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Neopentylglycolborylation of Aryl Chlorides Catalyzed by the Mixed Ligand System $NiCl_2$(dppp)/dppf

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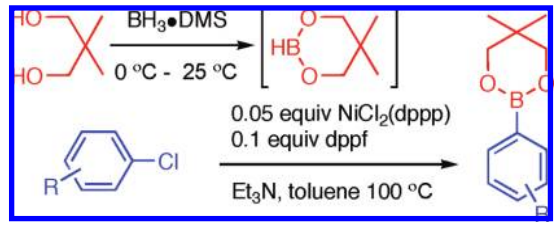
ABSTRACT



The mixed ligand system 10 mol % $NiCl_2$(dppp) with 5 mol % dppf was discovered to be an extremely efficient catalyst for the neopentylglycolborylation of a diversity of electron-rich and electron-deficient aryl chlorides. Optimization showed that 5 mol % catalyst with 10% dppf was even more efficient. These results highlight the complexity of the relationship between catalyst and coligand in Ni catalysis and the benefit of combinations of mixed ligand in catalyst design.

Interest in boronic acids as synthetic intermediates for cross-coupling, as medicinal agents, and as components of supramolecular assemblies and functional materials[1] served to amplify the necessity for more efficient and robust methods for the synthesis of arylboronic acids and esters. Arylboronic acids and esters are often synthesized from their corresponding aryl halides via hard-metalation approaches.[2] Pd-catalyzed Miyaura borylation[3] provides milder conditions that are tolerated by a greater diversity of functional groups on the substrate. Most frequently, Pd-catalyzed borylation of aryl bromides, iodides, and triflates employs tetraalkoxydiboron[3a,4] and pinacolborane[3b,5] as a boron source.

Our laboratory is involved in the development of Ni-catalyzed approaches to the synthesis of complex molecular architectures[6] and their precursors.[7] Inspired by an earlier publication wherein Ni-catalyzed pinacolborylation of two aryl bromides was reported,[8] we developed an efficient two-step, one-pot $NiCl_2$(dppp)/dppp-catalyzed neopentylglycol-

(1) (a) Niu, W.; O'Sullivan, C.; Rambo, B. M.; Smith, M. D.; Lavigne, J. *J. Chem. Commun.* **2005**, 4342. (b) Jamese, T. D.; Shinkai, S. *Top. Curr. Chem.* **2002**, *218*, 159.

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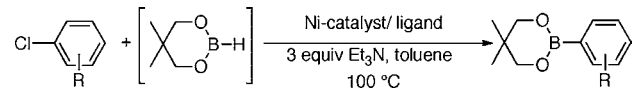
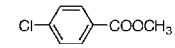
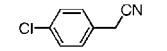
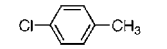
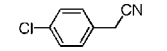
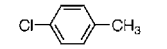
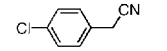
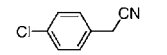
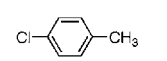
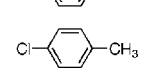
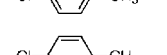
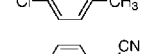
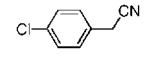
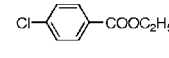
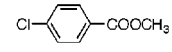
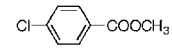
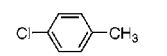
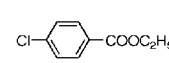
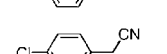
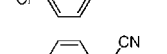
borylation of aryl bromides and iodides[9] and their sequential Ni-catalyzed[9a] or complementary Pd-catalyzed[9b] cross-coupling. Both approaches[9] relied on the development of a novel and cost-effective borylating reagent, neopentylglycolborane. As demonstrated for some applications of pinacolborane,[5] this reagent is prepared in situ and used without purification or isolation. Arylneopentylglycolboronate esters are typically easier to purify and hydrolyze than arylpinacolboronate esters. Additionally, they enhance the diversity of boronate esters that can be installed catalytically. Recent work has demonstrated that bis(2-di-*tert*-butylphosphinophenyl) ether[10] or Buchwald-type ligands[11,12] activate Pd for the pinacolborylation of aryl chlorides,[10,11] tosylates,[12] and mesylates.[12]

Atom-inefficient bis(pinacolato)diboron[10,11b] as a boron source was more general for aryl chlorides than more cost-effective pinacolborane.[11a] Ni(II) catalysts containing conventional ligands are more reactive toward aryl chlorides[7e] than the corresponding Pd(II) catalysts. Herein, a general method for the Ni-catalyzed neopentylglycolborylation of aryl chlorides is reported. Ni-catalyzed neopentylglycolborylation of aryl bromides and iodides is performed using 2−10% $NiCl_2$(dppp)/dppp as a catalytic system.[9] The use of dppp coligand suppresses deborylation. This catalytic system was not sufficiently reactive with aryl chlorides (Table 1, entries 7 and 8). $NiCl_2(PPh_3)/PPh_3$, $NiCl_2$(dppe)/dppe, $NiCl_2(PCy_3)/PCy_3$, $NiCl_2$(dppf)/(dppf), $Ni(COD)_2/PCy_3$, and $Ni(COD)_2/PPh_3$ exhibited similarly poor yields (Table 1. entries 1−6, 9, and 10). However, $NiCl_2$(dppf)/(dppf) exhibited improved reactivity (Table 1, entries 9 and 11). Previously, it was shown that $NiCl_2$(dppe) with PPh_3 coligand was the most general and solvent-independent catalytic system for the Ni-catalyzed cross-coupling of aryl iodides, bromides, chlorides, mesylates, and tosylates with arylboronic acids.[7e] Application of mixed ligand systems to Ni-catalyzed neopentylglycolborylation reiterated their enhanced performance (Table 1, entries 12−19).

$NiCl_2$(dppp)/PPh_3 and $NiCl_2(PPh_3)_2$/dppp showed significantly improved activity for the electron-deficient methyl 4-chlorobenzoate (Table 1, entries 12−14) but were not as effective for electron-rich substrates (Table 1, entries 15, 17, and 18). The use of $NiCl_2$(dppf) with dppp as coligand did not improve catalytic activity (Table 1, entry 19), suggesting that the reactivity enhancement provided by dppf is through its role as coligand. A variety of catalytic systems employing dppf as coligand were investigated (Table 2), including: $NiCl_2(PPh_3)_2$/dppf, $NiCl_2$(dppe)/dppf, $NiCl_2$(dppb)/dppf, and $NiCl_2$(dppp)/dppf. Of these catalytic systems, the combination of $NiCl_2$(dppp), the optimal catalyst for Ni-catalyzed borylation of aryl bromides and iodides,[9] with dppf as coligand provided the most efficient catalytic system for both electron-rich and electron-deficient aryl chlorides (Table 2, entries 5−8). Unlike the mixed $NiCl_2$(dppe)/PPh_3 that served as a universal catalyst for the Ni-catalyzed cross-coupling of arylboronic acids with aryl halides and pseudohalides,[7] $NiCl_2$(dppp)/dppf as catalyst for neopentylglycolborylation is very sensitive to solvent conditions. Toluene is the most effective solvent, while the use of anisole and dioxane resulted in significantly diminished yields (Table 2, entries 9 and 10).

Table 1. Neopentylglycolborylation of Aryl Chlorides: Screening for Optimum Combination of Catalyst and Ligand



entry	substrate	catalyst (%)	ligand (%)	time (h)	convn[a]/yield[b] (%)
1		$Ni(COD)_2$ (5)	PCy_3 (10)	20	11 / 2
2		$Ni(COD)_2$ (5)	PCy_3 (10)	20	<2 / 0.3
3		$Ni(COD)_2$ (5)	PCy_3 (10)	18	4 / 4
4		$Ni(COD)_2$ (5)	PPh_3 (5)	19	5 / 0.3[c]
5		$NiCl_2(PPh_3)_2$ (10)	PPh_3 (20)	21	0.2 / 0.2[d]
6		$NiCl_2$(dppe) (10)	dppe (10)	18	3 / 0.2
7		$NiCl_2$(dppp) (10)	dppp (10)	22	3 / 1
8		$NiCl_2$(dppp) (10)	dppp (10)	20	<3 / <3
9		$NiCl_2$(dppf) (5)	dppf (5)	23	12 / 11[c]
10		$NiCl_2(PCy_3)_2$ (5)	PCy_3 (10)	21	0.3 / 0.3[c]
11		$NiCl_2$(dppf) (10)	dppf (10)	21	60 / 38
12		$NiCl_2(PPh_3)_2$ (5)	dppp (10)	18	54 / 51[d]
13		$NiCl_2$(dppp) (5)	PPh_3 (10)	20	50 / 46
14		$NiCl_2$(dppp) (10)	PPh_3 (20)	19	79 / 75
15		$NiCl_2$(dppp) (10)	PPh_3 (20)	21	5 / 5
16		$NiCl_2$(dppe) (10)	PPh_3 (5)	18	4 / 3
17		$NiCl_2$(dppp) (10)	PPh_3 (20)	21	35 / 27
18		$NiCl_2$(dppp) (10)	dppe (10)	21	25 / 23
19		$NiCl_2$(dppf) (10)	dppp (10)	19	10 / 7

[a] Conversion calculated from GC. [b] Yield determined by GC. [c] Reaction performed at 90 °C. [d] Reaction performed at 80 °C.

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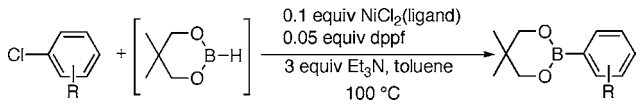
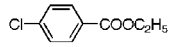
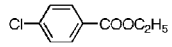
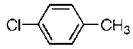
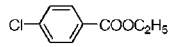
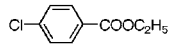
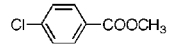
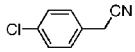
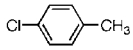
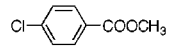
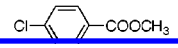
(10) Murata, M.; Sambommatsu, T.; Watanabe, S.; Masuda, Y. *Synlett* **2006**, 1867.

(11) (a) Billingsely, K. L.; Barder, T. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5359. (b) Billingsley, K. L.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5589.

(12) Bhayana, B.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 3954.

Table 2. Neopentylglycolboryaltion of Aryl Chlorides: Screening for Optimum Combination of Catalyst and Solvent with dppf



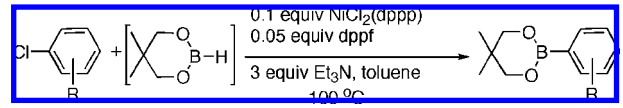
entry	substrate	catalyst	time (h)	convn[a]/yield[b] (%)
1		$NiCl_2(PPh_3)_2$	20	4 / 1[c]
2		$NiCl_2$(dppe)	18	70 / 35
3		$NiCl_2$(dppe)	23	47 / 47 (42)
4		$NiCl_2$(dppb)	18	25 / 9
5		$NiCl_2$(dppp)	20	97 / 89 (75)
6		$NiCl_2$(dppp)	19	100 / 95 (85)
7		$NiCl_2$(dppp)	6	98 / 96[d] (60)
8		$NiCl_2$(dppp)	21	88 / 88 (71)
9		$NiCl_2$(dppp)	21	58 / 55[e] (47)
10		$NiCl_2$(dppp)	20	27 / 23[f]

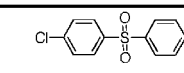
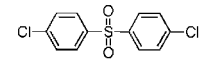
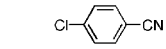
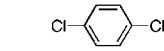
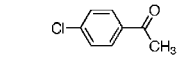
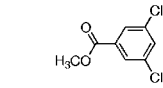
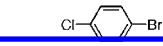
[a] Conversion calculated from GC. [b] Yield determined by GC. Isolated yields in parentheses. [c] Reaction performed at 80 °C. [d] 0.1 equiv of ligand. [e] Anisole used as solvent. [f] Dioxane used as solvent.

Application of the $NiCl_2$(dppp)/dppf mixed ligand catalytic system to monochlorinated, electron-deficient arenes was extremely effective and resulted in excellent yields (Table 2, entries 5 and 6; Table 3, entries 1, 3, and 5). Diverse functional groups such as cyano, sulfonyl, keto, and carboxylic ester groups were tolerated. $NiCl_2$(dppp)/dppf-catalyzed neopentylglycolborylation of dichlorinated, electron-deficient arenes was also possible, but the results were variable. 4,4′-Sulfonyl bis(chlorobenzene) and *p*-dichlorobenzene produced the diborylated product in excellent yield (Table 3, entries 2 and 4), while in another case, a 1:1 mixture of mono- and diborylated products (Table 3, entry 6) was observed. $NiCl_2$(dppp)/dppf-catalyzed neopentylglycolborylation of 1-bromo-4-chlorobenzene demonstrated completely selective borylation of the bromide (Table 3, entry 7), demonstrating that this catalytic system is likely a universal catalyst for the borylation of aryl halides.

$NiCl_2$(dppp)/dppf was also an extremely competent catalyst for the neopentylglycolborylation of monochlorinated, electron-rich arenes (Table 4, entries 1−4, 7, and 8) as well as heteroaryl or polyaryl chlorides (Table 4, entries 9 and 10). It is remarkable that 4-chlorophenol, which forms an electron-rich phenolate under the reaction conditions, is

Table 3. Neopentylglycolborylation of Aryl Chlorides Containing Additional Electron-Withdrawing Substituents



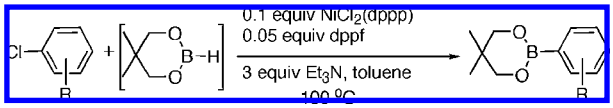
entry	substrate	time (h)	convn[a] / yield[b] (%)
1		19	100 / 95 (80)
2		20	95 / 82 (74)[c]
3		20	100 / 100 (77)
4		48	100 / 100 (68)[c]
5		6.5	100 / 100 (75)
6		18	100 / (45/41)[d]
7		20	100 / 99 (83)[e,f]

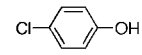
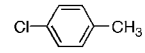
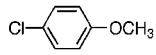
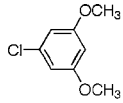
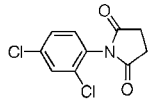
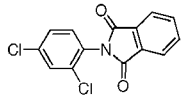
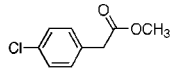
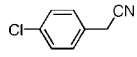
[a] Conversion calculated from GC. [b] Yield determined by GC. Isolated yield in parentheses. [c] Diborylated product. [d] 1:1 Mono/diborylated products. [e] Selective borylation of bromide. [f] Monoborylated product.

compatible with Ni-catalyzed neopentylglycolborylation (Table 4, entry 1). $NiCl_2$(dppp)/dppf-catalyzed neopentylglycolborylation of electron-rich, dichlorinated substrates provided monoborylation in the para-position, leaving the ortho-position untouched (Table 4, entries 5 and 6). This selectivity can be harnessed for sequential functionalization reactions.

As the $NiCl_2$(dppp)/dppf-catalyzed neopentylglycolborylation of aryl chlorides bearing sensitive electrophilic groups is of great general utility, optimization with the substrate methyl 4-chlorobenzoate was performed (Table 5). Using 10 mol % $NiCl_2$(dppp), reduction of the amount of dppf from 10 to 5 mol % resulted in a modest increase in conversion. Reduction in temperature from 100 to 90 °C resulted in only a slight decrease in yield (Table 5, entry 10), while at 80 or 60 °C a significant decrease in conversion and yield was observed (Table 5, entries 11 and 12). At 10 mol % catalyst, optimal yields were achieved for a 1:1 or 2:1 ratio of $NiCl_2$(dppp) to dppf coligand. Suprisingly, reducing the catalyst level to 5 mol % required a 1:2 ratio for complete conversion and optimal yield in about 3 times shorter reaction time (Table 5, entry 3). A decrease in dppf concentration increased the reaction time (Table 5, entries 4−6). Further reduction of catalyst loading level to 3 mol % required a 1:2.67 ratio of $NiCl_2$(dppp) to dppf for optimal results (Table 5, entries 6−8). Below 3 mol % catalyst loading, only poor yields could be achieved (Table 5, entry 9). The increasing demand of coligand when lower catalyst loading levels are

Table 4. Neopentylglycolborylation of Aryl Chlorides with Electron-Donating Substituents



entry	substrate	time (h)	convn[a]/yield[b] (%)
1		20	70 / 68 (40)
2		21	88 / 88 (71)
3		20	64 / 64 (56)
4		20	60 / 60 (34)
5		18	95 / (39)[c]
6		18	99 / (47)[c]
7		20	70 / 64 (50)
8		6	98 / 96 (60)
9		20	100 / 100 (66)
10		20	100 / 84 (56)

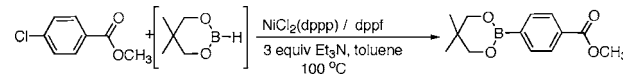
[a] Conversion calculated from GC. [b] Yield determined by GC. Isolated yields in parentheses. [c] Monoborylated in *para* position.

employed highlights the complex relationship between catalyst and coligand in Ni-catalyzed borylation.

The discovery of $NiCl_2$(dppp)/dppf for neopentylglycolborylation significantly expands the scope of cost-effective Ni-catalyzed borylation to the more abundant and more economical aryl chlorides and reinforces the discovery process via the investigation of libraries.[13] The combination of mixed ligand discovery strategy and highly active Ni catalysts is expected to provide the borylation of even more challenging substrates.

(13) (a) Percec, V. *Nature* **2003**, *424*, 135. (b) Peterca, M.; Percec, V.; Imam, R. M.; Leowanawat, P.; Morimitsu, K.; Heiney, P. A. *J. Am. Chem. Soc.* **2008**, *130*, 14840.

Table 5. Neopentylglycolborylation of Aryl Chlorides: Optimization of Reaction Conditions



no.	catalyst (%)	ligand (%)	temp (°C)	time (h)	convn[a]/yield[b] (%)
1	$NiCl_2$(dppp) (10)	dppf (10)	100	19	97/95
2	$NiCl_2$(dppp) (10)	dppf (5)	100	20	100/95
3	$NiCl_2$(dppp) (5)	dppf (10)	100	7.5	100/100
4	$NiCl_2$(dppp) (5)	dppf (5)	100	19	100/91
5	$NiCl_2$(dppp) (5)	dppf (3)	100	19	88/86
6	$NiCl_2$(dppp) (3)	dppf (3)	100	19	83/82
7	$NiCl_2$(dppp) (3)	dppf (6)	100	19	92/91
8	$NiCl_2$(dppp) (3)	dppf (8)	100	20	95/95
9	$NiCl_2$(dppp) (1)	dppf (2)	100	26	38/17
10	$NiCl_2$(dppp) (10)	dppf (5)	90	24	97/94
11	$NiCl_2$(dppp) (10)	dppf (5)	80	24	85/81
12	$NiCl_2$(dppp) (10)	dppf (5)	60	24	29/25

[a] Conversion calculated from GC. [b] Yield determined by GC.

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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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