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Highly efficient *N*-Heterocyclic carbene–palladium complex-catalyzed multicomponent carbonylative Suzuki reaction: novel practical synthesis of unsymmetric aryl ketones

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Highly efficient and chemoselective *N*-heterocyclic carbene palladium complexes-catalyzed multicomponent carbonyltive Suzuki reaction with sodium tetraphenylborate used as phenylating reagent has been demonstrated in this article. Both electron-rich and electron-deficient aryl iodides gave unsymmetric aryl ketones in excellent yields. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: carbonylative Suzuki reaction; *N*-Heterocyclic carbene; palladium; unsymmetric ketone

INTRODUCTION

Aryl ketones are important building blocks in the synthesis of natural products and pharmaceutical compounds.[1] Among many well-documented synthetic methods, such as Friedel–Crafts acylation of substituted aromatic rings,[2] the acylation of aryl metal species with functional carboxylic acid derivatives,[3] the transition metal-catalyzed three-component cross-coupling reaction between arylmetal reagents, carbon monoxide and aryl electrophiles is a straightforward and convenient route for the synthesis of unsymmetrical biaryl ketones.[4] Various arylmetal reagents including magnesium,[5] aluminum,[6] silicon,[7] tin[8] and boron derivatives[9] have been reported to undergo the carbonylative coupling. Organoboron compounds, which are generally nontoxic and temperature-, air- and moisture-stable, offer an obvious practical advantage compared with other cross-coupling processes. Owing to these advantages, the cross-coupling of aryl halides, carbon monoxide and organoboron reagents, the carbonylative Suzuki reaction, provides a convenient means of obtaining diaryl ketones. However, the main drawback of the carbonylative Suzuki reaction is often the significant amounts of biaryl coupled product, the result of Suzuki cross-coupling without carbon monoxide insertion, particularly with electron-deficient aryl halides.[10] Recently, Andrus and co-workers have reported the imidazolium-based Pd catalyzed carbonylative coupling of diazonium salts with boronic acids to give aryl ketone;[11] Castanet and co-workers also reported imidazolium-based Pd catalyzed carbonylative reaction to give pyridyl ketone.[12] In these works it is supposed the *N*-heterocyclic carbene (NHC) palladium complex formed *in situ* were the active species. Although it is not isolated in the reaction, these reported results showed that NHC palladium complex could be an efficient catalyst in carbonylative Suzuki reaction of aryl boronic acids with aryl halide.

Transition metal complexes containing NHCs have gained a considerable reputation as homogeneous catalysts because these complexes are stable toward high temperature, air and moisture. A broad range of reactions, including Heck, Suzuki and Kumada couplings,[13] olefin metathesis,[14] telomerization[15] and hydrosilylation,[16] have been studied thoroughly using NHC–palladium complex-type catalysts. Although there are two reports of carbonylative Suzuki reaction using *in-situ* generated NHC–palladium complex-type

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catalysts with special substrates, diazonium salts or pyridyl halides with aryl boronic acids,[11,12] the development of a novel procedure for the preparation of general unsymmetric aryl ketones via NHC–palladium complex-catalyzed carbonylative Suzuki reaction is necessary. We want to develop a more practical procedure for the preparation of unsymmetric aryl ketones, via the multicomponent cross-coupling reaction of aryl halides, carbon monoxide and organoboron reagents by the NHC–Pd complex.

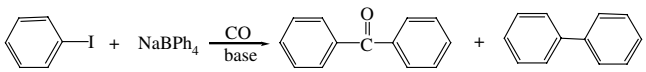
RESULTS AND DISCUSSION

First, we tried to use sodium tetraphenylborate as the phenylating reagent since sodium tetraphenylborate was very cheap and could easily be obtained in comparison to other organoboron reagents. Fortunately, as shown in Table 1, the work showed that sodium tetraphenylborate was an efficient phenylating reagent with different catalytic NHC–Pd complexes. The NHC–Pd complex **1**-catalyzed[17] carbonylative Suzuki reaction of sodium tetraphenylborate with iodobenzene showed better catalytic activity than complexes **2** and **3**. The base was critical for the selectivity of the reaction. Cs_2CO_3 was recognized to be an effective additive for preventing the formation of undesirable biaryl by-products (Table 1, entry 1). Owing to the high cost of Cs_2CO_3, we also turned our attention to screening other bases for the present reaction. K_3PO_4, Na_3PO_4, NaOH and triethylamine had a strong tendency to produce a direct coupling product due to their higher ability to accelerate the rate of transmetallation[18] (Table 1, entries 2–5). To our satisfaction, the use of K_2CO_3, an inexpensive base, resulted in the carbonylative coupled product with excellent selectivity of 97% (Table 1, entry 6).

Dioxane (1,4-dioxane) was a suitable solvent in this carbonylative Suzuki reaction (Table 1, entry 6). Other low polar solvents, such as tetrahydrofuran (THF) or toluene, could also lead to high yields with good chemoselectivity (Table 1, entries 7 and 8). On the other hand, the reaction almost did not proceed when carried out in polar solvents, such as *N*,*N*-dimethylformamide (DMF) and dimethylsulfoxide (DMSO) (Table 1, entries 10 and 11). When acetonitrile was used as solvent, acceptable conversion was obtained, but the selectivity for aryl ketone was greatly decreased (Table 1, entry 9).

It is known that the performance of homogeneous catalysts is highly dependent on the ancillary ligand coordinated to the metal center.[19] Non-NHC ligands have a remarkable effect on the properties of Pd–NHC complexes.[17] Other complexes, **2** and **3**, were also synthesized and applied to the carbonylative Suzuki reaction (Scheme 1). As show in Table 1, the catalytic activities of three types of NHC—Pd complexes (NHC–phosphine ligands in **1**, two NHC ligands in **2** and NHC–pyridine ligands in **3**) were comparable but with different chemoselectivities in the carbonylative Suzuki reaction. According to above reaction results, complex **1** with more steric bulk PPh_3 showed remarkable selectivity of ketones (97 : 3%) superior to complexes **2** and **3** (81 : 19 and 79 : 21%). These results indicate phosphine ligands have a remarkable influence on the catalytic activity of Pd–NHC

Table 1. NHC–Pd complex-catalyzed carbonylative cross-coupling of $NaBPh_4$ with iodobenzene



Entry	Catalyst	Solvent	Base	Conversion (%)[a]	Selectivity (%)[a]	
					Biphenyl	Ketone
1	**1**	Dioxane	Cs_2CO_3	100	5	95
2	**1**	Dioxane	K_3PO_4	100	13	80
3	**1**	Dioxane	Na_3PO_4	58	22	78
4	**1**	Dioxane	NaOH	100	34	66
5	**1**	Dioxane	Et_3N	100	31	69
6	**1**	Dioxane	K_2CO_3	100	3	97
7	**1**	THF	K_2CO_3	99	4	94
8	**1**	Toluene	K_2CO_3	97	5	95
9	**1**	Acetonitrile	K_2CO_3	91	12	88
10	**1**	DMF	K_2CO_3	5	61	trace
11	**1**	DMSO	K_2CO_3	18	81	trace
12	**2**	Dioxane	K_2CO_3	98	19	81
13	**3**	Dioxane	K_2CO_3	99	21	79

Reaction conditions: 0.4 mmol iodobenzene; 0.5 mmol of $NaBPh_4$; 1 mol% catalyst, 1.2 mmol of base, 5 ml of solvent, at 100 °C temperature, 1 atm CO, for 5 h.
[a] Determined by GLC based on iodobenzene.

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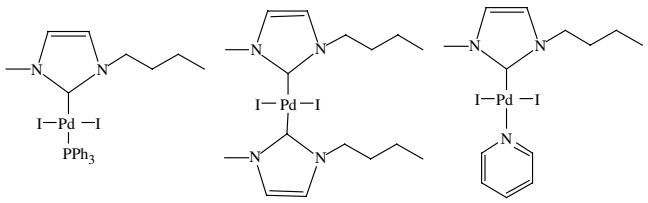


1 **2** **3**

Scheme 1. NHC–Pd complexes.

complexes in this reaction.

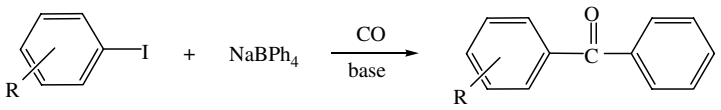
With the optimized reaction conditions, we extended the scope to a variety of different aryl iodides in the carbonylative Suzuki reaction of sodium tetraphenylborate. As shown in Table 2, electron-rich substrates *p*-iodoanisole and *p*-iodotoluene can successfully give corresponding diaryl ketones in excellent isolated yields (entries 2 and 4). The yield of corresponding product from steric hindrance substrates was decreased slightly (entries 3 and 6). Electron-deficient *p*-chloro, *p*-acetyl and naphthyl iodobenzene also showed high activities and excellent yields were also obtained (entries 7–9). In general, electron-deficient halides typically gave higher amounts of Suzuki product, non-carbonylative biaryl derivatives. It is known that insertion of carbon monoxide into active spieces is fast in electron-rich aryls and the electron-withdrawing groups slow the insertion by reversely accelerating the rate of direct coupling,[20,21] so the selectivity of electron-deficient halides is lower than that of electron-rich substrates.[9] However and interestingly, both electron-rich and electron-deficient aryl iodides gave aryl ketones in excellent yield by the means of Pd–NHC complex (**1**) catalyst systems. It is no problem that NHC–Pd complex has a significant improvement of CO insertion in the carbonylative Suzuki reaction, even with electron-deficient substrates.

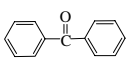
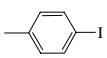
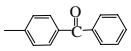
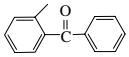
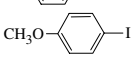
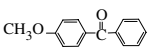
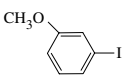
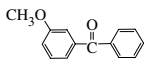
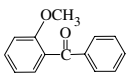
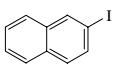
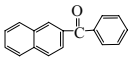
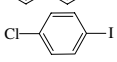
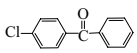
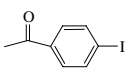
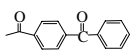
Phenylboronic acids as phenylating reagent were also investigated, as shown in Table 3, and good to excellent yields were also obtained. Similarly, electron-deficient substrates showed the same high selectivity as electron-rich aryl iodides (Table 3, entries 7–9).

CONCLUSIONS

In summary, a highly efficient carbonylative Suzuki reaction of sodium tetraphenylborate and phenylboronic acid with aryl iodides was developed. The NHC–Pd complex showed excellent catalytic activity in the reaction. This catalyst system was also suitable for the electron-deficient aryl iodides and gave aryl ketones in excellent yield with good selectivity.

Table 2. NHC–Pd **1**-catalyzed carbonylative cross-coupling of $NaBPh_4$ with aryl iodides



Entry	Substrate	Product	Yield (%)[a]
1			96
2			92
3			85
4			97
5			93
6			86
7			96
8			97
9			98

Reaction conditions: 0.4 mmol of aryl iodide, 1 mol% of catalyst **1**, 0.5 mmol of $NaBPh_4$, 1.2 mmol of K_2CO_3, 5 ml of dioxane, 1 atm of CO, at 100 °C of temperature, for 5 h.
[a] Isolated yields.

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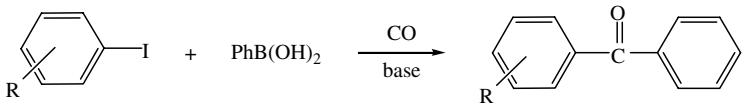
Table 3. NHC–Pd **1**-catalyzed carbonylative cross-coupling of phenylboronic acid with aryl iodides



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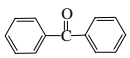
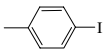
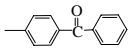
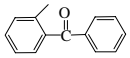
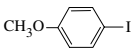
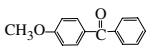
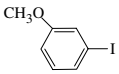
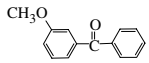
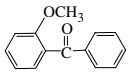
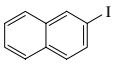
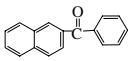
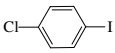
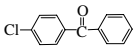
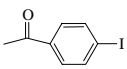
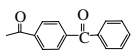
1			87
2			84
3			84
4			85
5			79
6			76
7			90
8			89
9			90

Reaction conditions: 0.4 mmol of aryl iodide, 1 mol% of catalyst **1**, 0.5 mmol of phenylboronic acid, 1.2 mmol of K_2CO_3, 5 ml of dioxane, 1 atm of CO, at 100 °C of temperature, for 5 h.
[a] Isolated yields.

Work aimed at understanding the nature of the catalyst is ongoing.

EXPERIMENTAL SECTION

General

THF was purified by distillation from sodium/benzophenone immediately before use as a reaction solvent. Except where noted, all other chemicals were purchased from commercial vendors and used without further purification. Di-μ-iodobis (1-methyl-3-butylimidazolin-2-ylidene) diiododipalladium[17] and NHC–Pd complexes **1**[17] and **2**[13a] were were prepared according to the literature procedures. Silica gel for flash chromatography was 200–300 mesh. GC analyses were conducted using an HP 6890/5973 GC-MS and a HP 5890 GC. Nuclear magnetic resonance spectra were obtained on a Varian 400 MHz FT-NMR spectrometer.

Synthesis of NHC–Pd complex3

A 25 µl aliquot of pyridine was added to a solution of 150 mg di-μ-iodobis (1-methyl-3-butylimidazolin-2-ylidene) diiododipalladium in 2 ml THF, the mixture was stired for 10 min at room temperature and the color of the solution changed from red to yellow. Then 10 ml hexane was added. The precipitated yellow solid was filtered, washed three times with hexane, and dried *in vacuo* to yield complex **3** 166 mg (96%). ^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm): 9.02(q, 2H, pyridine), 7.71 (t, 1H, pyridine), 7.30 (t, 2H, pyridine), 6.91 (d, 2H, NCH), 4.37 (t, 2H, NCH_2), 3.95 (s, 3H, NCH_3), 2.01 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 1.01 (t, 3H, CH_3). ^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm): 153.8 (N_2CH),139.7 (pyridine), 124.4 (pyridine), 123.1 (pyridine), 121.5 (NCH), 109.8(NCH), 51.3 (NCH_2), 39.2 (NCH_3), 31.4 (CH_2), 19.9 (CH_2), 13.7 (CH_3). Anal. calcd for $C_{13}H_{19}N_3PdI_2$: C, 27.04; H, 3.32; N, 7.27. Found: C, 26.96; H, 3.50; N, 7.44.

General procedure for catalytic reactions

Experiments were carried out in a 75 ml autoclave equipped with magnetic stirring and automatic temperature control, and the reactor was charged with known amounts (Table 2 and 3) of aryl iodides, base, $NaBPh_4$ or phenylboronic acid, catalyst (1%) and solvent (5 ml) and then pressurized with carbon monoxide at a pressure of 1 atm (CO purity 99.99%). The reactor was heated to 100 °C for 5 h. After cooling, the autoclave was degassed and analyzed by GC-MS and GC. The reaction mixture was worked up by removing the solvent under vacuum and the residue was purified by chromatography on silica gel.

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Spectroscopic data of ketones

Benzophenone

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.78$ (d, 4H, phenyl), 7.57 (t, 2h, phenyl), 7.47 (t, 4h,phenyl). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 196.7$, 137.5, 132.3, 130.0, 128.2.

4-Methylbenzophenone

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.79$ (d, 2H,phenyl), 7.77 (d, 2H, phenyl), 7.57 (t, 1H, phenyl), 7.46 (d, 2H, phenyl), 7.25 (d, 2H, phenyl), 2.42 (s, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 196.7$, 137.8, 132.4, 130.0, 128.2.

2-Methylbenzophenone

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.80$ (d, 1H,phenyl), 7.78 (d, 1H, phenyl), 7.55 (t, 1H, phenyl), 7.44 (t, 2H, phenyl), 7.39 (t, 1H, phenyl), 7.26 (t, 2H, phenyl), 7.23 (t, 1H, phenyl), 2.32 (s, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 196.5$, 157.3, 137.3, 134.7, 132.9, 131.9, 130.9, 129.8, 128.8, 120.4, 111.4, 55.5.

4-Methoxybenzophenone

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.82$ (d, 2H,phenyl), 7.73 (d, 2H, phenyl), 7.54 (t, 1H, phenyl), 7.48 (d, 2H, phenyl), 6.93 (d, 2H, phenyl), 3.86 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): $\delta = 195.6$, 159.5, 137.1, 132.5, 133.8, 130.8, 129.9, 128.1, 127.7, 55.4.

3-Methoxybenzophenone

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.78$ (d, 2H,phenyl), 7.57 (t, 1H, phenyl), 7.46 (t, 2H, phenyl), 7.30–7.33 (m, 3H, phenyl), 7.11 (d, 1H, phenyl), 3.85 (s, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 196.5$, 159.5, 137.5, 132.4, 129.9, 128.2, 122.8, 118.8, 114.2, 55.5.

2-Methoxybenzophenone

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.78$ (d, 2H,phenyl), 7.54 (t, 1H, phenyl), 7.44–7.47 (m, 3H, phenyl), 7.35 (d, 1H, phenyl), 7.02 (d, 1H, phenyl), 6.97 (d, 1H, phenyl), 3.69 (s, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 196.5$, 157.3, 137.7, 134.7, 132.9, 129.8, 128.1, 120.4, 111.4, 55.5.

4-Chlorobenzophenone

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$ (d, 2H,phenyl), 7.73 (d, 2H, phenyl), 7.60 (t, 1H, phenyl), 7.47 (d, 2H, phenyl),7.43 (d, 1H, phenyl). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 195.5$, 138.9, 137.2, 135.8, 132.6, 131.4, 129.9, 128.6, 128.4.

4-Acetylbenzophenone

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.03$ (d, 2H, phenyl), 7.83 (d, 2H, phenyl), 7.77 (d, 2H, phenyl), 7.59 (t, 1H, phenyl), 7.47 (d, 2H, phenyl), 2.65 (s, 3H, CH_3). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 197.5$, 195.9, 141.2, 139.5, 136.8, 134.7, 132.9, 130.1, 130.0, 128.4, 128.1, 127.8, 26.9.

2-Benzoylnaphthalene

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.11$ (d, 1H, naphthyl), 8.00 (td, 1H, naphthyl), 7.92 (d, 1H, naphthyl),7.90 (s, 1H, naphthyl), 7.88 (d, 1H, naphthyl),7.56–7.60 (m, 2H, naphthyl), 7.51–7.54 (m, 3H, phenyl), 7.46–7.49 (m, 2H, phenyl). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 197.9$, 138.2, 136.2, 133.6, 133.1, 130.9, 130.3, 128.4, 128.3, 127.7, 127.2, 126.4, 125.6, 124.2.

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