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Simple Palladium(II) Precatalyst for Suzuki–Miyaura Couplings: Efficient Reactions of Benzylic, Aryl, Heteroaryl, and Vinyl Coupling Partners

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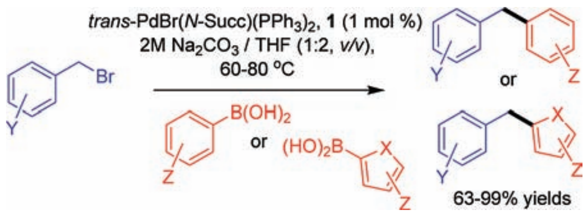
ABSTRACT



***trans*-PdBr(*N*-Succ)(PPh$_3$)$_2$ (1) is a universally effective precatalyst for Suzuki–Miyaura cross-couplings of benzylic halides with aryl- or heteroarylboronic acids. Substituted aryl halides and halogenated cyclic enones can be cross-coupled with aryl- or vinylboronic acids in excellent yields. Catalyst recycling is also demonstrated.**

Pd^0-catalyzed C−C bond-forming processes have attracted considerable attention in many applied research fields, including target-directed synthesis.[1,2] Significant effort has been placed on the development of new catalyst systems for a diverse array of coupling partners, particularly aryl components. The majority of new catalysts possess an electron-rich donor ligand, e.g., X-Phos,[3] or an *N*-heterocyclic carbene ligand,[4] including the excellent PEPPSI catalysts,[5] or utilize palladacycles.[6] While such catalysts are extremely versatile for many substrates, especially aryl/heteroaryl chlorides and alkyl halides, the coupling of benzylic halides with organoboronic acids has been little studied[7] and has unexplored potential.[8] Their generic use in Suzuki−Miyaura cross-couplings, to give diarylmethanes, is relatively rare, particularly compared to aryl halides. In the 1990s, it was reported that successful benzylic halide couplings were reliant on the use of excess organoboronic acid (1.5−2 equiv).[9] Molander and co-workers[10] recently developed a valuable synthetic protocol using potassium organotrifluoroborates as the nucleophilic boron coupling partner. The precatalyst, PdCl$_2$(dppf)·CH$_2$Cl$_2$ (2 mol %), exhibited the highest catalytic performance (S-Phos and X-Phos, more activated

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[1] *Metal-catalyzed Cross-coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004.

[2] *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1.

[3] Nguyen, H.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818 and references cited therein.

[4] Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431.

[5] O'Brien, C. J.; Kantchev, E. A. B.; Hadei, N.; Valente, C.; Chass, G. A.; Nasielski, J. C.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem.−Eur. J.* **2006**, *12*, 4743, and references cited therein.

[6] Bedford, R. B. *Chem. Commun.* **2003**, 1787.

[7] For use of palladacycles, with *n*-Bu$_4$NBr as a stoichiometric additive, in reactions of benzylic halides and arylboronic acids, see: (a) Botella, L.; Nájera, C. *J. Organomet. Chem.* **2002**, *663*, 46. (b) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *J. Org. Chem.* **2002**, *67*, 5588.

[8] Two other approaches to diarylmethanes have been reported. See: (a) Vanier, C.; Lorgé, F.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1679. (b) Nakao, Y.; Ebata, S.; Chen, J.; Imanaka, H.; Hiyama, T. *Chem. Lett.* **2007**, *36*, 606. For cross-coupling of an in situ generated organoborane with a substituted benzyl chloride, see: Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6501.

[9] (a) Nobre, S. M.; Monteiro, A. L. *Tetrahedron Lett.* **2004**, *45*, 8225. (b) Chahen, L.; Doucet, H.; Santelli, M. *Synlett* **2003**, *11*, 1668. (c) Chodhury, S.; Georghiou, P. *Tetrahedron Lett.* **1999**, *40*, 7599.

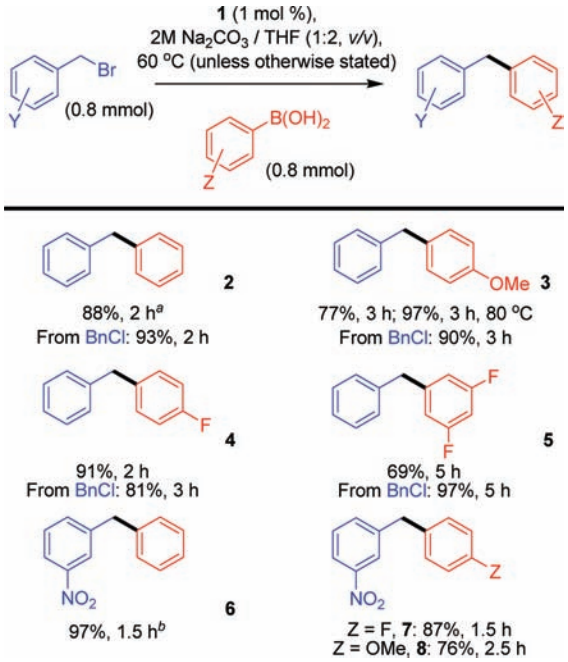
[10] Molander, G. A.; Elia, M. D. *J. Org. Chem.* **2006**, *71*, 9198.

10.1021/ol702291r CCC: $37.00

ligands, were *not as good* for this specific transformation); a THF/H_2O solvent mixture and Cs_2CO_3 (3 equiv) base were preferred. Kuwano and Yokogi reported that benzylic acetates can be used in Suzuki−Miyaura cross-couplings using a catalyst system composed of DPEphos−$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$.[11] Given the considerable interest in diarylmethanes in medicinal chemistry[12] and in view of the efficiency of the Pd^{II} complex PdBr(*N*-Succ)$(PPh_3)_2$ (**1**) (Sigma-Aldrich; Cat. No. 643742) in Stille cross-couplings of allylic and benzylic halides with organostannanes, we envisaged that efficient Suzuki−Miyaura cross-couplings of benzylic substrates[13] could be achieved using this simple Pd source.[14] PPh_3 is a strong enough activating ligand for benzylic substrates. The imidate anion[15] is also likely to play an important role in the global catalyst efficacy. Our findings using precatalyst **1**[16] in Suzuki−Miyaura cross-couplings of benzylic halides with organoboronic acids are thus reported herein. Other tricky cross-couplings are presented, in addition to a valuable recycling protocol.

The initial benchmark was the reaction of substituted benzylic halides with an equivalent amount of substituted arylboronic acids using 1 mol % of **1**, in a mixture of 2 M Na_2CO_3 and THF (1:2, v/v) at 60 °C (Scheme 1). Under these simple conditions, a library of cross-coupled products could be formed efficiently. For example, benzyl bromide effectively reacted with phenylboronic acid to give diphenylmethane **2** in 88% yield after 2 h. The catalyst loading may be lowered to 0.01 mol %, which after 20 h gave an 81% yield (turnover number of 8100). The incorporation of substituents onto the aryl group of the boronic acid ($Z =$ 4-OMe, 4-F, and 3,5-F) was also possible, giving high yields of the corresponding cross-coupled products (**3**−**5**, respectively). Where the yield dropped slightly for **3**, it could be improved by heating to 80 °C. Benzyl chlorides can also be used (at 80 °C). 3-Nitrobenzyl bromide reacts with various organoboronic acids to give cross-coupled products in very good yields ($Z =$ H, 4-F, and 4-OMe, **6**−**8**). In a reaction with $PhB(OH)_2$, the catalyst loading was once again lowered to 0.01 mol % (>99% conversion in 20 h; TON = ∼10 000), exemplifying the stability and longevity of the catalyst system.[17]

Scheme 1. Cross-Coupling of Benzyl Halides and Arylboronic Acids (Isolated Yields Given)[c]



[a] Using 0.01 mol % of **1**, 81% (20 h). [b] Using 0.01 mol % of **1**, >99% (20 h). [c] All BnCl couplings were run at 80 °C.

Heteroarylboronic acids are also coupled effectively with benzylic halides (Scheme 2). For example, thiophene-2-boronic acid couples with BnBr to give **9** in 91% yield. Other thiopheneboronic acids ($Z =$ 5-Cl, 5-acetyl) participate well in these reactions affording **10** and **11** in ∼80% yields for both BnBr and BnCl. For 5-formylthiophene-2-boronic acid, a small amount of protodeborylation was observed (∼10%). Thiophene-3-boronic acid reacts equally well with BnBr and BnCl to give **13** in 93% and 91% yields, respectively. Coupling of furan-2-boronic acid[18] with BnBr and 3-methoxybenzyl bromide was possible, giving the coupled products **14** and **15** in excellent yields (94% and >99%, respectively). Organotrifluoroborates[19] can be used as replacements for the organoboronic acid coupling components. However, under our reaction conditions, there is no real advantage over related organoboronic acids in terms of yields and reaction times.

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(11) Kuwano, R.; Yokogi, M. *Chem. Commun.* **2005**, 5899.

(12) (a) McPhail, K. L.; Rivett, D. E. A.; Lack, D. E.; Davies-Coleman, M. T. *Tetrahedron* **2000**, *56*, 9391. (b) Long, Y.-Q.; Jiang, X.-H.; Dayam, R.; Sachez, T.; Shoemaker, R.; Sei, S.; Neamati, N. *J. Med. Chem.* **2004**, *47*, 2561.

(13) Benzylic carbonates have been employed in Suzuki−Miyaura cross-couplings. See: Kuwano, R.; Yokogi, M. *Org. Lett.* **2005**, *7*, 945.

(14) (a) Crawforth, C. M.; Burling, S.; Fairlamb, I. J. S.; Taylor, R. J. K.; Whitwood, A. C. *Chem. Commun.* **2003**, 2194. (b) Crawforth, C. M.; Fairlamb, I. J. S.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 461. (c) Burling, S.; Crawforth, C. M.; Fairlamb, I. J. S.; Kapdi, A. R.; Taylor, R. J. K.; Whitwood, A. C. *Tetrahedron* **2005**, *61*, 9736. Note that *cis*-**1** was used in these studies. The commerical source of PdBr(*N*-Succ)$(PPh_3)_2$ has a *trans*-geometry. This material was used in all of the examples presented in this paper.

(15) (a) Fairlamb, I. J. S.; Kapdi, A. R.; Lynam, J. M.; Taylor, R. J. K.; Whitwood, A. C. *Tetrahedron* **2004**, *60*, 5711. (b) Chaignon, N. M.; Fairlamb, I. J. S.; Kapdi, A. R.; Taylor, R. J. K.; Whitwood, A. C. *J. Mol. Catal. A: Chem.* **2004**, *219*, 191. (c) Serrano, J. L.; Fairlamb, I. J. S.; Sánchez, G.; García, L.; Pérez, J.; Vives, J.; López, G.; Crawforth, C. M.; Taylor, R. J. K. *Eur. J. Inorg. Chem.* **2004**, 2706. (d) Crawforth, C. M.; Fairlamb, I. J. S.; Kapdi, A. R.; Serrano, J. L.; Taylor, R. J. K.; Sanchez, G. *Adv. Synth. Catal.* **2006**, *348*, 405. (e) Young, G. L.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 3797. (f) Fairlamb, I. J. S.; Taylor, R. J. K.; Serrano, J. L.; Sanchez, G. *New J. Chem.* **2006**, *30*, 1685.

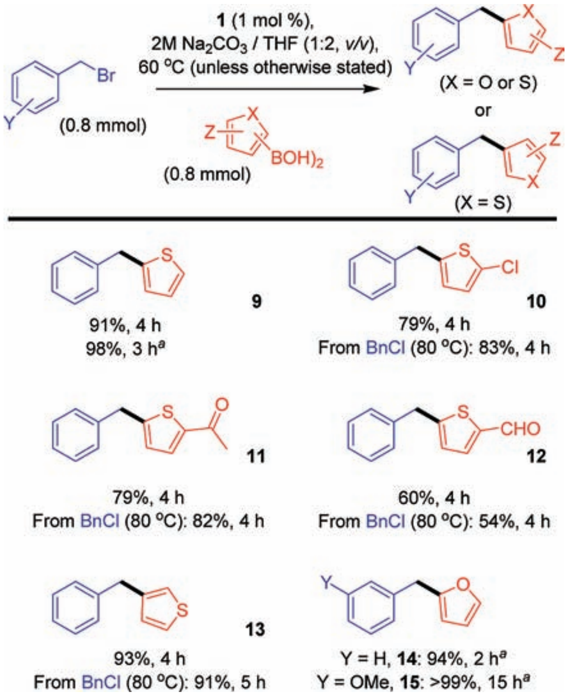
(16) In ref 15a, we reported that Pd(*N*-Succ)$_2(PPh_3)_2$ is an effective precatalyst for Suzuki−Miyaura cross-couplings of aryl halides with arylboronic acids. The coupling of 4-nitrobromobenzene with phenylboronic acid was tested with *cis*-**1** as the precatalyst in this paper. For this specific example, *cis*-**1** was less effective than Pd(*N*-Succ)$_2(PPh_3)_2$. Since this report, it has emerged that couplings of this aryl halide, and related compounds, can be complicated by electron-transfer processes, making it a poor benchmark substrate for screening catalysts/precatalysts.

(17) For selected examples given in Schemes 1 and 2, Pd(*N*-Succ)$_2(PPh_3)_2$ has been tested (see Supporting Information). Precatalyst **1** compares well with Pd(*N*-Succ)$_2(PPh_3)_2$; it is clear that both are useful precatalysts for coupling benzylic halide components in this reaction.

(18) Commercial sources of furan-2-boronic acid and thiophene-2-boronic acid were found to degrade at 25 °C in the presence of moisture.

(19) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49.

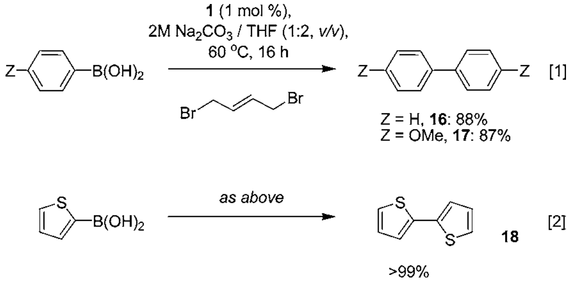
Scheme 2. Heteroaryl Couplings (Isolated Yields Given)



[a] 1.5 equiv of the organoboronic acid required.

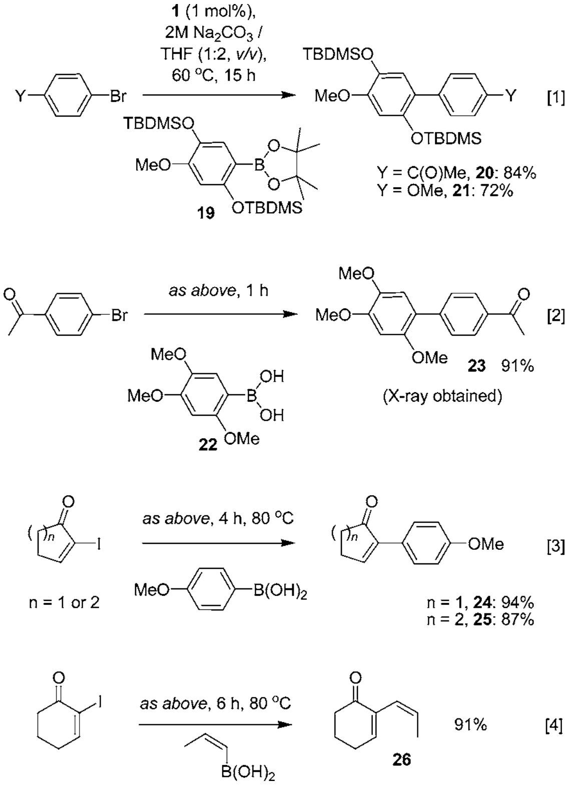
In contrast to benzylic halides, allylic halides do not react so readily with organoboronic acids under the standard reaction conditions.[20] Only where an activated arylboronic acid is used was any coupled product detected (see Supporting Information). Interestingly, *E*-1,4-dibromo-but-2-ene can be used as an oxidant in homocoupling reactions of the organoboronic acids affording biaryls in high yield (Scheme 3). For example, $PhB(OH)_2$ and 4-methoxyphenylboronic acid gave homocoupled products **16** and **17** in 88% and 87% yields, respectively. Thiophene-2-boronic acid homocouples more effectively, affording **18** in quantitative yield. The product selectivity and yields compare favorably against equivalent reactions using air as the oxidant.[21]

Scheme 3. Facile Homocoupling Using *E*-1,4-Dibromo-but-2-ene as the Oxidant (Isolated Yields Given)



In view of the versatility of **1** with benzylic substrates, its reactivity toward awkward aryl coupling partners was also explored.[22] More demanding arylboron reagents (**19** and **22**), susceptible to protodeborylation, effectively cross-couple with aryl bromides (Scheme 4, reactions 1 and 2). For example, in eq 1, the sterically cumbersome arylboronic acid **19** couples well with two aryl bromides (Y = C(O)Me, **20** in 84% yield; Z = OMe, **21** in 72% yield). The less-hindered, but as electron-releasing, 2,4,5-trimethoxyphenylboronic acid **22** is also a useful nucleophilic coupling partner (eq 2), revealing the highly oxygenated biaryl product **23** (X-ray structure determined). Furthermore, both 2-iodocyclopent-2-enone and 2-iodocyclohex-2-enone react with 4-methoxyphenylboronic acid to give **24** and **25** in 94% and 87% yields, respectively (eq 3). Finally, *Z*-prop-1-enylboronic acid reacts well with 2-iodocyclohex-2-enone to give **26** in 91% yield, providing a useful synthon for further manipulation.

Scheme 4. Other Cross-Coupling Reactions (Isolated Yields Given)



Catalyst recycling has been evaluated using a procedure modified from that originally reported by Monteiro and coworkers for $Pd(OAc)_2/PPh_3$[23] and used by our group with palladacycles,[24] using a poly(ethylene oxide) (PEO) solid

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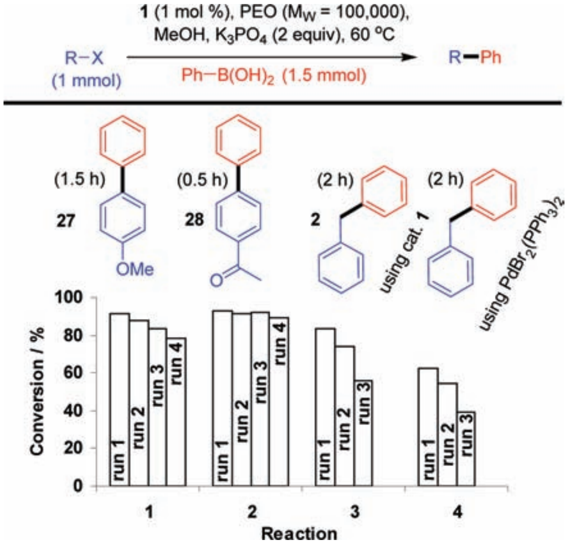
[20] For Suzuki−Miyaura cross-couplings using allylic halides, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1998**, *576*, 147, and references cited therein.

[21] For use of O_2 (air) as an oxidant in homocoupling of organoboronic acids, see: (a) Smith, C. A.; Campi, E. M.; Jackson, R.; Marcuccio, S.; Naeslund, C. G. M.; Deacon, G. B. *Synlett* **1997**, 131. (b) Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087. (c) Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829.

[22] Many monosubstituted aryl bromides and arylboronic acids effectively cross couple in good yields using the generic reaction conditions.

support[25] in methanol. At the end of the reaction, the product is extracted into a nonpolar phase, with the Pd catalyst remaining in the polar phase. The polar phase is then recharged with new reactants, allowing the Pd source to be reused (Scheme 5).

Scheme 5. Catalyst Recycling (Conversions by GC)



For example, coupling of 4-methoxyphenyl bromide with PhB(OH)$_2$ leads to good yields of **27**, in short reaction times, over several runs (reaction 1). No appreciable loss of catalytic activity is seen over four runs for an activated aryl substrate (to give **28**, reaction 2). For BnBr and PhB(OH)$_2$ cross-coupling, to give **2**, recycling is possible, but the conversions slowly deteriorate over three runs (reaction 3). However, the yields are consistently higher using **1** than for PdBr$_2$(PPh$_3$)$_2$ (reaction 4). The recycling study demonstrates that catalyst stability and longevity are assisted by the succinimidate anion in **1**.

In summary, **1** is shown to be a universal precatalyst for the Suzuki−Miyaura cross-coupling of benzylic bromides with aryl and heteroarylboronic acids. For the examples tested, catalyst loading can be significantly reduced (from 1 mol % to 0.01 mol %), allowing high TONs to be attained. The synthetic protocol reported in this paper complements the report by Molander and co-workers.[10] For the examples listed here, lower palladium loadings may be employed using the inexpensive base, Na$_2$CO$_3$. Moreover, the ratio of benzyl halide to organoboronic acid is 1:1 (in the majority of cases), improving substantially on previous protocols using excess organoboronic acid.[9] Also, **1** is an effective but *simple* precatalyst for aryl cross-couplings and offers good catalyst recyclability on a PEO solid support. Mechanistic studies on cross-coupling processes mediated by **1**, and related precatalysts, will be reported in due course.

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Supporting Information Available: Full experimental procedures, characterization (including spectroscopic data), and literature references to novel and known compounds, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Nobre, S. M.; Wolke, S. I.; da Rosa, R. G.; Monteiro, A. L. *Tetrahedron Lett.* **2004**, *45*, 6527. PEO with a molecular weight of 100 000 was employed in this study.

(24) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F.; Sánchez, G.; López, G.; Serrano, J. L.; García, L.; Pérez, J.; Pérez, E. *Dalton Trans.* **2004**, 3970.

(25) PEO acts as an organic stabilizer for in situ formed palladium colloids/nanoparticles (formed by degradation of the palladium(II) precatalyst), produced by aggregation of palladium(0).