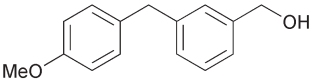
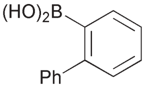
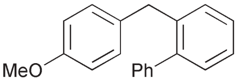
The scope of the cross couplings of benzylic acetates **4** with arylboronic acids **2** is summarised in Table 2. Electron-poor benzylic acetate **4c** as well as electron-rich **4a** reacted with **2a** to produce a cross-coupling product **3c** in high yield (entry 2). The electronic property of **2** barely affected the rate of the catalytic reaction and the yield of diarylmethane (entries 6 and 7). Some reactive functional groups, *e.g.* ester (entry 3), chloro (entry 4), and hydroxy (entry 8), were tolerable for the cross-coupling. As the reaction proceeded, the reaction of **4a** with **2d** formed a gel, and the gelation appeared to produce a low yield of **3i**. However, this problem was solved by conducting the reaction in a mixture of *tert*-amyl alcohol and DMF. The *ortho*-phenyl substituent of **2e** hardly hampered the formation of diarylmethane **3j** (entry 9). (Naphthyl)methyl esters exhibited a considerably higher reactivity than benzyl ester in the palladium-catalyzed benzylic substitutions with soft nucleophiles,[11] while the cross-coupling of (2-naphthyl)methyl acetate with **2a** yielded the desired diarylmethanes in <10% yield (GC) at 24 h.

The one-pot transformation of benzylic alcohol **5a** into diarylmethane **3a** was attempted by means of the above-mentioned catalytic reaction (Scheme 2). The acetylation of **5a** was conducted in *tert*-amyl alcohol with acetic anhydride and triethylamine. Benzylic acetate **4a** was selectively obtained with no formation of *tert*-amyl acetate. Potassium carbonate, the palladium catalyst, and **2a** were successively added to the mixture, which was then heated at 80 °C. The one-pot reaction produced diarylmethane **3a** in 75% isolated yield. The other benzylic alcohols, **5b** and **5c**, were successfully transformed into **3c** and **3d** in good yields, respectively.

We have demonstrated that benzylic acetates function as electrophilic substrates in palladium-catalysed cross-coupling with organoboron compounds. To our knowledge, this is the first reaction involving the activation of the benzylic C–O bond of

Table 2 Cross-coupling of benzylic acetates (**4**) with arylboronic acids (**2**)[a]



Entry	4	2	Time/h	Product (3)	Yield (%)[b]
1	 **4b**	 **2a**	96	 **3b**	83
2	 **4c**	**2a**	24	 **3c**	86
3	 **4d**	**2a**	72	 **3d**	85
4[c]	 **4e**	**2a**	72	 **3e**	65
5[d]	 **4f**	**2a**	48	 **3f**	80
6	 **4a**	 **2b**	48	 **3g**	92
7[d]	**4a**	 **2c**	48	 **3h**	89
8[e]	**4a**	 **2d**	48	 **3i**	92
9	**4a**	 **2e**	24	 **3j**	86

[a] Reactions were conducted on a 1 mmol scale in *tert*-amyl alcohol (1.0 cm^3) unless otherwise noted. The ratio of **4** : **2** : K_2CO_3 : [Pd(η^3-C_3H_5)Cl]$_2$: DPEphos was 100 : 110 : 220 : 1.0 : 2.2. [b] Isolated yield. [c] The reaction was conducted on a 0.5 mmol scale with 1.5 molar equivalents of **2a** and 5 mol% palladium. [d] The reactions were conducted in 2.0 cm^3 of *tert*-amyl alcohol. [e] The reaction was conducted in a mixture of *tert*-amyl alcohol (3.0 cm^3) and DMF (0.5 cm^3).

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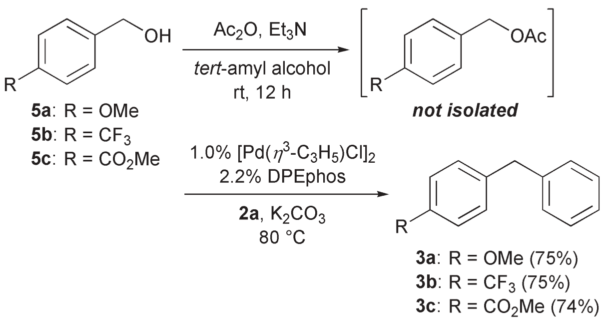

Scheme 2 One-pot transformation of **5** to **3**.

benzyl acetate with homogeneous catalysis.[12,13] The catalytic cross-coupling was significantly accelerated by the tertiary alcohol solvent. Although the observation is consistent with our working hypothesis, it is unclear whether or not *tert*-amyl alcohol accelerates the transmetalation step. Mechanistic investigations focusing on the effect of alcoholic solvents are in progress.

This work was supported by the Tokuyama Science Foundation and Grant-in-Aids (Nos. 16685011 and 17035062) from MEXT.

Notes and references

‡ The yield of **3a** was significantly affected by ligand. Use of PPh_3, $(t\text{-}Bu)_3P\cdot HBF_4$, DPPE, and DPPB gave **3a** in 0%, 0%, 0%, and 8% yield, respectively. When $Pd(OAc)_2$ was used in place of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, the reaction produced **3a** in 11% yield after 3 h.

§ General procedure for the cross-coupling of benzylic acetates with arylboronic acids: under a nitrogen atmosphere, a benzylic acetate **4** (1.0 mmol) was added to a suspension of an arylboronic acid **2** (1.1 mmol), potassium carbonate (304 mg, 2.2 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (3.6 mg, 10 μmol), and DPEphos (11.8 mg, 22 μmol) in *tert*-amyl alcohol (1.0 cm^3). The suspension was stirred at 80 °C until **4** was completely consumed (monitored by GC). After brine was added, the mixture was extracted several times with hexane. The combined organic layer was dried with $MgSO_4$, and was evaporated under reduced pressure. The residue was purified by a flash column chromatography (EtOAc–hexane) to give the desired product.

1 Recent reviews: A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176; S. Kotha, K. Lahiri and D. Kashinath, *Tetrahedron*, 2002, **58**, 9633; J. Tsuji, in *Palladium Reagents and Catalysts*, John Wiley & Sons, West Sussex, 2004, p. 105; A. C. Frisch and M. Beller, *Angew. Chem., Int. Ed.*, 2005, **44**, 674; K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442.

2 Recent examples: W. Su, S. Urgaonkar, P. A. McLaughlin and J. G. Verkade, *J. Am. Chem. Soc.*, 2004, **126**, 16433; K. W. Anderson and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2005, **44**, 6137.

3 Example: D. Milstein and J. K. Stille, *J. Am. Chem. Soc.*, 1979, **101**, 4992; E.-i. Negishi, H. Matsushita and N. Okukado, *Tetrahedron Lett.*, 1981, **22**, 2715; R.-J. de Lang, M. J. C. M. van Hooijdonk, L. Brandsma, H. Kramer and W. Seinen, *Tetrahedron*, 1998, **54**, 2953; S. Chowdhury and P. E. Georghiou, *Tetrahedron Lett.*, 1999, **40**, 7599; L. Chahen, H. Doucet and M. Santelli, *Synlett*, 2003, 1668; S. Langle, M. Abarbri and A. Duchêne, *Tetrahedron Lett.*, 2003, **44**, 9255.

4 C. Vanier, F. Lorgé, A. Wagner and C. Mioskowski, *Angew. Chem., Int. Ed.*, 2000, **39**, 1679.

5 E.-i. Negishi, A. O. King and N. Okukado, *J. Org. Chem.*, 1977, **42**, 1821; M. Piber, A. E. Jensen, M. Rottlander and P. Knochel, *Org. Lett.*, 1999, **1**, 1323; G. A. Molander and T. Ito, *Org. Lett.*, 2001, **3**, 393; K. Itami, M. Mineno, T. Kamei and J. Yoshida, *Org. Lett.*, 2002, **4**, 3635.

6 J. S. Wai, M. S. Egbertson, L. S. Payne, T. E. Fisher, M. W. Embrey, L. O. Tran, J. Y. Melamed, H. M. Langford, J. P. Guare, L. Zhuang, V. E. Grey, J. P. Vacca, M. K. Holloway, A. M. Naylor-Olsen, D. J. Hazuda, P. J. Felock, A. L. Wolfe, K. A. Stillmock, W. A. Schleif, L. J. Gabryelski and S. D. Young, *J. Med. Chem.*, 2000, **43**, 4923; Y.-Q. Long, X.-H. Jiang, R. Dayam, T. Sanchez, R. Shoemaker, S. Sei and N. Neamati, *J. Med. Chem.*, 2004, **47**, 2561.

7 D. Philp and J. F. Stoddart, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1154; M. M. Conn and J. Rebek, Jr., *Chem. Rev.*, 1997, **97**, 1647; A. Jasat and J. C. Sherman, *Chem. Rev.*, 1999, **99**, 931.

8 R. Kuwano and M. Yokogi, *Org. Lett.*, 2005, **7**, 945.

9 N. Miyaura, K. Yamada, H. Suginome and A. Suzuki, *J. Am. Chem. Soc.*, 1985, **107**, 972; R. Kakino, I. Shimizu and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, 2001, **72**, 371.

10 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.

11 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.

12 Examples of catalytic reaction involving the cleavage of C–O bond in (naphthyl)methyl acetates: J. M. Baird, J. R. Kern, G. R. Lee, D. J. Morgans and M. L. Sparacino, *J. Org. Chem.*, 1991, **56**, 1928; J.-Y. Legros and J.-C. Fiaud, *Tetrahedron Lett.*, 1992, **33**, 2509; J.-Y. Legros, M. Toffano and J.-C. Fiaud, *Tetrahedron*, 1995, **51**, 3235; M. Assié, J.-Y. Legros and J.-C. Fiaud, *Tetrahedron: Asymmetry*, 2005, **16**, 1183.

13 Examples of catalytic reaction involving the cleavage of C–O bond in benzyl trifluoroacetate: K. Nagayama, I. Shimizu and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, 1999, **72**, 799; H. Narahashi, A. Yamamoto and I. Shimizu, *Chem. Lett.*, 2004, **33**, 348.