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Two-Step, One-Pot Ni-Catalyzed Neopentylglycolborylation and Complementary Pd/Ni-Catalyzed Cross-Coupling with Aryl Halides, Mesylates, and Tosylates

Daniela A. Wilson, Christopher J. Wilson, Brad M. Rosen, and Virgil Percec*

Roy & Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

percec@sas.upenn.edu

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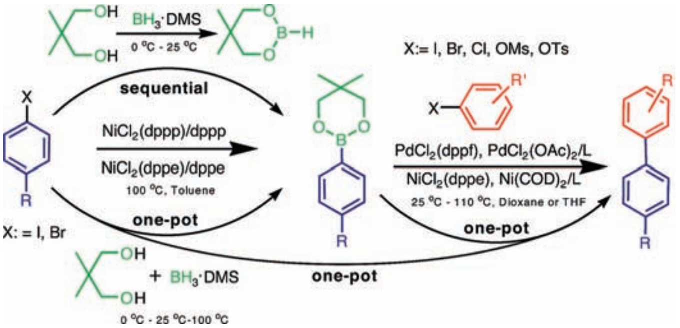
ABSTRACT



Two-step, one-pot neopentylglycolborylation of aryl iodides and bromides catalyzed by NiCl$_2$(dppe) and NiCl$_2$(dppp) is reported. Electron-rich and electron-deficient aryl neopentylglycolboronates were efficiently cross-coupled with aryl iodides, bromides, chlorides, mesylates, and tosylates by exploiting complementary Pd/Ni and Ni/Ni catalysis. The borylation route was further extended to a three-step, one-pot synthesis of biaryls via in situ Ni-catalyzed borylation and Pd-mediated cross-coupling.

Our laboratory is involved in the synthesis of supramolecular complex architectures, for which robust, functional group tolerant, and cost-effective synthetic methods are required.[1] As part of the ongoing effort to develop cost-effective cross-coupling methods, Ni-catalysis provides a powerful tool in the implementation of alternative routes to Pd.[2] In a previous publication, an efficient and inexpensive route to aryl boronate precursors via NiCl$_2$(dppp)-catalyzed borylation of aryl bromides and iodides with freshly prepared pinacolborane and neopentylglycolborane was reported.[3a] This method required fresh synthesis[3b] of the neopentylglycolborane,[3a] which was subsequently cannulated into the main reaction flask without purification. Ni-catalyzed borylation was followed by NiCl$_2$(dppe)-catalyzed cross-coupling with aryl bromides and iodides using K$_3$PO$_4$ as base for electron-deficient aryl boronate esters, and NaOH for electron-rich

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(1) (a) Percec, V.; Chu, P. W.; Ungar, G.; Zhou, H. *J. Am. Chem. Soc.* **1995**, *117*, 11441. (b) Percec, V.; Holerca, M. N.; Nummelin, S.; Morrison, J. J.; Glodde, M.; Smidrkal, J.; Peterca, M.; Rosen, B. M.; Uchida, S.; Balagarusamy, V. S. K.; Sienkowska, M. J.; Heiney, P. A. *Chem.—Eur. J.* **2006**, *12*, 5731. (c) Percec, V.; Won, B. C.; Peterca, M.; Heiney, P. A. *J. Am. Chem. Soc.* **2007**, *129*, 11265.

(2) (a) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060. (b) Percec, V; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447. (c) Percec, V.; Bae, J.-Y.; Hill, D. H.; Zhao, M. *J. Org. Chem.* **1995**, *60*, 1066. (d) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 6895. (e) Percec, V.; Bae, J.-Y.; Zhao, M.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 176. (f) Percec, V.; Zhao, M.; Bae, J.-Y.; Hill, D. H. *Macromolecules* **1996**, *29*, 3727. (g) For a review, see: Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

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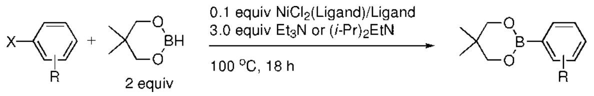
aryl boronates. However, NaOH leads to incompatibility for cross-coupling with aryl halides that contain base-sensitive functional groups.

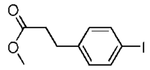
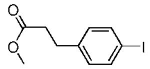
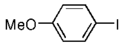
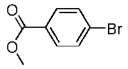
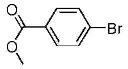
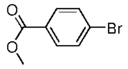
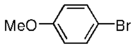
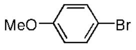
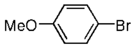
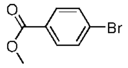
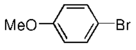
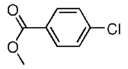
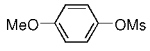
Herein we report what we believe to be the first example of a three-step, one-pot methodology comprising two-step, one-pot in situ preparation of neopentylglycolborane, followed by complementary Ni/Pd or Ni/Ni borylation and subsequent cross-coupling with aryl bromides, iodides, chlorides, mesylates, and tosylates.

One-pot borylation and cross-coupling reactions require quantitative conversion of aryl halide to boronate as residual aryl halide from the first step is a potential competitive coupling partner. To identify the most suitable catalysts for complete conversion, several $NiCl_2$ complexes with dppp, dppe, PPh_3, dppf, Et_3N, and bpy were screened. The catalytic activity toward aryl iodides, bromides, and chlorides was investigated by systematic variation of the catalyst loading, reaction temperature, solvent, and base. It was found that a decrease of the catalyst loading level from 10%[3] to 5% and 2% for neopentylglycolborylation of aryl iodides did not affect the conversion. Instead, a marked increase in the recovered yield was observed (Table 1, entries 1 and 2). Although aryl iodides are less atom efficient and synthetically accessible, they display enhanced reaction rates, achieving complete conversion in only 2 h. The less reactive aryl bromides required higher catalyst loading (5−10%) for complete consumption of the substrate. Screening the activity of different Ni-catalysts showed that $NiCl_2$(dppp) and $NiCl_2$(dppe) were the optimum catalysts in the borylation reactions with yields in the range of 78−98%. Table 1 and Table ST1 (Supporting Information) summarize the most significant data obtained. Poor yields were obtained in the case of $NiCl_2(PPh_3)_2$, $NiCl_2$(dppf), $NiCl_2(Et_3N)_2$, $NiCl_2(bpy)_2$, and $NiCl_2$. Aryl iodides were found to be less sensitive to the Ni-catalyst/coligand employed, showing complete conversion with $NiCl_2$(dppe)/dppe. Aryl bromides resulted in mild but often noticeable decreases in conversion, when dppe replaced dppp as catalyst and anisole was used as solvent (Table 1, entries 8 vs 9, and Table 2 entry 3). Since dppe is a less expensive ligand, its interchangeability with dppp in the case of iodides is notable. In some cases, when toluene is used as solvent (Table 1, entries 6 and 10) dppe can be used with aryl bromides without diminished conversion. $Ni(COD)_2$ with PCy_3 coligand is known to be active toward the catalytic cross-coupling of aryl mesylates and tosylates.[4] Application of this catalytic system to neopentylglycolborylation of an electron-rich aryl mesylate resulted in low yield (Table 1, entry 13).

Pinacolborylations using $PdCl_2$(dppf) and purified HBPin are known.[5] However, the use of $PdCl_2$(dppf)[5a] in borylation with in situ prepared neopentylglycolborane was ineffective, most probably due to Pd catalyst poisoning in the presence of excess DMS from the BH_3•DMS complex.

Table 1. Two-Step Sequential Neopentylglycolborylation



entry	substrate	catalyst[a] (%)	solvent	convn[d]:yield[e] (%)
1		$NiCl_2$(dppp) (5)	toluene	100:86
2		$NiCl_2$(dppp) (2)	toluene	100:95
3		$NiCl_2$(dppe) (10)	toluene	100:98
4		$NiCl_2$(dppp) (10)	toluene	100:81
5		$NiCl_2$(dppp) (10)	anisole	94:89
6		$NiCl_2$(dppe) (10)	toluene	100:90
7		$NiCl_2$(dppp) (10)	toluene	91:90
8		$NiCl_2$(dppp) (10)	anisole	100:94
9		$NiCl_2$(dppe) (10)	anisole	78:78
10[c]		$NiCl_2$(dppe) (10)	toluene	100:87
11[c]		$NiCl_2$(dppe) (10)	toluene	93:83
12		$NiCl_2$(dppp) (5)	toluene	20:10
13		$Ni(COD)_2$[b] (6)	toluene	16:8

[a] Coligand added in 1:1 ratio to catalyst. [b] Coligand $P(Cy)_3$ 18%. [c] (i-Pr)$_2$NEt as base. [d] Conversion determined by GC. [e] Isolated yield.

One of the primary advantages rendered by transition metal-catalyzed borylations is tolerance to sensitive functional groups.[6] Triethylamine is incompatible with many reagents bearing alkyl halides due to its nucleophilicity. *N*,*N*-Diisopropylethylamine (Hünig's base) is sterically hindered and exhibits reduced nucleophilicity. Pd-catalyzed pinacolborylation[5a,7] in the presence of Hünig's base was less effective than triethylamine. In Ni-catalyzed neopentylglycolborylation this was not the case (Table 1, entries 10 and 11). It has been proposed for Pd-catalyzed borylations that dialkoxyboranes work as a single entity with amine base.[7] This hypothesis may not hold in the case of Ni-catalyzed borylation as little decrease in conversion was observed despite the strong steric shielding of the diisopropyl groups in Hünig's base.

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(3) (a) Rosen, B.; Huang, C.; Percec, V. *Org. Lett.* **2008**, *10*, 2597. (b) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482.

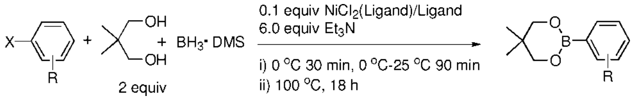
(4) Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058.

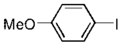
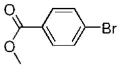
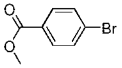
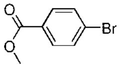
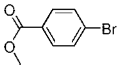
(5) (a) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458. (b) Billingsley, K. L.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5589.

(6) *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2005.

(7) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164.

Table 2. Two-Step One-Pot Neopentylglycolborylation



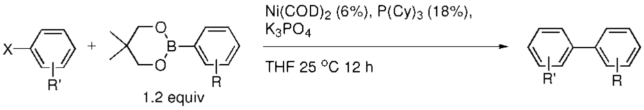
entry	substrate	catalyst[a] (%)	solvent	convn[b]:yield[c] (%)
1		$NiCl_2$(dppp) (10)	toluene	100:95
2		$NiCl_2$(dppp) (10)	dioxane	95:63
3		$NiCl_2$(dppp) (10)	anisole	100:94
4		$NiCl_2$(dppp) (10)	toluene	100:98
5		$NiCl_2$(dppe) (10)	toluene	90:75

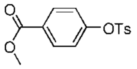
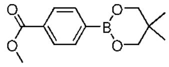
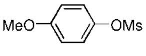
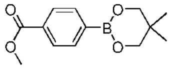
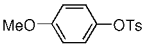
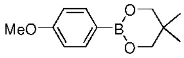
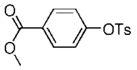
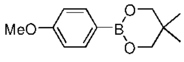
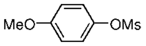
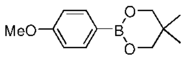
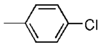
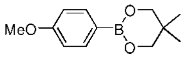
[a] Coligand added in 1:1 ratio to catalyst. [b] Conversion determined by GC. [c] Isolated yield.

Toluene and anisole were found to be effective solvents for Ni-catalyzed borylation. The more polar dioxane, although suitable for Ni-catalyzed Suzuki cross-coupling,[2b] and for Pd-catalyzed pinacolborylation[5] gave lower yields in neopentylglycolborylation (Table 1, entries 5, 8, and 9).

Table 2 demonstrates that aryl neopentylglycolborane can be synthesized in a two-step, one-pot reaction. BH_3·DMS complex was slowly added to a suspension of the Ni-catalyst, coligand substrate, and neopentylglycol maintained at 0 °C. After 1 h at rt, the base was added and the reaction temperature was increased to 100 °C. High yields for electron-rich and electron-deficient aryl iodides and bromides were obtained. $NiCl_2$(dppe)/dppe was also compatible with the two-step one-pot procedure, but with lower conversion and yield (Table 1, entry 5).

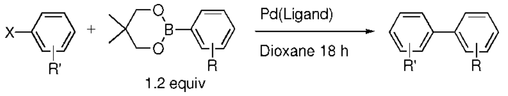
Table 3. Ni-Catalyzed Cross-Coupling of Chlorides, Mesylates, and Tosylates

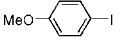
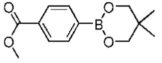
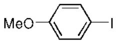
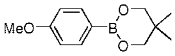
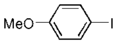
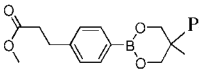
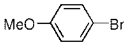
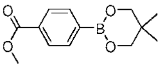
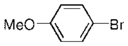
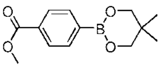
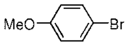
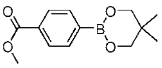
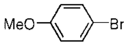
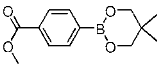
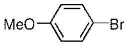
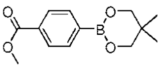
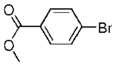
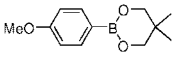
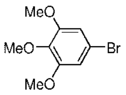
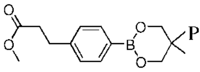
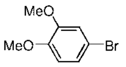
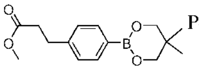
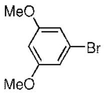
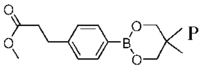
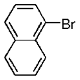
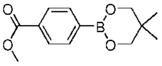
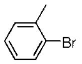
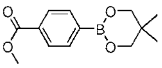
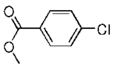
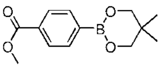
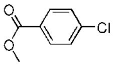
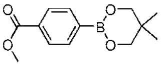


entry	substrate	boronate ester	convn[a]:yield[b]
1			100:93
2			100:98
3			100:95
4			100:91
5			100:94
6			79:76

[a] Conversion determined by GC. [b] Isolated yield.

Table 4. Pd-Catalyzed Cross-Coupling of Aryl Halides



entry	aryl halide	boronate ester	catalyst (%)	base	temp (°C)	convn[b] : yield[c] (%)
1			$PdCl_2$(dppf) (10%)	K_3PO_4	80	100:90
2			$PdCl_2$(dppf) (10%)	K_3PO_4	110	100:93
3			$PdCl_2$(dppf) (10%)	K_3PO_4	110	100:90
4			$PdCl_2$(dppf) (2%)	K_3PO_4	110	100:95
5			$Pd(OAc)_2$ (10%)	K_3PO_4	110	95:82
6			$PdCl_2$	K_3PO_4	110	100:81
7			$PdCl_2$(dppf) (10%)	CsF	25	85:84
8			$PdCl_2$(dppf) (10%)	K_3PO_4	110	100:94
9			$PdCl_2$(dppf) (10%)	K_3PO_4	110	100:95
10			$PdCl_2$(dppf) (10%)	K_3PO_4	110	100:93
11			$PdCl_2$(dppf) (10%)	K_3PO_4	110	100:92
12			$PdCl_2$(dppf) (10%)	K_3PO_4	110	100:94
13			$Pd(OAc)_2$[a] (10%)	CsF	25	100:97
14			$Pd(OAc)_2$[a] (10%)	CsF	25	100:99
15			$Pd(OAc)_2$[a] (10%)	CsF	25	100:99
16			$PdCl_2$(dppf) (10%)	K_3PO_4	110	23:17

[a] Coligand 2-(dicyclohexylphosphino)biphenyl (20%). [b] Conversion determined by GC. [c] Isolated yield.

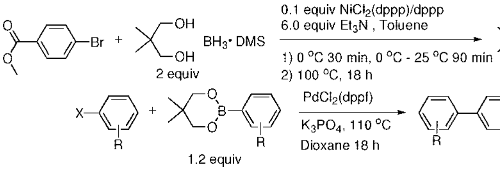
Aryl mesylates and tosylates are inexpensive coupling partners with arylboronic acids[2a,b] and provide a desirable method of carbon−carbon bond formation starting from phenols.[2]

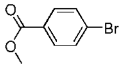
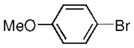
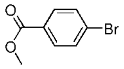
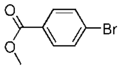
In the only other reported use of Ni-catalysis with aryl neopentylglycolboronate esters, $Ni(COD)_2/PPh_3$ or PCy_3 was able to mediate cross-coupling of 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane with vinyl phosphates using K_3PO_4 as base.[8] The success achieved with $Ni(COD)_2$ suggested that the difficulties with $NiCl_2(dppe)$ and $NiCl_2(PCy_3)_2$ arrose in the reduction of Ni(II) precatalysts to the active Ni(0) species. By switching to $Ni(COD)_2/PCy_3$, these problems were eliminated (Table 3). At rt complete conversion was achieved with both electron-deficient (entries 1 and 2) and electron-rich (entries 3−5) aryl neopentylglycolboronate with both electron-rich and electron-deficient aryl mesylates and tosylates. Good yields were also obtained with aryl chlorides.

Pd-catalyzed cross-coupling also provides a complementary pathway to biaryls from aryl neopentylglycolboronate esters. $PdCl_2(dppf)$-catalyzed cross-coupling was achieved with excellent conversion and yield with diverse aryl bromides/iodides including fused aromatics, ortho-substituted, electron-rich and electron-deficient aryl neopentylglycolboronate ester (Tables 4 and ST2, Supporting Information). Pd-catalyzed cross-coupling is tolerant to a wider array of catalysts and temperatures than Ni-catalyzed cross-coupling. Aryl chlorides (Table 4, entry 15) reached high conversion and yield through the use of a Buchwald ligand.[9] Pd-catalyzed cross-coupling does not provide cost advantages or increased scope in comparison to $Ni(COD)_2/PCy_3$. However, it does lead to a very simple synthetic method for three-step one-pot procedure that includes in situ synthesis of neopentylglycolborane and cross-coupling (Table 5).

In this three-step, one-pot procedure, the same conditions for the borylation as employed in the two-step one-pot borylation procedure were used. However, at the completion of the reaction, the product was not isolated. Rather, the solvent was removed in a rotary evaporator and the crude solid redissolved in dioxane followed by addition of Pd catalyst, ligand, aryl halide, and K_3PO_4. The cross-coupling proceeds with good overall yield (Table 5).

Table 5. One-Pot Borylation and Cross-Coupling of Neopentylglycolboronate Esters with Aryl Halides



entry	aryl halide 1	aryl halide 2	Yield (%)
1			i) 77[a] ii) 72[b]
2			i) 77[a] ii) 74[b]

[a] Yield determined by GC. [b] Overall isolated yield.

In conclusion, a versatile $NiCl_2(dppp)$- and $NiCl_2(dppe)$-catalyzed neopentylglycolborylation of aryl iodides and bromides that proceeds at low catalyst loading, in toluene, anisole, and dioxane in a two-step one-pot procedure was developed. The cross-coupling step was compatible with both electron-rich and electron-deficient aryl neopentylglycolboronates in the presence of K_3PO_4 base. High yield Ni-catalyzed cross-coupling at rt of neopentylglycolboronates with aryl mesylates, tosylates, and chlorides was obtained in the presence of $Ni(COD)_2/PCy_3$. Likewise, efficient Pd-catalyzed cross-coupling was elaborated for a broad array of aryl neopentylglycolboronates with aryl chlorides, bromides and iodides. This complementary approach gives rise to the rapid synthesis of biphenyls through a three-step one-pot method and demonstrates the synthetic competitiveness of in situ prepared neopentylglycolborane[3a] versus that of tetra(alkoxy)diboron derivatives.[10]

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Supporting Information Available: Experimental procedures and spectral data for isolated products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Noefe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

(10) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.