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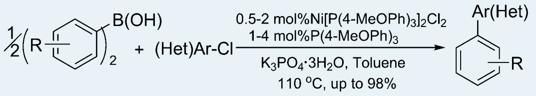
Nickel-Catalyzed Cross-Coupling of Diarylborinic Acids with Aryl Chlorides

Xiaofeng Chen, Haihua Ke, and Gang Zou*

Department of Fine Chemicals, East China University of Science & Technology, 130 Meilong Rd., Shanghai, People's Republic of China

Supporting Information

ABSTRACT: A highly efficient nickel/triarylphosphine catalyst system, $Ni[P(4\text{-}MeOPh)_3]_2Cl_2/2P(4\text{-}MeOPh)_3$, has been developed for cross-coupling of diarylborinic acids with a wide range of aryl chlorides. A variety of unsymmetrical biaryl and heterobiaryl compounds with various functional groups and steric hindrance could be obtained in good to excellent yields using 0.5−2 mol % catalyst loadings in the presence of $K_3PO_4{\cdot}3H_2O$ in toluene. The high atom economy of diarylborinic acids and cost-effectiveness of the nickel/phosphine catalyst system make the cross-coupling truly practical in the production of biaryl fine chemicals. Usefulness of the nickel/phosphine catalyzed cross-coupling of diarylborinic acids with aryl chlorides has been demonstrated in the development of a scalable and economical process for synthesis of 4′-methyl-2-cyanobiphenyl, Sartan biphenyl.



KEYWORDS: *nickel, phosphine, cross coupling, diarylborinic acid, aryl chloride*

INTRODUCTION

The Suzuki−Miyaura cross-coupling is more attractive than other transition-metal-catalyzed cross-coupling reactions in modern organic synthesis because of the friendly properties of organoboronic acids (e.g., nontoxicity, air/moisture stability, and tolerance of a variety of functional groups).[1] In the evolution of this synthetic methodology, the introduction of nickel-based catalysts by Percec et al. in 1995[2] has proven to be another milestone, as important as the conquest of aryl chlorides[3] and making use of organotrifluoroborates.[4] The replacement of palladium catalysts with nickel catalysts in Suzuki−Miyaura cross-coupling not only promises great potential for its applications in industry but also remarkably extends its scope, with respect to electrophile counterparts.[5] For example, aryl chlorides, which are the most practical aryl halides, have represented a big challenge in palladium-catalyzed Suzuki−Miyaura cross-coupling unless using a few privileged phosphines[3a−e] or N-heterocyclic carbene ligands.[3f−j] However, aryl chlorides, including the electron-rich thus deactivated ones, could be cross-coupled by using common nickel catalysts, such as $NiCl_2(PPh_3)_2$ under appropriate conditions. The Suzuki−Miyaura cross-coupling of a variety of aryl C−O based electrophiles, e.g., sulfonates,[2,5d,6] esters,[5d,6d,7] sulfamates,[5d,6h−j,8] carbamates,[5d,8,9] phosphates,[10] ethers,[5d,11] and even phenolates,[12] has been effected in the past decade by using nickel-based catalysts while palladium catalysts have been rarely applied to these sorts of substrates.[13] Recently, a long-standing problem, coupling of alkyl electrophiles with organoborons, has been more elegantly solved by Fu et al. by taking advantage of nickel-based catalysts.[14]

In sharp contrast to the greatly extended scope of electrophiles, arylboronic acids and derivatives are still the overwhelming aryl nucleophile counterparts in Suzuki−Miyaura cross-coupling, including the nickel-catalyzed one. Although high-order arylborons, e.g., diarylborinic acids, triarylboranes, and tetraarylborates, have higher atom economy as arylation reagents than arylboronic acids, they have been rarely applied in cross-coupling,[15] especially Suzuki−Miyaura cross-coupling with aryl chlorides. In fact, highly active aryl halides (I and Br) or/and nontraditional reaction conditions had to be used in the scatteredly reported Suzuki−Miyaura cross-coupling of high-order arylborons.[16] We have recently reported an efficient cross-coupling of diarylborinic acids with aryl halides, using a palladium catalyst system co-supported by sterically demanding N-heterocyclic carbene (NHC) and phosphite $P(OR)_3$.[17] Diarylborinic acids ($Ar_2B(OH)$) not only have comparable properties to arylboronic acids but also possess higher atom economy and could be prepared more economically from arylhalides, boronates, and magnesium under noncryogenic conditions if no hampered by sensitive functional groups.[18] However, high cost of the palladium/NHC/phosphite catalyst still remains an obstacle in application of the cross-coupling of diarylborinic acids in large-scale production. Compared with palladium(II) species, the divalent nickel(II) ones are not only much less expensive but also more compatible with the high reducing ability of high-order arylborons.[19] Therefore, nickel-based catalysts should be more suitable for a highly efficient and practical cross-coupling of diarylborinic acids with aryl chlorides.

RESULTS AND DISCUSSION

Establishment of Catalyst System. For the convenience of stoichiometry and monitoring, cross-coupling of dehydration-resisting bis(*p*-tolyl)borinic acid **1a** with representative

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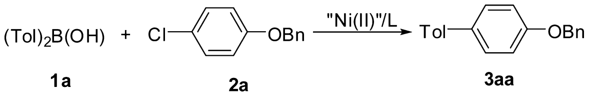
Table 1. Condition Screening for Nickel-Catalyzed Cross-Coupling of Diarylborinic Acids with Aryl Chlorides[a]



entry	$NiCl_2(L)_2$ Data		Extra L Data		base	solvent	temp, *T* (°C)	yield (%)[b]
	$NiCl_2(L)_2$	(mol %)	extra L	(mol %)				
1	$NiCl_2$	3			$K_3PO_4{\cdot}3H_2O$	Tol	110	0
2	$NiCl_2$	3	NHC/$P(OPh)_3$	3/3	$K_3PO_4{\cdot}3H_2O$	*t*-BuOH	80	trace
3	$NiCl_2(Py)_2$	3			$K_3PO_4{\cdot}3H_2O$	Tol	110	30
4	$NiCl_2(PPh_3)_2$	3			$K_3PO_4{\cdot}3H_2O$	Tol	110	62
5	$NiCl_2(Py)_2$	3	Py	6	$K_3PO_4{\cdot}3H_2O$	Tol	110	35
6	$NiCl_2(Py)_2$	3	PPh_3	6	$K_3PO_4{\cdot}3H_2O$	Tol	110	83
7	$NiCl_2(PPh_3)_2$	3	PPh_3	6	$K_3PO_4{\cdot}3H_2O$	Tol	110	90
8	$NiCl_2(PPh_3)_2$	3	PPh_3	6	$K_3PO_4{\cdot}3H_2O$	dioxane	100	63
9	$NiCl_2(PPh_3)_2$	3	PPh_3	6	$K_3PO_4{\cdot}3H_2O$	DME	80	10
10	$NiCl_2(PPh_3)_2$	3	PPh_3	6	$K_3PO_4{\cdot}3H_2O$	THF	70	77
11	$NiCl_2(PPh_3)_2$	3	PPh_3	6	$K_3PO_4{\cdot}3H_2O$	CH_3CN	70	19
12	$NiCl_2(PPh_3)_2$	3	PPh_3	6	$K_3PO_4{\cdot}3H_2O$	DMF	110	26
13	$NiCl_2(PPh_3)_2$	3	PPh_3	6	$K_3PO_4{\cdot}3H_2O$	*i*-PrOH	80	trace
14	$NiCl_2(PPh_3)_2$	3	PPh_3	6	K_2CO_3	Tol	110	trace
15	$NiCl_2(PPh_3)_2$	3	PPh_3	6	Cs_2CO_3	Tol	110	trace
16	$NiCl_2(PPh_3)_2$	3	PPh_3	6	KOH	Tol	110	15
17	$NiCl_2(PPh_3)_2$	3	PPh_3	6	NaOH	Tol	110	46
18	$NiCl_2(PPh_3)_2$	3	PPh_3	6	$K_3PO_4{\cdot}3H_2O$	Tol	110	82[c]
19	$NiCl_2(PCy_3)_2$	3	PCy_3	6	$K_3PO_4{\cdot}3H_2O$	Tol	110	trace
20	$NiCl_2$(dppm)	3	dppm	3	$K_3PO_4{\cdot}3H_2O$	Tol	110	6
21	$NiCl_2$(dppe)	3	dppe	3	$K_3PO_4{\cdot}3H_2O$	Tol	110	27
22	$NiCl_2$(dppp)	3	dppp	3	$K_3PO_4{\cdot}3H_2O$	Tol	110	33
23	$NiCl_2$(dppb)	3	dppb	3	$K_3PO_4{\cdot}3H_2O$	Tol	110	86
24	$NiCl_2$(dppf)	3	dppf	3	$K_3PO_4{\cdot}3H_2O$	Tol	110	66
25	$NiCl_2(PPh_3)_2$	3	$(C_6F_5)_3P$	6	$K_3PO_4{\cdot}3H_2O$	Tol	110	56
26	$NiCl_2(PPh_3)_2$	3	$(4\text{-MeOPh})_3P$	6	$K_3PO_4{\cdot}3H_2O$	Tol	110	98
27	$NiCl_2(PPh_3)_2$	3	$(4\text{-MeOPh})_3P$	3	$K_3PO_4{\cdot}3H_2O$	Tol	110	85
28	$NiCl_2(PPh_3)_2$	2	$(4\text{-MeOPh})_3P$	4	$K_3PO_4{\cdot}3H_2O$	Tol	110	93
29	$NiCl_2(PPh_3)_2$	2	$(4\text{-MeOPh})_3P$	2	$K_3PO_4{\cdot}3H_2O$	Tol	110	77
30	$NiCl_2(PPh_3)_2$	2	$(2\text{-MeOPh})_3P$	4	$K_3PO_4{\cdot}3H_2O$	Tol	110	62
31	$NiCl_2(PPh_3)_2$	2	(*m*-trimethoxylPh)$_3$P	4	$K_3PO_4{\cdot}3H_2O$	Tol	110	67
32	$NiCl_2[(4\text{-MeOPh})_3P]_2$	2			$K_3PO_4{\cdot}3H_2O$	Tol	110	79
33	$NiCl_2[(4\text{-MeOPh})_3P]_2$	2	$(4\text{-MeOPh})_3P$	4	$K_3PO_4{\cdot}3H_2O$	Tol	110	97
34	$NiCl_2[(4\text{-MeOPh})_3P]_2$	1	$(4\text{-MeOPh})_3P$	2	$K_3PO_4{\cdot}3H_2O$	Tol	110	66
35	$NiCl_2[(4\text{-MeOPh})_3P]_2$	2	$(4\text{-MeOPh})_3P$	2	$K_3PO_4{\cdot}3H_2O$	Tol	110	88
36	$NiCl_2[(4\text{-MeOPh})_3P]_2$	2	PPh_3	4	$K_3PO_4{\cdot}3H_2O$	Tol	110	92
37	$NiCl_2[(4\text{-MeOPh})_3P]_2$	2	$(4\text{-MeOPh})_3P$	4	$K_3PO_4{\cdot}3H_2O$	Tol	110	69[d]

[a] Reaction conditions: **1a** (0.65 mmol), **2a** (1.0 mmol), base (2.60 mmol), solvent (4 mL), N_2, 10 h. [b] Isolated yields. [c] 0.55 mmol of **1a** was used. [d] Run in the presence of 100 mg of mercury.

deactivated aryl chloride, 4-(benzyloxy)phenyl chloride (**2a**), was chosen as the model reaction to screen reaction conditions (see Table 1). It was reported that simple $NiCl_2$ without any supporting ligand could catalyze the Suzuki–Miyaura coupling of arylboronic acids to some extent.[20] However, no reaction was detected using 3 mol % $NiCl_2$ as catalyst for the model reaction. A nickel/NHC/phosphite system, $NiCl_2$/IPr/P-$(OPh)_3$ (IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) also failed although the corresponding palladium system, $PdCl_2$/IPr/$P(OPh)_3$, had worked well in cross-coupling of diarylborinic acids with aryl halides.[17] However, when 3 mol % $Ni(Py)_2Cl_2$ or $Ni(PPh_3)_2Cl_2$ was used as catalyst, the cross-coupling product (**3aa**) was obtained in 30% and 62% yields, respectively, with a boron (**1a**)/chloride (**2a**) molar ratio of 0.65:1 (1.3 equiv *p*-tolyl group, relative to C_{Ar}–Cl) in the presence of 2.6 equiv $K_3PO_4{\cdot}3H_2O$ in toluene (see Table 1, entries 3 and 4). The **3aa** yields further increased to 83% and 90%, respectively, when an additional 2 equiv PPh_3, with respect to nickel, was used along with $Ni(Py)_2Cl_2$ and $Ni(PPh_3)_2Cl_2$, although the addition of 2 more equiv pyridine (Py) did not improve the catalytic performance of $Ni(Py)_2Cl_2$ (Table 1, entries 5–7).

Screening of several common solvents (dioxane, DME, THF, CH_3CN, *i*-PrOH, and DMF) and bases (Cs_2CO_3, K_2CO_3, NaOH, and KOH) provided no better results than those with the combination of toluene and $K_3PO_4{\cdot}3H_2O$. A slight excess of bis(*p*-tolyl)borinic acid **1a** (1.3 equiv *p*-tolyl) appeared to be necessary since the **3aa** yield decreased from 90% to 82% with the molar ratios of **1a** to **2a** decreased from 0.65 to 0.55 (1.1 equiv *p*-tolyl) (Table 1, entries 7 and 18). Surprisingly, no reaction was detected using $NiCl_2(PCy_3)_2/2PCy_3$ as catalyst under otherwise identical conditions since tricyclohexylphosphine (PCy_3) has been often reported to be a good supporting ligand in Suzuki–Miyaura coupling of arylboronic acids. It was reported that some nickel complexes supported by bidentate phosphine ligands, such as $Ni(dppe)Cl_2$,[21] $Ni(dppf)Cl_2$,[22] or $Ni(dppp)Cl_2$,[23] displayed high catalytic activities in the related cross-coupling of arylboronic acids with aryl chlorides. Therefore, we investigated the performance of the most common bidentate phosphines, e.g., 1,1-bis(diphenylphosphino)methane (dppm), 1,2-bis(diphenylphosphino)ethane (dppe), 1,3-bis(diphenylphosphino)propane (dppp), 1,4-bis(diphenylphosphino)butane (dppb), and 1,1′-bis(diphenylphosphino)ferrocene (dppf), in the nickel/phosphine catalyst system. Generally, the bidentate phosphines with a large bite angle,[24] dppb (86%) and dppf (66%), gave the cross-coupling product **3aa** in higher yields than those with a small one, dppm (6%), dppe (27%), and dppp (33%) (Table 1, entries 20–24). However, the highest yield (86%, with $Ni(dppb)Cl_2$/dppb) was just comparable to that with $Ni(PPh_3)_2Cl_2/2PPh_3$ (90%) (Table 1, entries 7 and 23).

According to the mostly accepted mechanism for Ni-catalyzed cross-coupling processes, only low-valency nickel (Ni(0) or Ni(I)) species are truly catalytically active.[5] Divalent nickel catalyst precursors must be reduced at first in the catalytic cycle. In fact, strong reducing agents, such as DIBAL-H, BuLi,[3k,l] or Zn powder,[5b,25] etc., had to be used to generate catalytically active species from nickel(II) precursors in early reported Suzuki–Miyaura coupling of arylboronic acids using Ni(II)-based catalysts. It has been found later that the Ni(II)-based catalyst systems with extra free phosphine ligands could performed well without additional reductants.[5b,f,26] Therefore, to elucidate the role of extra phosphine ligands in the nickel/phophine-catalyzed cross-coupling of diarylborinic acids with aryl halides, a couple of phosphine ligands with various electronic and steric properties were investigated as extra ligands to catalyst precursor $Ni(PPh_3)_2Cl_2$ in the model reaction. Electron-rich $P(4\text{-}MeOPh)_3$ performed better than PPh_3 with the yield of **3aa** increasing from 90% to 98% while no effect was observed for the extremely electron-poor $P(C_6F_5)_3$. The yield of **3aa** significantly decreased to 85% with lowering the ratio of $P(4\text{-}MeOPh)_3$ to $Ni(PPh_3)_2Cl_2$ to 1:1 (mol/mol) at 3 mol % loading, which was even lower than that obtained with 2 mol % $Ni(PPh_3)_2Cl_2$ loading (93%) along with 2 equiv (4 mol %) $P(4\text{-}MeOPh)_3$, confirming the importance of the extra phosphine ligand. However, when the electron richer but sterically demanding tris(2,4,6-trimethoxyphenyl)phosphine, $[m\text{-}(MeO)_3Ph]_3P$, was used as extra ligand the **3aa** yield (67%) was just comparable to that with $Ni(PPh_3)_2Cl_2$ alone (62%). A similar result was also obtained with $P(2\text{-}MeOPh)_3$ as extra phosphine. That is to say, the positive effect of extra phosphines on the catalytic activity of $Ni(PPh_3)_2Cl_2$ disappeared completely with sterically demanding $P(2\text{-}MeOPh)_3$ and $[m\text{-}(MeO)_3Ph]_3P$ although they have compatible or even stronger reducing abilities than PPh_3. The divalent nickel catalyst precursor may be reduced by diarylborinic acids to initiate the catalysis, which is consistent with the high reducing ability and requirement of an excess amount of diarylborinic acids.

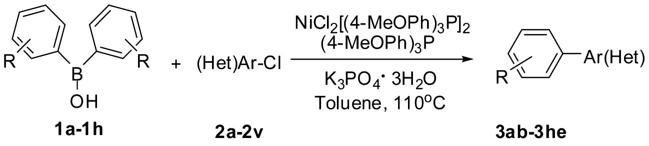
Since $P(4\text{-}MeOPh)_3$, as an extra phosphine ligand, could improve the catalytic performance of $Ni(PPh_3)_2Cl_2$, we anticipated the nickel precursor supported by $P(4\text{-}MeOPh)_3$, $Ni[P(4\text{-}MeOPh)_3]_2Cl_2$, should be more efficient than $Ni(PPh_3)_2Cl_2$. In fact, the model reaction catalyzed by 2 mol % $Ni[P(4\text{-}MeOPh)_3]_2Cl_2$ alone could give **3aa** in a significantly higher yield (79%) than that with 3 mol % $Ni(PPh_3)_2Cl_2$ (62%) under otherwise identical conditions (Table 1, entries 4 and 32). The **3aa** yields further increased to 88% and 97% when 2 mol % $Ni[P(4\text{-}MeOPh)_3]_2Cl_2$ was used along with 1.0 equiv (2 mol %) and 2.0 equiv (4 mol %) extra $P(4\text{-}MeOPh)_3$, respectively, while the reaction could not complete with 1 mol % catalyst loading (Table 1, entries 32–35). Based on these results, the optimal catalyst system for the model reaction was set as 2 mol % $NiCl_2[P(4\text{-}MeOPh)_3]_2$/4 mol% $P(4\text{-}MeOPh)_3$ with 2.6 equiv $K_3PO_4{\cdot}3H_2O$ in toluene. When the reaction was run in the presence of mercury (mercury poisoning test), a modest yield (69%) of **3aa** could still be obtained, supporting a homogeneous catalyst system (Table 1, entry 37).

Scope and Limitation. Scope of the nickel catalyzed cross-coupling of aryl chlorides with diarylborinic acids was explored using an established catalyst system (see Table 2).

Similar to **2a**, 4-chlorotoluene (**2b**), 4-chloroanisole (**2d**), and *N*,*N*-dimethyl-4-chloroaniline (**2f**) reacted with bis(*p*-tolyl)borinic acid (**1a**) smoothly to give the corresponding products **3ab** (97%), **3ad** (93%), and **3af** (91%) in excellent yields, using 2 mol % catalyst loading (Table 2, entries 1, 3, and 5). Aryl chlorides bearing a small ortho-substituent, such as methyl (**2c**) or methoxyl (**2e**), still gave cross-coupling products **3ac** (91%) or **3ae** (89%) in good yields (Table 2, entries 2 and 4). A free amino group (NH_2) on aryl chlorides appeared to be tolerable although the yields decreased significantly for both 4-chloroaniline (**2g**, 78%) and its ortho-isomer (**2h,** 73%) (Table 2, entries 6 and 7). Electron-deficient aryl chlorides with an electron-withdrawing group, e.g., CN, CH_3CO, CHO, and CO_2Me, displayed higher reactivity in reaction with **1a** than the above electron-neutral and electron-rich ones. Excellent yields of the desired cross-coupling products could be obtained for these activated substrates, even with lower catalyst loadings (0.5–1.5 mol %) and in shorter reaction time (5–8 h), except for 2-chloroacetophone, for which the cross-coupling product **3am** was obtained in a modest yield (63%), because of dechlorination and steric hindrance as well (Table 2, entries 8–15).[26,27] A nitro group (NO_2) proved deleterious to the nickel/phosphine catalyst system, since no reaction was observed for 4-chloronitrobenzene (**2p**). 3-Chloropyridine reacted smoothly with 0.5 mol % catalyst loading to give cross-coupling product (**3aq**) in 93% yield, while methyl-2-chloronicotinate required 2 mol % catalyst loading to achieve a modest yield (**3ar**) (Table 2, entries 17 and 18).

Structural effects of diarylborinic acids on the nickel/phosphine catalyzed cross-coupling reaction were also investigated. Electron-donating (MeO, **1c**), electron-neutral (H, **1b**), and electron-withdrawing (F, **1d**) groups on the aromatic ring of diarylborinic acids appeared to have negligible influence on the reaction, providing the corresponding products in excellent yields (Table 2, entries 19–21). However, an obvious steric effect was observed (Table 2, entries 22–25). For example, the reactions of bis(2-ethylphenyl)borinic acid (**1f**) with 4-(benzyloxy)phenyl chloride (**2a**) and 2-chloroanisole (**2e**) gave **3fa** (78%) and **3fe** (73%) in significantly lower yields than those of **1a**. Surprisingly, the corresponding reaction of bis(2-methoxyphenyl)borinic acid (**1g**) with **2a** proceeded more efficiently to afford **3ga** in 92% yield. Even an ortho-isopropoxy group appeared not to hamper the cross-coupling. The reaction

Table 2. Scope of the Cross-Coupling of Aryl Chlorides with Diarylborinic Acids[a]



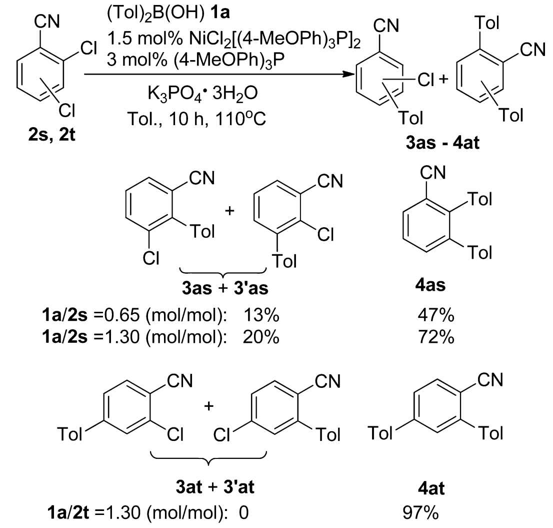
entry	R_1 (**1**)	(Het)ArCl (**2**)	cat. (mol %)	time, *T* (h)	yield (%)[b]
1	4-Me (**1a**)	4-MeC_6H_4Cl (**2b**)	2	6	97 (**3ab**)
2	4-Me (**1a**)	2-MeC_6H_4Cl (**2c**)	2	8	91 (**3ac**)
3	4-Me (**1a**)	4-$MeOC_6H_4Cl$ (**2d**)	2	10	93 (**3ad**)
4	4-Me (**1a**)	2-$MeOC_6H_4Cl$ (**2e**)	2	10	89 (**3ae**)
5	4-Me (**1a**)	4-$Me_2NC_6H_4Cl$ (**2f**)	2	10	91 (**3af**)
6	4-Me (**1a**)	4-$H_2NC_6H_4Cl$ (**2g**)	2	10	78 (**3ag**)
7	4-Me (**1a**)	2-$H_2NC_6H_4Cl$ (**2h**)	2	10	73 (**3ah**)
8	4-Me (**1a**)	4-CNC_6H_4Cl (**2i**)	1	5	94 (**3ai**)
9	4-Me (**1a**)	3-CNC_6H_4Cl (**2j**)	1	5	98 (**3aj**)
10	4-Me (**1a**)	2-CNC_6H_4Cl (**2k**)	1	5	89 (**3ak**)
11	4-Me (**1a**)	2-CNC_6H_4Cl (**2k**)	1.5	5	98 (**3ak**)
12	4-Me (**1a**)	4-AcC_6H_4Cl (**2l**)	0.5	6	98 (**3al**)
13	4-Me (**1a**)	2-AcC_6H_4Cl (**2m**)	1	10	63 (**3am**)
14	4-Me (**1a**)	4-$(CO_2Me)C_6H_4Cl$ (**2n**)	0.5	8	95 (**3an**)
15	4-Me (**1a**)	4-$CHOC_6H_4Cl$ (**2o**)	0.5	8	87 (**3ao**)
16	4-Me (**1a**)	4-$NO_2C_6H_4Cl$ (**2p**)	0.5	10	trace
17	4-Me (**1a**)	3-ClC_5H_4N (**2q**)	0.5	8	93 (**3aq**)
18	4-Me (**1a**)	2-Cl-3-$(CO_2Me)C_5H_3N$ (**2r**)	2	10	74 (**3ar**)
19[c]	H (**1b**)	4-$BnOC_6H_4Cl$ (**2a**)	2	10	95 (**3ba**)
20	4-MeO (**1c**)	4-$BnOC_6H_4Cl$ (**2a**)	2	10	97 (**3ca**)
21	4-F (**1d**)	4-$BnOC_6H_4Cl$ (**2a**)	2	10	89 (**3da**)
22	2-Me (**1e**)	4-$BnOC_6H_4Cl$ (**2a**)	2	10	91 (**3ea**)
23	2-Me (**1e**)	2-$MeOC_6H_4Cl$ (**2e**)	2	10	94 (**3ee**)
24	2-Et (**1f**)	4-$BnOC_6H_4Cl$ (**2a**)	2	10	78 (**3fa**)
25	2-Et (**1f**)	2-$MeOC_6H_4Cl$ (**2e**)	2	10	73 (**3fe**)
26	2-MeO (**1g**)	4-$BnOC_6H_4Cl$ (**2a**)	2	10	92 (**3ga**)
27	2-^{i}PrO (**1h**)	4-$BnOC_6H_4Cl$ (**2a**)	2	10	93 (**3ha**)
28	2-^{i}PrO (**1h**)	2-$MeOC_6H_4Cl$ (**2e**)	2	10	64 (**3he**)

[a] Reaction conditions: diarylborinic acid (0.65 mmol), aryl chloride (1.0 mmol), $K_3PO_4 \cdot 3H_2O$ (2.60 mmol), Tol (4 mL), N_2, 110 °C. [b] Isolated yields. [c] 0.33 mmol of diphenyllborinic anhydride was used.

of bis(2-isopropoxyphenyl)borinic acid (**1h**) with **2a** afforded **3ha** in 93% yield and a modest yield (64%) of **3he** could still be obtained for the reaction of (**1h**) and 2-chloroanisole (**2e**) (Table 2, entries 26−28). The exact reason is not clear for the smaller steric effect of ortho-alkoxy groups than alkyl ones in the diarylborinic acids on the nickel/phosphine catalyzed cross-coupling reaction. One possibility lies in an intramolecular coordination between the O and B atoms,[28] which could facilitate the transmetallation between diarylborinic acids and intermediate nickel species in the catalytic cycle.

Considering the significant steric effects observed in the reactions of 2-chloroacetophone (**2m**) and methyl-2-chloronicotinate (**2r**), it had appeared that there could be a possibility in monoarylation of ortho-polychloroarenes since the second arylation should experience a much larger steric hindrance than the first one. Therefore, the coupling of bis(*p*-tolyl)borinic acid (**1a**) with 2,3-dichlorobenzonitrile (**2s**) was investigated (Scheme 1). However, a mixture consisting of substrate **2s**, diarylation product **4as**, and a small amount of monoarylation (inseparable **3as** and isomer **3′as**) was obtained with 0.65:1 molar ratio of **1a**/**2s**. When the **1a**/**2s** molar ratio was increased to 1.3:1 diarylation product **4as** was isolated in 72% yield along with monoarylation isomers **3as** and **3′as** (together in 20% yield).

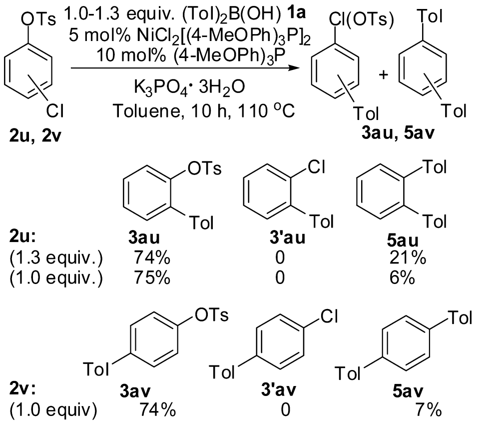
Scheme 1. Selectivity in Arylation of Dichloroarenes



The relative ease in overcoming the sequentially increasing steric hindrance in the double arylation of ortho-dihaloarenes could be attributed to a preference of intramolecular sequential oxidative addition of the C−X bond of dihaloarenes in transition-metal-catalyzed cross-coupling, which was first observed by Hu et al.[29] Not surprisingly, an excellent yield (97%) of the double-arylation product **4at** was obtained in the cross-coupling of **1a** and 2,4-dichlorobenzonitrile (**2t**), because of the absence of the sequentially increasing steric hindrance.

In general, the aryl C_{Ar}-O based electrophiles, except for triflates, are more inert than C_{Ar}−Cl in palladium-catalyzed cross-couplings. However, nickel-based catalysts have proven efficient in Suzuki−Miyaura coupling of arylboronic acids with a variety of phenol derivatives. Aryl tosylates are the most commonly used phenol derivative in cross-coupling, because of their ready availability, low cost, high stability, and good crystallization properties. Therefore, it is interesting to explore the intramolecular chemical selectivity between C_{Ar}−Cl and C_{Ar}−OTs. The cross-coupling of bis(*p*-tolyl)borinic acid (**1a**) with 2-chlorophenol tosylate (**2u**) was investigated (Scheme 2).

Scheme 2. Chemical Selectivity in the Cross-Coupling of Chlorophenol Tosylates

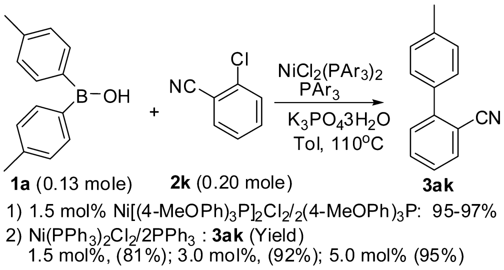


Surprisingly, only the C_{Ar}−Cl cross-coupling product **3au**, one of the two possible monoarylation products, was isolated, along with a small amount of diarylation product (**5au**). Use of 1.0 equiv (0.5 molar ratio, relative to C_{Ar}−Cl) bis(*p*-tolyl)borinic acid (**1a**) increased the selectivity of monoarylation to diarylation from 74:21 to 75:6. A similar result was obtained for 4-chlorophenol tosylate (**2v**). Similar to the diarylation of dihaloarenes (vide supra), the bias reactivity of C_{Ar}−OTs in the intermediate monoarylation products (**3au** and **3av**) to that in the initial chlorophenol tosylates (**2u** and **2v**) could be attributed to the preferable oxidation addition of intramolecular C_{Ar}−OTs over the intermolecular one to the regenerated active nickel species in the catalytic cycle.

Application Exploration. Application of the nickel/phosphine catalyzed cross-coupling of diarylborinic acids with aryl chlorides in production of fine chemicals was demonstrated in synthesis of 4′-methyl-2-cyanobiphenyl (Sartan biphenyl), which is a key intermediate for the synthesis of a family of angiotensin II receptor antagonists, Sartans, for the treatment of hypertension.[30] Sartan biphenyl has been commercially produced by nickel-catalyzed Kumada coupling of 2-chlorobenzonitrile with *p*-tolylmagnesium chloride instead of Suzuki−Miyaura cross-coupling due to the high cost of *p*-tolyl boronic acid. We have recently developed a scalable process for Sartan biphenyl via cross-coupling of di(*p*-tolyl)borinic acid with 2-chlorobenzonitrile catalyzed by 0.2 mol % $Pd(OAc)_2$/NHC/$P(OPh)_3$. However, the expensive palladium catalyst system still hampered the process in practical applications. Therefore, to develop a more cost-effective and practical process for production of Sartan biphenyl, we conducted the nickel/phosphine catalyzed cross-coupling of di(*p*-tolyl)borinic acid (**1a**) with 2-chlorobenzonitrile (**2k**) in dozen gram scale. Under the above optimized conditions, Sartan biphenyl could be isolated in 95%−97% yields using 1.5 mol % $Ni[P(4\text{-}MeOPh)_3]_2Cl_2/2P(4\text{-}MeOPh)_3$ catalyst loading in experiments in 0.2 mol scale (see Scheme 3).

The cost of nickel-based catalyst was only ∼10% of that using 0.2 mol % $Pd(OAc)_2$/NHC/$P(OPh)_3$.[31] Attempt to further decrease the catalyst cost, the synthesis was also carried out using the triphenylphosphine-based catalyst, $Ni(PPh_3)_2Cl_2/2PPh_3$, which has also shown good activity in the model reaction during catalyst screening (Table 1, entry 7). However, because of the lower catalytic activity, higher catalyst loadings (3−5 mol % nickel) had to be used to obtain satisfactory yields (92%−95%) under similar conditions.

Scheme 3. Synthesis of Sartan Biphenyl in Dozen Gram Scales



■ CONCLUSION

In summary, a highly efficient and practical nickel/triarylphosphine catalyst system, $Ni[P(4\text{-}MeOPh)_3]_2Cl_2/2P(4\text{-}MeOPh)_3$, has been developed for cross-coupling of diarylborinic acids with a wide range of aryl chlorides in the presence of $K_3PO_4 \cdot 3H_2O$ in toluene. Electron-rich and sterically undemanding tri(4-methoxylphenyl)phosphine, $P(4\text{-}MeOPh)_3$, proven to be the most efficient supporting ligand in the nickel/phosphine catalyst system for both activated and deactivated aryl chlorides, while tricyclohexylphosphine showed poor performance. At least 4 equiv triarylphosphine, relative to nickel, was found to be necessary to coordinatively stabilize the catalytically active Ni(0) or Ni(I) species as the supporting ligand. A catalyst loading as low as 0.5 mol % (based on nickel) seemed to be sufficient for the cross-coupling of activated aryl chlorides without steric hindrance to provide products in good to excellent yields. The aryl chlorides deactivated by either electron-donating groups or steric hindrance could also be coupled efficiently by simply increasing the catalyst loading to 1−2 mol % under otherwise identical conditions. Modest steric hindrance in diarylborinic acids, especially that from a coordinative ortho-substituent, could be overcome successfully. The high atom economy of diarylborinic acids and cost-effectiveness of nickel/phosphine catalyst system make the cross-coupling truly practical in the production of biaryl fine chemicals. As an application demonstration of the nickel-catalyzed cross-coupling of diarylborinic acids with aryl chlorides, a scalable and economical process has been developed from bis(tolyl)borinic acid and 2-chlorobenzonitrile for the synthesis of Sartan biphenyl, which is a key intermediate of a family of angiotensin II receptor antagonists.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of all new and known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gangzou@ecust.edu.cn.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A.; Diederich, F., Eds.; Willey-VCH: Weinheim, 2004, pp 41−123. (c) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 2−18. (d) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062−5085.

(2) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060−1065.

(3) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (b) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366−374. (c) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461−1473. (d) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555−1564. (e) Fleckenstein, C. A.; Plenio, H. *Chem. Soc. Rev.* **2010**, *39*, 694−711. (f) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194−16195. (g) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440−1449. (h) Würtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523−1533. (i) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *40*, 5151−5169. (j) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314−3332. (k) Saito, S.; Sakai, M.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 2993−2996. (l) Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024−8030.

(4) (a) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49−56. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275−286. (c) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623−3658. (d) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288−325. (e) Darses, S.; Genêt, J.-P. *Tetrahedron Lett.* **1997**, *38*, 4393−4396. (f) Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* **1999**, 1875−1883. (g) Xia, M.; Chen, Z.-C. *Synth. Commun.* **1999**, *29*, 2457−2465.

(5) (a) Goo*β*en, L. J.; Goo*β*en, K.; Stanciu, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 3569−3571. (b) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346−1416. (c) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417−1492. (d) Leowanawat, P.; Zhang, N.; Percec, V. *J. Org. Chem.* **2012**, *77*, 1018−1025. (e) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, 19−30. (f) Han, F.-S. *Chem. Soc. Rev.* **2013**, *42*, 5270−5298.

(6) (a) Butler, T. A.; Swift, E. C.; Lipshutz, B. H. *Org. Biomol. Chem.* **2008**, *6*, 19−25. (b) Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058−3059. (c) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447−3452. (d) Molander, G. A.; Beaumard, F. *Org. Lett.* **2010**, *12*, 4022−4025. (e) Guan, B.-T.; Lu, X.-Y.; Zheng, Y.; Yu, D.-G.; Wu, T.; Li, K.-L.; Li, B.-J.; Shi, Z.-J. *Org. Lett.* **2010**, *12*, 396−399. (f) Leowanawat, P.; Zhang, N.; Resmerita, A.-M.; Rosen, B. M.; Percec, V. *J. Org. Chem.* **2011**, *76*, 9946−9955. (g) Fan, X.-H.; Yang, L.-M. *Eur. J. Org. Chem.* **2011**, 1467−1471. (h) Xing, C.-H.; Lee, J.-R.; Tang, Z.-Y.; Zheng, J. R.; Hu, Q.-S. *Adv. Synth. Catal.* **2011**, *353*, 2051−2059. (i) Leowanawat, P.; Zhang, N.; Safi, M.; Hoffman, D. J.; Fryberger, M. C.; George, A.; Percec, V. *J. Org. Chem.* **2012**, *77*, 2885−2892. (j) Zhang, N.; Hoffman, D. J.; Gutsche, N.; Gupta, J.; Percec, V. *J. Org. Chem.* **2012**, *77*, 5956−5964.

(7) (a) Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422−14423. (b) Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 14468−14470.

(8) (a) Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748−17749. (b) Baghbanzadeh, M.; Pilger, C.; Kappe, C. O. *J. Org. Chem.* **2011**, *76*, 1507−1510. (c) Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Snieckus, V.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 6352−6363.

(9) (a) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750−17752. (b) Xu, L.; Li, B.-J.; Wu, Z.-H.; Lu, X.-Y.; Guan, B.-T.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Org. Lett.* **2010**, *12*, 884−887.

(10) (a) Chen, H.; Huang, Z.; Hu, X.; Tang, G.; Xu, P.; Zhao, Y.; Cheng, C.-H. *J. Org. Chem.* **2011**, *76*, 2338−2344. (b) Zhao, Y.-L.; Li, Y.; Li, Y.; Gao, L.-X.; Han, F.-S. *Chem.—Eur. J.* **2010**, *16*, 4991−4994. (c) Chen, G.-J.; Huang, J.; Gao, L.-X.; Han, F.-S. *Chem.—Eur. J.* **2011**, *17*, 4038−4042.

(11) (a) Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866−4869. (b) Li, X.-J.; Zhang, J.-L.; Geng, Y.; Jin, Z. *J. Org. Chem.* **2013**, *78*, 5078−5084.

(12) Yu, D.-G.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7097−7100.

(13) For Pd catalyzed Suzuki coupling of tosylates see: (a) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818−11819. (b) Steinhuebel, D.; Baxter, J. M.; Palucki, M.; Davies, I. W. *J. Org. Chem.* **2005**, *70*, 10124−10127. (c) Zhang, L.; Meng, T.; Wu, J. *J. Org. Chem.* **2007**, *72*, 9346−9349. For Pd catalyzed Suzuki coupling of mesylates see: (d) So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8059−8063.

(14) (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525−1532. (b) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340−1341. (c) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674−688. (d) González-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360−5361. (e) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602−9603. (f) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694−6695. (g) Duncton, M. A. J.; Estiarte, M. A.; Tan, D.; Kaub, C.; O'Mahony, D. J. R.; Johnson, R. J.; Cox, M.; Edwards, W. T.; Wan, M.; Kincaid, J.; Kelly, M. G. *Org. Lett.* **2008**, *10*, 3259−3262. (h) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656−2670. (i) Lu, Z.; Fu, G. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6676−6678. (j) Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027−11029. (k) Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908−11909. (l) Molander, G. A.; Argintaru, O. A.; Aron, I.; Dreher, S. D. *Org. Lett.* **2010**, *12*, 5783−5785. (m) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 15362−15364. (n) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154−8157. (o) Huang, K.; Li, G.; Huang, W.-P.; Yu, D.-G.; Shi, Z.-J. *Chem. Commun.* **2011**, *47*, 7224−7226. (p) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794−5797. (q) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624−627.

(15) (a) Partyka, D. V. *Chem. Rev.* **2011**, *111*, 1529−1595. Examples relating to diarylborinic acids and derivatives in cross-coupling: (b) Ito, T.; Iwai, T.; Mizuno, T.; Ishino, Y. *Synlett* **2003**, 1435−1438. (K[Ar_2BF_2]). (c) Winkle, D. D.; Schaab, K. M. *Org. Process Res. Dev.* **2001**, *5*, 450−451. (in situ). (d) Haag, B. A.; Sämann, C.; Jana, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7290−7294. (undefined mixture). (e) Li, X.; Feng, Y.; Lin, L.; Zou, G. *J. Org. Chem.* **2012**, *77*, 10991−10995 (metal-free, reductive coupling)..

(16) (a) Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437−14450. (b) Villemin, D.; Gómez-Escalonilla, M. J.; Saint-Clair, J.-F. *Tetrahedron Lett.* **2001**, *42*, 635−637. (c) Bai, L.; Wang, J.-X. *Adv. Synth. Catal.* **2008**, *350*, 315−320. (d) Zhou, W.-J.; Wang, K.-H.; Wang, J.-X.; Gao, Z.-R. *Tetrahedron* **2010**, *66*, 7633−7641. (e) Monot, J.; Brahmi, M. M.; Ueng, S.-H.; Robert, C.; Murr, M. D.-E.; Curran, D. P.; Malacria, M.; Fensterbank, L.; Lacôte, E. *Org. Lett.* **2009**, *11*, 4914−4917.

(17) Chen, X.; Ke, H.; Chen, Y.; Guan, C.; Zou, G. *J. Org. Chem.* **2012**, *77*, 7572−7578.

(18) (a) Hall, D. G., Eds.; *Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine*, Willey-VCH: Weinheim, 2005. (b) Cole, T. E.; Haly, B. D. *Organometallics* **1992**, *11*, 652−657. (c) Brown, H. C.; Racherla, U. S. *J. Org. Chem.* **1986**, *51*, 427−432. (d) Huang, S.; Shan, Z.; Zhao, D. *Youji Huaxue* **1995**, *15*, 64−67.

(19) (a) Turner, W. R.; Elving, P. J. *Anal. Chem.* **1965**, *37*, 207−211. (b) Geske, D. H. *J. Chem. Phys.* **1959**, *63*, 1062−1070.

(20) Zim, D.; Monteiro, A. L. *Tetrahedron Lett.* **2002**, *43*, 4009−4011.

(21) (a) Rosen, B. M.; Huang, C.; Percec, V. *Org. Lett.* **2008**, *10*, 2597−2600. (b) Lukashev, N. V.; Latyshev, G. V.; Donez, P. A.; Skryabin, G. A.; Beletskaya, I. P. *Synthesis* **2006**, 533−539.

(22) Ge, S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 12837−12841.

(23) Zhao, Y.-L.; Li, Y.; Li, S.-M.; Zhou, Y.-G.; Sun, F.-Y.; Gao, L.-X.; Han, F.-S. *Adv. Synth. Catal.* **2011**, *353*, 1543−1550.

(24) For the bite angle data of phosphines see: (a) Dierkes, P.; Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1519−1529. (b) Freixa, Z.; Leeuwen, P. W. N. M. *Dalton Trans.* **2003**, 1890−1901.

(25) (a) Percec, V.; Bae, J.-Y.; Zhao, M.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 176−185. (b) Galland, J.-C.; Savignac, M.; Genêt, J.-P. *Tetrahedron Lett.* **1999**, *40*, 2323−2326. (c) Yu, X.; Yang, T.; Wang, S.; Xu, H.; Gong, H. *Org. Lett.* **2011**, *13*, 2138−2141. (d) Qian, Q.; Zang, Z.; Wang, S.; Chen, Y.; Lin, K.; Gong, H. *Synlett* **2013**, 619−624.

(26) Inada, K.; Miyaura, N. *Tetrahedron* **2000**, *56*, 8657−8660.

(27) One reviewer suggests that a C═O--Ni interaction in the oxidation addition product, which might stabilize this intermediate, also could lead to the low yield of **3am**.

(28) (a) Kawashima, T.; Yamashita, N.; Okazaki, R. *J. Am. Chem. Soc.* **1995**, *117*, 6142−6143. (b) Kawashima, T.; Okazaki, R. *Synlett* **1996**, 600−608. (c) Ibrahim, M. R. *J. Comput. Chem.* **1992**, *13*, 423−428. (d) One reviewer suggests that a six-membered ring involving H-bonding O—H-OB may be an alternative explanation.

(29) Dong, C.-G.; Hu, Q.-S. *J. Am. Chem. Soc.* **2005**, *127*, 10006−10007.

(30) (a) Burnier, M. *Circulation* **2001**, *103*, 904−912. (b) Liefde, I. V.; Vauquelin, G. *Mol. Cell. Endocrinol.* **2009**, *302*, 237−242. (c) de Gasparo, M.; Catt, K. J.; Inagami, T.; Wright, J. W.; Unger, T. *Pharmacol. Rev.* **2000**, *52*, 415−472.

(31) In Sigma-Aldrich catalog, Pd(OAc)$_2$ in (¥37000/100 g) is about 50 times more expensive than anhydrous NiCl$_2$ (¥1800/250 g). In fact, according to the current market price for nickel ($6−7/lb) and palladium metal (about $700/oz), palladium is about 1500 times more expensive than nickel.