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Triphenylphosphine as Ligand for Room Temperature Ni(0)-Catalyzed Cross-Coupling Reactions of Aryl Chlorides with Arylboronic Acids

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Abstract

Room temperature Ni(0)-catalyzed cross-coupling reactions of deactivated aryl chlorides with arylboronic acids with inexpensive triphenylphosphine (PPh₃) as a supporting ligand have been accomplished in good to excellent yields. Air-stable Ni(PPh₃)₂Cl₂ has also been established as catalyst precursor and highly active nickel catalysts were obtained when the reduction of Ni(PPh₃)₂Cl₂ with *n*-BuLi was carried out in presence of an aryl chloride.

Room temperature Pd(0)-catalyzed Suzuki-Miyaura cross-coupling reactions involving deactivated aryl chlorides as coupling partners represent a remarkable advance in organometallic chemistry in recent years.¹⁻⁸ Sterically hindered, electron-rich monodentate ligands such as *tert*-Bu₃P¹ and dialkylarylphosphines,^{2,3} and *N*-heterocyclic carbenes^{4,5} have been demonstrated as a privileged group of ligands for reported catalyst systems. The bulkiness and electron-richness of these monodentate ligands are believed to be essential for the observed fast oxidative addition and reductive elimination rates. Less bulky and less electron-rich monophosphines such as PPh₃ have thus been considered as inappropriate ligands for room temperature Suzuki-Miyaura cross-couplings of deactivated aryl chlorides. In fact, their application as efficient ligands for room temperature Pd(0)- or Ni(0)-catalyzed Suzuki-Miyaura cross-couplings of deactivated aryl chlorides has not been established, although they have been employed as ligands for Ni(0)-catalyzed Suzuki cross-coupling reactions at elevated temperature.^{1,9-11} In our laboratory, we are interested in developing highly active, cost-effective Pd(0) and Ni(0) catalysts for cross-coupling reactions involving challenging substrates including deactivated aryl chlorides and aryl/alkenyl tosylates.^{7,12} On the basis of previously reported results include: (a) nickel is smaller and more nucleophilic than palladium which suggested that the ligand bulkiness and electron-richness requirement for nickel might not be as stringent as that for palladium; and (b) Ni(PPh₃)₃ undergoes oxidative addition with deactivated aryl chlorides at room temperature;¹³ we reasoned that less bulky and less electron-rich monophosphines such as PPh₃ might be suitable ligands for room temperature Ni(0)-catalyzed Suzuki cross-couplings of deactivated aryl chlorides. Here, we established such possibility.

Ni(PPh₃)₂Cl₂-catalyzed cross-couplings of deactivated aryl chlorides with arylboronic acids at elevated temperature (80–100 °C) have been previously reported.^{1,10,11} Based on the fact that Ni(PPh₃)₂Cl₂- and Ni(acac)₂/PPh₃-catalyzed cross-coupling reactions of aryl chlorides with Grignard reagents, which are believed to have the same oxidative addition step as that of the Suzuki cross-coupling, occurred at room temperature,¹⁴ we believed that the elevated

temperature requirement for $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ -catalyzed cross-couplings of deactivated aryl chlorides with arylboronic acids might mainly serve the purposes of generating the catalytically active $\text{Ni}(0)$ species in situ. Because the catalytically active $\text{Ni}(0)$ species could be readily accessible from either commercially available $\text{Ni}(0)$ complexes such as $\text{Ni}(\text{COD})_2$ or reduction of $\text{Ni}(\text{II})$ complexes at room temperature, we reasoned that the difficulty to employ PPh_3 as efficient room temperature ligand might lie in how to realize the transmetallation/reductive eliminations at room temperature. Our experience in this field suggested that it would be possible if the right combination of solvent and base was employed.^{7,12} We thus screened different solvents and bases for $\text{Ni}(\text{COD})_2/\text{PPh}_3$ -catalyzed cross-coupling of *p*-tolyl chloride with phenylboronic acid, and the results are shown in Table 1. We found that moderate conversions were observed for dioxane and toluene, which are excellent solvents when $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ was the catalyst at elevated temperature.¹⁰ THF and DMF were found to be the best solvents (Table 1, entries 4, 6). Among the bases screened, K_3PO_4 gave the best results (Table 1, entry 6). We further established that the catalyst derived from a 1 : 2 ratio of $\text{Ni}(\text{COD})_2$ and PPh_3 gave the best results (Table 2, entries 2-5). We have also tested $\text{Ni}(\text{PPh}_3)_4$ as catalyst, and our results showed that its efficiency was comparable to that of $\text{Ni}(\text{COD})_2/\text{PPh}_3$ system (Table 2, entry 6).

Our success in using PPh_3 as ligand prompted us to investigate other commercially available phosphines for this transformation and our results are also listed in Table 2. We found that bidentate phosphines including 1,1'-bis(diphenylphosphino)ferrocene (DPPF), which has been demonstrated as an active ligand at elevated temperature for this transformation,^{10b,c} were poor ligands (Table 2, entries 7, 8). Among the monophosphines tested, only tricyclohexylphosphine showed a similar efficiency to PPh_3 . Other monophosphines, bulkier and/or more electron-rich than PPh_3 , only gave low to moderate conversions. These results suggested that both the size and electron-richness of the monophosphine play important roles in generating highly active room temperature $\text{Ni}(0)$ catalyst systems.

Under our established reaction condition ($\text{Ni}(\text{COD})_2/\text{PPh}_3$ as catalyst, THF as solvent and K_3PO_4 as base), electron-rich, as well as electron-deficient, aryl chlorides with one or none substituent at the *ortho* position coupled efficiently with arylboronic acids and our results are shown in Table 3. However, very sterically hindered 1-chloro-2,6-dimethylbenzene was found to be inert substrate (Table 3, entry 12). For comparison purposes, a catalyst derived from more electron-rich PCy_3 , i.e., $\text{Ni}(\text{COD})_2/\text{PCy}_3$, has also been studied and the data are also listed in Table 3. Our study showed that although the overall efficiency of $\text{Ni}(\text{COD})_2/\text{PPh}_3$ is comparable to that of the $\text{Ni}(\text{COD})_2/\text{PCy}_3$ system, our NMR study suggested that these two catalyst systems behave differently towards the oxidative addition with 4-chloroanisole. We found that $\text{Ni}(\text{COD})_2/4 \text{ PCy}_3$ smoothly underwent oxidative addition with 4-chloroanisole to yield the oxidative addition product, which reacted with phenylboronic acid to give the coupling product in 100% conversion. This oxidative addition product was observed as the intermediate when mixing $\text{Ni}(\text{COD})_2$, PCy_3 , $\text{PhB}(\text{OH})_2$ and K_3PO_4 in THF to give the coupling product, suggesting that the oxidative addition step should not be the slow step. In contrast, although $\text{Ni}(\text{PPh}_3)_3$ was reported to undergo oxidative addition with 4-chloroanisole at room temperature,¹³ we were unable to obtain the oxidative addition product pure form. ^1H NMR showed that the oxidative addition was slow and the oxidative addition product started to decompose before the reaction completed. However, $\text{Ni}(\text{COD})_2/\text{PPh}_3$ catalyst did catalyze the cross-coupling reaction of *p*-chloroanisole with phenylboronic acid (Table 3). These observations suggest that the oxidative addition step in $\text{Ni}(\text{COD})_2/\text{PPh}_3$ catalyst system might be the rate-determining one.

Since $\text{Ni}(\text{COD})_2$ is more expensive and air-sensitive than $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$, we also sought to use $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ as catalyst precursor for the reaction. We found that although $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$, $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2/\text{Zn}$ ¹⁵ were ineffective catalysts, the catalyst generated from $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2/n\text{-BuLi}$

10b,d was as efficient as that of Ni(COD)₂/PPh₃ (Table 3, entries, 2, 4). Interestingly, we observed that the catalytic property of the nickel species generated from the reduction of Ni(PPh₃)₂Cl₂ with *n*-BuLi was highly dependent on how it was produced: the reduction of Ni(PPh₃)₂Cl₂ with *n*-BuLi in presence of aryl chloride generated highly active catalyst, while catalytically inactive species were obtained when the reduction of Ni(PPh₃)₂Cl₂ with *n*-BuLi was carried out in absence of aryl chloride. Such phenomena suggested that the newly generated low valent nickel species could not be stabilized by monodentate PPh₃ alone and could aggregate if no trapping reagent - aryl chlorides, which could undergo oxidative addition with the new generated nickel species - was present. These observations were consistent with reported results of cross-coupling reactions carried out at elevated temperature that catalysts generated from *in situ* reduction of Ni(DPPF)Cl₂ with *n*-BuLi or Grignard reagents were more efficient catalysts than that from Ni(PPh₃)₂Cl₂ because bidentate DPPF might stabilize the *in situ* generated nickel catalysts better than monodentate PPh₃.^{10,16}

In summary, we have demonstrated that widely available, inexpensive PPh₃ as well as PCy₃ can be used as efficient ligands for room temperature Ni(0)-catalyzed cross-coupling reactions of deactivated aryl chlorides with arylboronic acids, a process that previously required the use of expensive, bulky, electron-rich monophosphines and *N*-heterocyclic carbenes. We have also established that air-stable Ni(PPh₃)₂Cl₂ can be used as catalyst precursor and observed that the catalytic properties of the *in situ* generated nickel catalyst is highly dependent on how it was generated, with highly active nickel catalyst obtained when the reduction of Ni(PPh₃)₂Cl₂ with *n*-BuLi was carried out in presence of an aryl chloride.

Experimental Section

General procedure for the Suzuki couplings of aryl chlorides with arylboronic acids

Method A

In a glove box with N₂ atmosphere, to a mixture of phenylboronic acids (0.75 mmol), potassium phosphate (1.5 mmol), aryl chloride (0.5 mmol) and 2 ml THF (in a vial) were added bis(1,5-cyclooctadiene)nickel(0) (5.5 mg, 0.02 mmol) and triphenylphosphine (11 mg, 0.04 mmol). The mixture was allowed to stir for 30 hours. After quenching with water, the reaction mixture was extracted with ethyl acetate. The organic phase was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on the silica gel (hexane acetate = 100:0 to 85:15) yielded the cross-coupling products.

Method B

In a glove box with N₂ atmosphere, to a mixture of bis(triphenylphosphine) nickel(II) chloride (13 mg, 0.02 mmol), aryl chloride (0.5 mmol) and 2 ml THF (in a vial) were added *n*-Butyllithium (20 μ l, 2.5 M in hexane). After stirring for 10 minutes (the solution turned to deep red), phenylboronic acid (0.75 mmol) and potassium phosphate (1.5 mmol) were added. The mixture was allowed to stir for 30 hours. After quenching with water, the reaction mixture was extracted with ethyl acetate. The organic phase was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on the silica gel (hexane acetate = 100:0 to 85:15) yielded the cross-coupling products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. For a recent review: Littke AF, Fu GC. *Angew. Chem., Int. Ed* 2002;41:4176–4211.
2. Recent examples: (a) Barder TE, Walker SD, Martinelli JR, Buchwald SL. *J. Am. Chem. Soc* 2005;127:4685–4696. [PubMed: 15796535] (b) Walker SD, Barder TE, Martinelli JR, Buchwald SL. *Angew. Chem., Int. Ed* 2004;43:1871–1876.
3. For other recent examples: (a) Zapf A, Jackstell R, Rataboul F, Riermeier T, Monsees A, Fuhrmann C, Shaikh N, Dingerdissen U, Beller M. *Chem. Commun* 2004:38–39. (b) Kataoka N, Shelby Q, Stambuli JP, Hartwig JF. *J. Org. Chem* 2002;67:5553–5566. [PubMed: 12153253]
4. Recent reviews: (a) Herrmann WA. *Angew. Chem., Int. Ed* 2002;41:1290–130. (b) Hillier AC, Grasa GA, Viciu MS, Lee HM, Yang C, Nolan SP. *J. Organometallic Chem* 2002;653:69–82.
5. For recent examples: (a) Singh R, Viciu MS, Kramareva N, Navarro O, Nolan SP. *Org. Lett* 2005;7:1829–1832. [PubMed: 15844917] (b) Song C, Ma Y, Chai Q, Ma C, Jiang W, Andrus MB. *Tetrahedron* 2005;61:7438–7446. (c) Navarro O, Oonishi Y, Kelly RA, Stevens ED, Briel O, Nolan SP. *J. Organomet. Chem* 2004;689:3722–3727. (d) Altenhoff G, Goddard R, Lehmann CW, Glorius F. *J. Am. Chem. Soc* 2004;126:15195–15201. [PubMed: 15548016] (e) Navarro O, Kelly RA, Nolan SP. *J. Am. Chem. Soc* 2003;125:16194–16195. [PubMed: 14692753] (f) Altenhoff G, Goddard R, Lehmann CW, Glorius F. *Angew. Chem., Int. Ed* 2003;42:3690–3693.
6. Mukerjee A, Sarkar A. *Tetrahedron Lett* 2005;46:15–18.
7. Hu Q-S, Lu Y, Tang Z-Y, Yu H-B. *J. Am. Chem. Soc* 2003;125:2856–2857. [PubMed: 12617635]
8. Roca FX, Richards CJ. *Chem. Commun* 2003:3002–3003.
9. Grushin VV, Alper H. *Chem. Rev* 1994;94:1047–1062.
- 10(a). Inada K, Miyaura N. *Tetrahedron* 2000;56:8657–8660. (b) Saito S, Oh-tani S, Miyaura N. *J. Org. Chem* 1997;62:8024–8030. [PubMed: 11671907] (c) Indolese AF. *Tetrahedron Lett* 1997;38:3513–3516. (d) Saito S, Sakai M, Miyaura N. *Tetrahedron Lett* 1996;37:2993–2996.
- 11(a). For a review on nickel-on-charcoal with PPh₃ as ligand: Lipsitz BH. *Adv. Synth. Catal* 2001;343:313–326. (b) For an example of Ni(0)/bisphosphine-catalyzed Suzuki cross-couplings of aryl chlorides at elevated temperature: Percec V, Golding GM, Smidrkal J, Weichold O. *J. Org. Chem* 2004;69:3447–3452. [PubMed: 15132555]
- 12(a). Tang Z-Y, Hu Q-S. *J. Am. Chem. Soc* 2004;126:3058–3059. [PubMed: 15012129] (b) Tang Z-Y, Hu Q-S. *Advan. Synth. & Catal* 2004;346:1635–1637.
13. Hidai M, Kashiwagi T, Ikeuchi T, Uchida Y. *J. Organomet. Chem* 1971;30:279–282.
14. For examples: (a) House HO, Hrabie JA, VanDerveer D. *J. Org. Chem* 1986;51:921–929. (b) Pridgen LN. *J. Org. Chem* 1982;47:4319–4323. (c) Tiecco M, Testaferri L, Tingoli M, Wenkert DC. *Tetrahedron Lett* 1982;23:4629–4632.
15. For Ni(PPh₃)₂Cl₂/Zn as catalyst at elevated temperature: (a) Kende AS, Liebeskind LS, Braitsch DM. *Tetrahedron Lett* 1975:3375–3378. (b) Percec V, Bae J-Y, Zhao M, Hill DH. *J. Org. Chem* 1995;60:176–185.
16. For examples of nickel catalysts generated from *in situ* reduction of Ni(II) complexes by Grignard reagents: (a) Wolfe JP, Buchwald SL. *J. Am. Chem. Soc* 1997;119:6054–6058. (b) Tamao K, Sumitani K, Kiso Y, Zembayashi M, Fujioka A, Kodama S-I, Nakajima I, Minato A, Kumada M. *Bull. Chem. Soc. Jpn* 1976;49:1958–1969.

Table 1Solvent and Base Optimization^a

entry	solvent	base	conversion (%)
1	Dioxane	K ₃ PO ₄	27
2	Toluene	K ₃ PO ₄	41
3	CH ₂ Cl ₂	K ₃ PO ₄	0
4	DMF	K₃PO₄	82
5	DMA	K ₃ PO ₄	78
6	THF	K₃PO₄	83
7	THF	KF	54
8	THF	CsF	42
9	THF	Na ₂ CO ₃	12
10	THF	KOH	54
11	THF	Cs ₂ CO ₃	36
12	THF	K ₂ CO ₃	64

^aReaction conditions: tolyl chloride (1.0 equiv), phenylboronic acid (1.5 equiv), base (3 equiv), solvent (2 mL), room temperature.

Table 2Room Temperature Nickel(0)-Catalyzed Cross-Couplings of *p*-Tolyl Chloride with Phenylboronic Acid ^a

entry	catalyst	conversion (%)
1	Ni(COD) ₂	0
2	Ni(COD) ₂ + PPh ₃	44
3	Ni(COD)₂ + 2 PPh₃	83
4	Ni(COD) ₂ + 3 PPh ₃	78
5	Ni(COD) ₂ + 4 PPh ₃	70
6	(PPh ₃) ₄ Ni	77
7	Ni(COD) ₂ + 1-2 DPPF	9-13
8	Ni(COD) ₂ + 2 DPPE ^b	3
9	Ni(COD)₂ + 1-4 Cy₃P	74-88
10	Ni(COD) ₂ + 1-4 <i>n</i> -Bu ₃ P	35-50
11	Ni(COD) ₂ + 1-4 <i>i</i> -Bu ₃ P	24-40
12	Ni(COD) ₂ + 1-4 <i>t</i> -Bu ₃ P	0
13	Ni(COD) ₂ + 1-2 <i>o</i> -Tolyl ₃ P	21-43

^a Reaction conditions: aryl chlorides (1.0 equiv), phenylboronic acid (1.5 equiv), K₃PO₄ (3 equiv), THF (2 mL), room temperature.^b DPPE: 1,2-bis(diphenylphosphino)ethane.

Table 3Room Temperature Nickel(0)-Catalyzed Cross-Couplings of Aryl Chlorides with Arylboronic Acids ^a

$\text{Ar}-\text{Cl} + (\text{HO})_2\text{B}-\text{Ar}' \xrightarrow[\text{K}_3\text{PO}_4, \text{THF, rt, 30 h}]{4\%\text{Ni(COD)}_2/\text{Phosphine}} \text{Ar}-\text{Ar}'$				
Yield (%) ^b				
Entry	Ar-X	Ar'-B(OH) ₂	8% PPh ₃	16% PCy ₃
1			91	95
2			88 ^c	-
3			92	92
4			90 ^c	-
5			80	77
6			98	99
7			95	92
8			93	86
9			90	92
10			87	80
11			89	-
12			0	

^a Reaction conditions: aryl chlorides (1.0 equiv.), arylboronic acids (1.5 equiv), Ni(COD)₂/PPh₃ (4 mol%/8 mol%) or Ni(COD)₂/PCy₃ (4 mol%/16 mol %), K₃PO₄ (3 equiv), THF (2 mL), room temperature.

^b Isolated yields (average of two runs).

^c 4 mol% Ni(PPh₃)₂Cl₂/*n*-BuLi was used as catalyst.