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N-Heterocyclic carbene/phosphite synergistically assisted Pd/C-catalyzed Suzuki coupling of aryl chlorides

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An *N*-heterocyclic carbene and phosphite synergistically enhanced Pd/C catalyst system has been developed for Suzuki coupling of aryl chlorides and aryl boronic acids from commercially available Pd/C with sterically demanding *N*,*N*'-bis (2,6-diisopropylphenyl)imidazolylidene and trimethylphosphite. A remarkable increase in catalytic activity of Pd/C was observed when used along with 1 equiv. *N*,*N*'-bis(2,6-diisopropylphenyl)imidazolium chloride and 2 equiv. phosphite with respect to palladium in appropriate solvents that were found to play a crucial role in Pd/C-NHC-P(OR)₃-catalyzed Suzuki coupling. A dramatic *ortho*-substitution effect of carbonyl and nitrile groups in aryl chlorides was observed and explained by a modified quasi-heterogeneous catalysis mechanism. The Pd/C catalyst could be easily recovered from reaction mixtures by simple filtration and only low palladium contamination was detected in the biparyl products. A practical process for the synthesis of 4-biphenylcarbonitrile has therefore been developed using the *N*-heterocyclic carbene/phosphite-assisted Pd/C-catalyzed Suzuki coupling. Copyright © 2013 John Wiley & Sons, Ltd.

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Keywords: Suzuki coupling; palladium on carbon; N-heterocyclic carbene; phosphite; aryl chloride

Introduction

Suzuki cross-coupling represents the most popular method for production of unsymmetrical biaryls because of the friendly properties of organoboronic acids, e.g. non-toxicity, air/moisture stability and tolerance of a variety of functional groups.^[1–4] Since the discovery of this reaction, innumerable improvements on the original protocol have been reported, especially with respect to catalysts, which have led to some highly efficient systems.^[5-9] Potential in industrial applications has become a major concern in further development of this technique. In this context, the use of heterogeneous palladium catalysts has attracted increasing attention because of the drawbacks of homogeneous transition metal catalysis, such as tedious catalyst separation processes, loss of expensive noble metal and residual metal impurities in the products.^[10-15] Although a variety of heterogeneous palladium catalysts have been reported for Suzuki coupling, most of them are either less active or more tedious to prepare, and/or give less reproducible results than their homogeneous counterparts. Therefore, there has been an increasing interest to use commercially available Pd/C for development of practical Suzuki coupling procedures.^[16-26] In fact, both of the commercially available reduced and unreduced Pd/C catalysts have proven to be efficient for Suzuki coupling of active aryl halides, such as aryl iodides and bromides. However, it is still a challenge to use Pd/C to catalyze Suzuki coupling of more practical aryl chlorides unless harsh conditions or extra additives, such as tetrabutylammonium bromide, were used.^[27-30] Alternatively, the activity of Pd/C has to be enhanced by the introduction of homogeneous phosphine ligands to effect a so-called quasi-heterogeneous catalysis,[31-33] which is believed to be, in fact, homogeneous catalysis of ligand-stabilized palladium species leaching from insoluble Pd/C.

Pioneered by Nolan and co-workers,^[34–36] palladium catalysts supported by single sterically demanding *N*-heterocyclic carbene (NHC) ligands have proven not only highly efficient but also more practical than air-sensitive palladium/phosphine catalysts in cross-coupling. Organ and Nolan and co-workers have further developed an elegant strategy to increase the catalytic activities of Pd/NHC catalysts by introduction of a secondary labile ancillary ligand, such as pyridines^[37–39] or phosphites.^[40] However, to the best of our knowledge, there is no report on using NHC to enhance the catalytic activity of Pd/C in Suzuki coupling. We report herein Suzuki coupling of aryl chlorides catalyzed by commercially available Pd/C with synergistic assistance from sterically demanding NHCs and phosphites in environmentally friendly alcohol solvent.

Results and Discussion

Establishment of Catalyst System

Suzuki coupling of phenylboronic acid (**1a**) with 4-chloroacetophenone (**2a**) was chosen as the model reaction using commercially available 5% Pd/C as a catalyst to screen reaction conditions (Table 1). The yields of the desired product, 4-phenylacetophenone (**3aa**), increased to 26% using 0.5 mol% palladium (5% Pd/C) and *N*,*N*'-bis(2,6-diisopropylphenyl)imidazolylidene (IPr, used

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Table 1. Suzuki coupling of 4-chloroacetophone with phenylboronic acid^a



Entry	NHC/L	Cat. mol% (Pd/NHC/L)	Solvent	Base ^b	Temp. (°C) ^c	<i>T</i> (h)	Yield (%) ^d
1	—/—	0.5/—/—	DMF	K ₃ PO ₄ .3H ₂ O	110	10	4
2	IPr/—	0.5/0.5/—	DMF	K ₃ PO ₄ .3H ₂ O	110	10	26
3	IPr/P(OPh) ₃	0.5/0.5/1	DMF	K ₃ PO ₄ .3H ₂ O	110	10	53
4	IPr/P(OPh) ₃	0.5/0.5/1	Dioxane	K₃PO₄.3H₂O	100	10	98
5	IPr/P(OPh) ₃	0.5/0.5/1	<i>t</i> BuOH	K ₃ PO ₄ .3H ₂ O	80	10	62
6	IPr/P(OPh) ₃	0.5/0.5/1	<i>i</i> PrOH	K₃PO₄.3H₂O	80	10	99
7	IPr/P(OPh) ₃	0.5/0.5/1	EtOH	K ₃ PO ₄ .3H ₂ O	80	10	98
8	IPr/P(OPh) ₃	0.5/0.5/1	EtOH	K ₃ PO ₄ .3H ₂ O	80	10	31 ^e
9	IPr/P(OPh) ₃	0.5/0.5/1	EtOH	K ₂ CO ₃	80	10	28
10	IPr/P(OPh) ₃	0.5/0.5/1	EtOH	NaOH	80	6	98
11	IPr/P(OPh) ₃	0.5/0.5/1	EtOH	КОН	80	6	91
12	IPr/Py	0.5/0.5/1	EtOH	NaOH	80	10	67
13	IPr/Et ₃ N	0.5/0.5/1	EtOH	NaOH	80	10	60
14	IPr/NMI	0.5/0.5/1	EtOH	NaOH	80	10	75
15	IPr/P(OPh) ₃	0.5/0.5/2	EtOH	NaOH	80	6	97
16	IPr/P(OPh) ₃	0.5/0.5/0.5	EtOH	NaOH	80	10	95
17	IPr/P(OPh) ₃	0.5/0.5/0.25	EtOH	NaOH	80	10	49
18	IPr/P(OMe) ₃	0.5/0.5/1	EtOH	NaOH	80	4	99
19	IPr/P(OEt) ₃	0.5/0.5/1	EtOH	NaOH	80	10	83
20	IPr/P(O ⁱ Pr) ₃	0.5/0.5/1	EtOH	NaOH	80	10	79
21	—/P(OMe) ₃	0.5/—/1	EtOH	NaOH	80	10	Trace
22	IPr/—	0.5/0.5/—	EtOH	NaOH	80	10	38
23	IMes/P(OMe) ₃	0.5/0.5/1	EtOH	NaOH	80	10	64
24	SIPr/P(OMe) ₃	0.5/0.5/1	EtOH	NaOH	80	10	88
25	SIMes/P(OMe) ₃	0.5/0.5/1	EtOH	NaOH	80	10	54
26 ^f	NHC/P(OMe) ₃	0.5/0.5/1	EtOH	NaOH	80	10	/
27 ^g	NHC/P(OMe) ₃	0.5/0.5/1	EtOH	NaOH	80	10	7
28	IPr/P(OMe) ₃	0.3/0.3/0.6	EtOH	NaOH	80	7	96
29	IPr/P(OMe) ₃	0.2/0.2/0.4	EtOH	NaOH	80	10	87
30	IPr/P(OMe) ₃	0.1/0.1/0.2	EtOH	NaOH	80	10	13
31 ^h	IPr/P(OMe) ₃	0.5/0.5/1	EtOH	NaOH	80	4	98
32 ⁱ	IPr/P(OMe) ₃	0.5/0.5/1	EtOH	NaOH	80	4	95

^aReaction run at 1 mmol scale with 5% Pd/C (Sinopharm Chemical Reagent), IPr used in form of IPr.HCl.

^b2.0 equiv. K₃PO₄.3H₂O or K₂CO₃ or 1.3–1.4 equiv. KOH or NaOH.

^cBath temperature.

^dlsolated yields.

^e5% H₂O in EtOH.

 $^{f}NHC = N, N'$ -bis(butyl)imidazolylidene and no reaction detected.

 g NHC = *N*,*N*'-bis(butyl)benzimidazolylidene.

^h5% Pd/C from Alfa Aesar.

ⁱ5% Pd/C from Acros.

in the form of IPr.HCl with Pd/IPr = 1:1 mol/mol) from 4% using Pd/C alone under a condition, K_3PO_4 in DMF, that has proven compatible for homogeneous NHC-Pd(OAc)₂ or NHC-PdCl₂ systems.^[41] With the assistance of a secondary ancillary ligand – triphenylphosphite (2.0 equiv. relative to palladium) – the yield of **3aa** further increased to 53% under otherwise identical

conditions (Table 1, entries 1–3). It is well known that bis (NHC) palladium complexes are overwhelmingly dominating species in solution in the presence of excess NHC but generally show low catalytic activities in Suzuki coupling. Therefore, considering the quasi-heterogeneous catalysis of Pd/C in Suzuki coupling,^[31–33] the unsatisfactory performance of Pd/C-IPr-P

(OPh)₃ in the preliminary investigation may be attributed to the favorable formation of bis(NHC) palladium complexes (IPr)₂Pd over more active heteroligated $(IPr)Pd[P(OR)_3]_n$, since only a small portion of palladium generally leaches into solution from Pd/C, while a large excess IPr relative to the leached palladium would be possibly present in solution. We anticipated that an appropriate solvent, in which the NHC (IPr) and/or its precursor (IPr.HCI) are also mainly absorbed on to carbon, would solve the problem. In fact, solvents did affect the catalytic activity of Pd/C-NHC-P(OPh)₃ significantly. When the model reaction was run in dioxane, the yield of 3aa increased to 98% under otherwise identical conditions (Table 1, entry 4). We have recently reported a highly efficient homogeneous Pd/NHC/P(OPh)₃ catalyst system for Suzuki coupling of diaryl borinic acids using K₃PO₄.3H₂O as base in tert-BuOH.^[42] Therefore, we tested alcohol solvents for the Pd/C-IPr-P(OPh)₃ catalyst system. Although it occurred less efficiently in tert-BuOH, the model reaction proceeded as well in environmentally friendly alcohol solvents – isopropanol and ethanol – as in dioxane (Table 1, entries 5–7). No reaction took place when water was used as solvent. In fact, water appeared to be deleterious to the catalytic activity of Pd/C-IPr-P(OPh)₃ even in alcohol solution. However, no extra step was needed to remove water from commercial solvents for the model reaction. Stronger bases, especially cheap NaOH and KOH, also performed well with appropriate stoichiometry (1.3 equiv.), while the reaction proceeded much more slowly with a weaker base such as K₂CO₃. N-containing ancillary ligands, such as 3-chloropyridine (3-CIPy),^[37-39] Et₃N (TEA)^[43] and N-methylimidazole (NMI),^[44-47] have been reported to remarkably improve the efficiency of homogeneous Pd-NHC catalyst systems in various cross-couplings. For example, the desired biaryls could be obtained in excellent yields from Suzuki coupling of aryl chlorides by using the structurally well-defined complexes (IPr)PdCl₂(TEA)^[43] or (IPr)PdCl₂(NMI)^[46] as catalysts even at room temperature, while the seminal (IPr) PdCl₂(3-ClPy)^[9,37,39] performed better in Kumada and Negishi couplings. However, these N-containing ancillary ligands appeared to be less compatible with Pd/C in the model reaction, giving product 3aa only in modest yields (Table 1, entries 12-14). The success of phosphites possibly benefits from a ligand synergy between the σ -donor NHC and π -acceptor phosphite originally proposed by Jamison and co-workers.^[48]

The influence of structure and stoichiometry of phosphites on the catalytic activity of the Pd/C-IPr-P(OR)₃ catalyst system was investigated. The system performed consistently well with more than 1 equiv. of $P(OPh)_3$ (1–4 equiv.) with respect to Pd/C-IPr loading, while lower stoichiometry, such as 0.5 equiv. P(OPh)₃, showed little effect compared with the Pd/C-IPr combination alone (Table 1, entries 7 and 15-17). The smallest-volume phosphite, P(OMe)₃, showed a slightly higher activity than P(OPh)₃, while P(OEt)₃ and P(O^IPr)₃ worked less efficiently in the system (Table 1, entries 18-20). Compared with the results of control experiments using Pd/C-P(OR)₃ and Pd/C-IPr catalyst systems, the enhanced catalytic efficacy of Pd/C-IPr-P (OR)₃ to aryl chlorides implied that the true catalytic species should be palladium co-supported by NHC and phosphite (NHC)Pd[P(OR)₃]_n (Table 1, entries 21 and 22). From a practical point of view, trimethylphosphite P(OMe)₃ has an obvious advantage over P(OPh)₃ with respect to cost owing to its higher atom economy and lower price. The structure of NHCs proved more crucial than that of phosphites to the activity of the Pd/C-NHC-P(OR)₃ catalyst system. With use of less sterically demanding N,N'-bis(mesityl)imidazolylidene (IMes), both the

rate and product yield of the model reaction decreased significantly, while only trace product **3aa** was detected or isolated with simple NHCs of N,N'-bis(butyl)imidazolylidene and N,N'bis(butyl)benzimidazolylidene under otherwise identical conditions. The saturated analogues of sterically demanding NHCs -N,N'-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene (SIPr) and N,N'-bis(mesityl)phenyl)-4,5-dihydroimidazol-2-ylidene (SIMes) – also displayed lower activity (Table 1, entries 23-27). Reducing the loading of Pd/C-IPr-P(OMe)₃ catalyst system from 0.5 to 0.2 mol%, the product yields decreased slightly from 98% to 87%. In fact, 0.3 mol% palladium loading appeared to be sufficient to obtain the coupling product **3aa** in excellent yield (96%), although the model reaction failed to complete with 0.1 mol% catalyst loading (Table 1, entries 28-30). Pd/C catalysts from different commercial sources showed negligible influence on the activity of the Pd/C-IPr-P(OMe)₃ catalyst system (Table 1, entries 31 and 32).

Scope and Limitation

The scope of the Pd/C-IPr-P(OMe)₃-catalyzed Suzuki coupling was investigated under the optimized conditions (Table 2). Electronrich (deactivated) aryl chlorides reacted with more difficulty than electron-deficient (activated) ones and gave products in poor yields unless a higher loading (1 mol%) of palladium was used. An ortho hetero-atom containing unsaturated groups, such as carbonyls and nitrile, on the aromatic ring of aryl chlorides unexpectedly blocked the Pd/C-IPr-P(OMe)₃-catalyzed Suzuki coupling. For example, almost no reaction was detected for 2-chloroacetophenone (2c) or even the highly active 2bromoacetophenone (2d), although 3-chloroacetophenone (2b) reacted well, similar to 4-chloroacetophenone (2a), to give crosscoupling product **3ab** in 95% yield under otherwise identical conditions (Table 2, entries 1–5). Similarly, 3- or 4-chlorobenzonitriles reacted smoothly, while 2-chlorobenzonitrile failed (Table 2, entries 8-15). Control experiments indicated that the orthosubstituent effect should be attributed to the heterogeneous palladium source, since the reactions of 2-chloroacetophenone (2c) and 2-chlorobenzonitrile (2h) occurred to provide the desired products **3ac** and **3ah**, respectively, in excellent yields using Pd (OAc)₂ (94%, 95%) or PdCl₂ (93%) as palladium source for the Pd-IPr-P(OMe)₃ catalyst system (Table 2, entries 6, 7 and 16). Surprisingly, this ortho-substituent effect would appear not to be from a simple steric hindrance associated with heterogeneous catalyst. The reaction of 2-chlorotoluene (2i) proceeded as smoothly as that of 4-chlorotoluene (21) and even the deactivated 2-methoxyphenyl chlorides reacted with 1 mol% catalyst loading to give **3ak** (41%) (Table 2, entries 17-22). These results implied that the substituent nature beyond steric hindrance, e.g. absorption on carbon,^[27,49] may also play a key role.

Electronic and steric effects from aryl boronic acids on the Pd/C-IPr-P(OMe)₃-catalyzed reaction were also investigated. In contrast to aryl chlorides, the electronic effect of aryl boronic acids on the Pd/C-IPr-P(OMe)₃-catalyzed Suzuki reaction was rather small except for the proton-deboronation side reaction of electron-deficient aryl boronic acids, which could be compensated for by slightly increasing the loading of aryl boronic acids. For example, all the investigated aryl boronic acids with an electron-donating or -withdrawing group at the *para* position on the aromatic ring, e.g. methyl (Me, 92%), methoxyl (MeO, 96%), fluoro (F, 90%), acetyl (Ac, 78–95%) and cyano

Table 2.	Scope of the cross-coupling of aryl boronic acids with aryl chlorides ^a									
	B(OH)2 B		Pd/C-IPr HCI-P(OMe) ₃ (1/1/2, mol/mol) NaOH (1.3equiv.) EtOH 80°C							
		R ₁	+ 112 <u></u>		3ab-3ia	2				
		1a-f	2a-0							
Entry	R ¹ (1)	Х	R ² (2)	Pd (mol%)	Time (h)	3	Yield (%) ^b			
1	H(1 a)	CI	3-COMe(2b)	0.3(Pd/C)	4	3ab	95			
2	H(1a)	CI	2-COMe(2c)	0.3(Pd/C)	4	3ac	8 ^c			
3	H(1a)	CI	2-COMe(2c)	0.3(Pd/C)	4	3ac	17 ^{c,d}			
4	H(1a)	CI	2-COMe(2c)	0.3(Pd/C)	4	3ac	9 ^{c,e}			
5	H(1a)	Br	2-COMe(2d)	0.03(Pd/C)	4	3ac	5 ^c			
6	H(1a)	CI	2-COMe(2c)	0.3(PdCl ₂)	3	3ac	93			
7	H(1a)	CI	2-COMe(2c)	$0.3(Pd(OAc)_2)$	3	3ac	94			
8	H(1a)	CI	4-CN(2e)	0.3(Pd/C)	3	3ae	93			
9	H(1 a)	CI	4-CN(2e)	0.3(Pd/C)	3	3ae	97 ^e			
10	H(1a)	CI	4-CN(2e)	0.3(Pd/C)	3	3ae	95 ^d			
11	H(1 a)	Br	4-CN(2f)	0.03(Pd/C)	1	3ae	98			
12	H(1a)	CI	3-CN(2g)	0.3/(Pd/C)	6	3aq	82			
13	H(1a)	CI	2-CN(2h)	0.3/(Pd/C)	6	3ah	7 ^c			
14	H(1a)	Cl	2-CN(2h)	0.3/(Pd/C)	6	3ah	4 ^{c,e}			
15	H(1a)	Cl	2-CN(2h)	0.3/(Pd/C)	6	3ah	11 ^{c,d}			
16	H(1a)	Cl	2-CN(2h)	0.3(Pd(OAc) ₂)	3	3ah	95			
17 ^f	H(1a)	Cl	2-Me(2i)	1(Pd/C)	10	3ai	86			
18	H(1a)	Br	2-Me(2j)	0.03(Pd/C)	6	3ai	96			
19	H(1a)	Cl	2-OMe(2k)	1(Pd/C)	10	3ak	41			
20 ^f	H(1a)	Cl	4-Me(2I)	1(Pd/C)	10	3al	82			
21	H(1a)	Cl	4-OMe(2m)	0.3(Pd/C)	10	3am	31			
22	H(1a)	Cl	4-OMe(2m)	1(Pd/C)	10	3am	73			
23	H(1a)	Cl	4-CO ₂ Me(2n)	0.3(Pd/C)	5	3an	95 ^g			
24	H(1a)	Cl	3-CO ₂ Et(20)	0.3(Pd/C)	5	3ao	89			
25	4-Me(1b)	Cl	4-COMe(2a)	0.3(Pd/C)	8	3ba	92			
26	2-Me(1c)	Cl	4-COMe(2a)	0.3(Pd/C)	10	3ca	74			
27	2-Et(1d)	Cl	4-COMe(2a)	0.3(Pd/C)	10	3da	53			
28	4-F(1e)	Cl	4-COMe(2a)	0.3(Pd/C)	8	3ea	90			
29	4-OMe(1f)	Cl	4-COMe(2a)	0.3(Pd/C)	8	3fa	96			
30	4-COMe(1g)	Cl	4-COMe(2a)	0.3(Pd/C)	5	3ga	78(95) ^h			
31	4-CN(1h)	Cl	4-COMe(2a)	0.3(Pd/C)	5	3ha	65(86) ^h			
32	2-COMe(1i)	Cl	4-COMe(2a)	0.3(Pd/C)	5	3ia	Trace ^c			
33	2-COMe(1i)	Cl	4-COMe(2a)	0.3(Pd(OAc) ₂)	5	3ia	30 ^c			

^aReaction run at 1 mmol scale with 5% Pd/C (Sinopharm Chemical Reagent).

^blsolated yields.

^cArCl recovered.

^d5% Pd/C from Acros.

^e5% Pd/C from Alfa Aesar.

^f3 equiv. aryl chloride relative to aryl boronic acid due to its low bp.

^gEthyl biphenyl-4-carboxylate isolated due to exchange with ethanol.

^h1.3 equiv. arylboronic acid used due to proton-deboronation.

(CN, 65–86%) provided the desired products in good to excellent yields (Table 2, entries 25 and 28–31). However, an obvious steric effect was observed. For example, reaction of 2-methylphenyl boronic acid with 4-chloroacetophenone **2a** gave the cross-coupling product **3ca** (74%) in significantly lower yield than **3ba** from 4-methylphenyl boronic acid (92%). The yield of cross-coupling product **3da** further decreased to 53% for the more sterically demanding 2-ethylphenyl boronic acid (**1d**) (Table 2, entries 26 and 27). 4-Acetyl and 4-cyanophenyl

boronic acids reacted with **2a** to provide **3ga** and **3ha** in good yields, respectively, although 1.3 equiv. aryl boronic acids had to be used due to proton-deboronation of electron-deficient aryl boronic acids (Table 2, entries 30 and 31). The failure of reaction of 2-acetylphenyl boronic acid (**1i**) with **2a** using the Pd/C-IPr-P (OMe)₃ system may be at least partly due to the instability of the former under the reaction conditions since a low yield (30%) was obtained even using the homogeneous catalyst system Pd(OAc)₂-IPr-P(OMe)₃.

Mechanistic Explanation

The unexpected ortho-substitution effect of carbonyl and nitrile groups in aryl halides on the Pd/C-IPr-P(OMe)₃-catalyzed Suzuki coupling appeared to be consistent with a quasi-heterogeneous catalysis proposed by Conlon, Simeone and Sowa and co-workers for ligand-assisted Pd/C catalysis.^[31,32] In the quasi-heterogeneous catalysis, Pd/C just serves as a reservoir of homogeneous ligand-stabilized palladium species that forms from the ligand and palladium leaching from the carbon frame to solution induced by oxidative addition of ArX to Pd(0) and eventually redeposits on the carbon surface as the reaction nears completion. The aryl halides with an ortho-carbonyl or nitrile substituent on the aromatic ring obviously failed to contact the active palladium site on carbon, possibly due to steric hindrance as well as absorption of the heterogeneous catalyst.^[49] Subsequently, the oxidative-addition induced leaching of palladium particles from the carbon frame to solution was blocked, which, in turn, led to failure of the catalysis. According to the quasi-heterogeneous catalysis mechanism, it is easy to anticipate that if there is an appropriate ArX in the reaction solution to induce palladium leaching from the carbon frame to solution by oxidative-addition of ArX to Pd(0), then the resulting homogeneous catalytic species would be able to catalyze the Suzuki coupling of ortho-carbonyl or nitrile-substituted aryl halides since the homogeneous catalyst systems Pd-IPr-P(OMe)₃ from Pd(OAc)₂ and PdCl₂ worked well. To test this, 4-chloroacetophenone (2a) was added on purpose to the reaction of 2-chloroacetophenone (2c) with phenylboronic acid catalyzed by 0.5 mol% Pd/C-IPr-P(OMe)₃, which had failed under otherwise identical conditions. After 10 h, the reaction was quenched and the components in the crude reaction mixture were analyzed by ¹H NMR (Scheme 1).

It can be seen that the coupling between 2-chloroacetophenone (2c) and phenylboronic acid (1a) gave the coupling product **3ac** in about 30% yield (by ¹H NMR) after 10 h when 1 mol% 4-chloroacetophenone (2a) was added to the reaction mixture, while almost no reaction occurred in the absence of 2a. However, the conversion of 2-chloroacetophenone (2c) was only slightly increased to about 50% when the amount of 2a was increased to 10 mol%. These results implied that the homogeneous catalytic palladium species forming via ligand stabilization of the leaching palladium from Pd/C could not constantly exist in solution during the reaction progress. In other words, the redeposition of homogeneous catalytic palladium species on the carbon surface should occur during the whole reaction progress instead of only taking place near completion of the

reaction as originally proposed.^[32] Therefore, the original quasi-heterogeneous catalysis mechanism has been slightly modified (Scheme 2).

In the modified mechanism, the oxidative-addition induced palladium leaching should occur at the site where palladium could be ligated by NHC at least, if not NHC and P(OR)₃ synergistically, considering the nearly complete non-activity of Pd/C in the absence of NHC (Table 1, entry 21). The homogeneous catalytic palladium species (NHC)Pd[P(OR)₃] could, at least partly, redeposit on the carbon surface throughout the progress of the reaction and has to re-leach to solution by the oxidative-addition of ArX to the Pd(0) process to start a new catalytic cycle.

Application Exploration

To demonstrate the potential of the NHC/phosphite-promoted Pd/C-catalyzed Suzuki coupling in practical applications, a process has been developed for the synthesis of 4-biphenylcarbonitrile (3ae), the key intermediate for the production of 3,6-di(biphenyl-4-yl)pyrrolo[3,4-c]pyrrole-1,4(2H,5H)-dione (C.I. DPP-264),^[50] a high-performance red pigment. Currently, 4-biphenylcarbonitrile is mainly produced on an industrial scale from biphenyl through Friedel-Crafts acylation or alkylation, followed by a set of functional group conversions, generating a lot of waste. Therefore, it is important to develop practical and environmentally friendly processes. The synthesis of 4-biphenylcarbonitrile (3ae) from 4-halobenzonitriles and phenylboronic acid via the NHC/ phosphite-promoted Pd/C-catalyzed Suzuki coupling was conducted at a 0.1 mol scale so that the desired biaryl product could be isolated by recrystallization instead of chromatography. Using the Pd/C-IPr-P(OMe)₃ catalyst system, the reaction of 4-chlorobenzonitrile with phenylboronic acid completed in 3 h under the above optimized conditions (Scheme 3). The Pd/ C catalyst was readily separated from the mixture by simple filtration along with inorganic by-products and recovered by washing with ethanol and water to remove organic and inorganic materials, respectively. Elemental analysis (inductively coupled plasma-atomic emission spectroscopy (ICP-AES)) of palladium indicated that more than 90% Pd was recovered. Unfortunately, almost no reactivity was found for the recovered

Pd/C

NHC



deactive

Pd/C³



Scheme 2. A slightly modified mechanism for the NHC/phosphite synergistically assisted Pd/C-catalyzed Suzuki coupling of aryl chlorides.



X = CI, 0.3 mol% cat., 31, 93-95% yieldsX = Br, 0.03 mol% cat., 1h, 97% yield

 $\mbox{Scheme 3.}\ \mbox{Synthesis of 4-biphenylcarbonitrile by the Pd/C-IPr-P(OMe)_3-catalyzed Suzuki coupling.}$

Pd/C in the coupling reaction possibly because of redeposition of palladium on to the carbon support that left the palladium in a different form.^[31,32,51] The filtrate was simply concentrated to afford crude **3ae**, in which the palladium residue was about 40 ppm (about 2-2.5% of the total quantity of palladium loading). The pure product **3ae** was obtained after recrystallization from ethanol as white fine crystals in 93-95% yield over repeated experiments. The palladium contamination in the product was less than 5 ppm by ICP-AES. Considering the loss of activity of recovered Pd/C catalyst in the coupling, we also investigated the reaction of 4-bromobenzonitrile with phenylboronic acid to synthesize 3ae, which required much lower loading of palladium catalyst. It was found that 0.03 mol% Pd/C-IPr-P(OMe)₃ catalyst loading with respect to 4-bromobenzonitrile was sufficient for the coupling reaction to complete within 1 h under otherwise identical conditions and provide 4-biphenylcarbonitrile (3ae) in 97% yield.

Conclusions

The catalytic activity of commercially available 5% Pd/C in Suzuki coupling of aryl chlorides has been remarkably increased by using it along with a synergistic σ -donor and π -acceptor pair of ligands: N,N'-bis(2,6-diisopropylphenyl)imidazolylidene (IPr) and trimethylphosphite. For activated aryl chlorides, the coupling reaction with aryl boronic acids could be effected to give the desired biaryl products in excellent yields with 0.3 mol% palladium (5%Pd/C) loading along with 0.3 mol% IPr.HCl and 0.6 mol% P(OMe)₃. The structure of the NHCs showed a significant impact on the activity of the Pd/C-NHC-phosphite catalyst system. The most sterically demanding N,N'-bis(2,6diisopropylphenyl)imidazolylidene performed best among the tested NHCs. A dramatic ortho-substitution effect of carbonyl and nitrile groups in aryl chlorides was observed, which could be attributed to steric hindrance and absorption associated with heterogeneous Pd/C. The original quasiheterogeneous catalysis mechanism for ligand-assisted Pd/ C-catalyzed Suzuki coupling has been modified according to the experimental results. The potential of the NHC/phosphite synergistically promoted Pd/C-catalyzed Suzuki coupling in practical applications has been demonstrated by developing a practical process for synthesis of 4-biphenylcarbonitrile, a key intermediate for production of C.I. DPP-264, from 4-halobenzonitriles and phenylboronic acid using sodium hydroxide as a base in environmentally friendly ethanol solvent. The Pd/C catalyst could be easily removed from reaction mixtures and less than 5 ppm palladium contamination was detected in the final product after one recrystallization.

Experimental

Materials and Methods

All reactions were carried out under an N₂ atmosphere unless otherwise stated. Commercially available chemicals were used as received. N,N'-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr.HCI),^[34] N,N'-bis(mesityl)imidazolium chloride (IMes.HCI),^[34] N,N'bis(butyl)imidazolium chloride,^[41] N,N'-bis(butyl)benzimidazolium chloride,^[41] N,N'-bis(2,6-diisopropylphenyl)imidazolidinium bromide (SIPr.HBr)^[52] and N,N'-bis(mesityl)imidazolidinium bromide (SIMes.HBr)^[52] were prepared according to previously reported procedures. ¹H and ¹³C NMR spectra were recorded in CDCl₃ at ambient temperature. Chemical shifts in NMR were reported in ppm (δ), relative to the internal standard of tetramethylsilane. High-resolution mass spectrometry (HRMS) was performed on an electron ionization mass spectrometer with a quadrupole analyzer. Elemental analysis (including ICP-AES) was conducted at the Analysis Center of ECUST. The known compounds were identified by their spectral data of ¹H NMR and ¹³C NMR (see supporting information), while characterization of the new compound 3da is given below.

Typical Procedure for Cross-Coupling Reactions of Aryl Chlorides

Under an N₂ atmosphere, to a 10 ml flask were added 4chloroacetophenone (130 μ l, 1.0 mmol), phenylboronic acid (0.13 g, 1.1 mmol), 5% Pd/C (0.003 mmol, 6.5 mg dried Pd/C or 13 mg wet Pd/C (containing 50% w/w water), IPr.HCl (0.003 mmol, 30 μ l of 0.1 μ stock solution in EtOH), P(OMe)₃ (0.7 μ l, 0.006 mmol), NaOH (1.3 ml, 1 μ stock solution in EtOH) and EtOH (2.0 ml). The mixture was stirred at 80°C and monitored by thin-layer chromatography until 4-chloroacetophenone was completely consumed. The reaction mixture was diluted with CH₂Cl₂ (15 ml), filtered and washed with H₂O. The organic layer was dried over Na₂SO₄, followed by filtration and solvent removal with a rotavapor to give the crude product. The pure product was obtained by column chromatography on silica gel with EtOAc/ petroleum ether.

1-(2'-Ethylbiphenyl-4-yl)ethanone (**3da**)

Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.01 (d, J = 8.4 Hz, 2H, H-3, H-5), 7.42 (d, J = 8.4 Hz, 2H, H-2, H-6), 7.34–7.33 (m, 2H, H-3', H-5'), 7.27–7.23 (m, 1H, H-4'), 7.18 (d, J = 7.2 Hz, 1H, H-6'), 2.65 (s, 3H, COCH₃), 2.59 (q, J = 7.6 Hz, 2H, CH_2), 1.09 (t, J = 7.6 Hz, 3H, CH_3); ¹³C NMR (100 MHz, CDCl₃) δ (ppm):197.9(C O), 147.1 (C-1), 141.4 (C-2'), 140.5 (C-1'), 135.6 (C-4), 129.6 (Ar), 129.5 (Ar), 128.8 (Ar), 128.2 (Ar), 128.1 (Ar), 125.8 (C-6'), 26.7 (COCH₃), 26.1 (ArCH₂), 15.7, CH_3 ; HRMS (EI) m/z (M⁺) calcd for C₁₆H₁₆O: 224.1201, found: 224.1200. Anal. for **3da**: calcd for C₁₆H₁₆O (%): C, 85.68; H, 7.19; found (%): C, 85.60; H, 7.28.

Synthesis of 4-biphenylcarbonitrile at 0.1 mol scale

Chlorobenzonitrile (13.75 g, 100 mmol), phenylboronic acid (13.40 g, 110 mmol), 5% Pd/C (0.64 g, 0.3 mmol), IPr.HCI (0.13 g, 0.3 mmol), P(OMe)₃ (70 μ I, 0.6 mmol), NaOH (5.20 g, 130 mmol) and EtOH (200 ml). The mixture was stirred at 80°C for 2 h and filtered directly. The residual solid was washed twice with hot EtOH (2 \times 20 ml). The filtrate was evaporated under reduced pressure to give a crude product, which was recrystallized from EtOH/H₂O to give 4-biphenylcarbonitrile (16.83 g, 94%).

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