Palladium-Catalyzed Synthesis of Biaryl Ketones via *tert*-Butyl Isocyanide Insertion

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Abstract: A simple and efficient palladium-catalyzed carbonylative Suzuki coupling via *tert*-butyl isocyanide insertion has been developed, which demonstrates the utility of isocyanides in intermolecular C–C bond construction. This methodology provides a novel pathway for the synthesis of diaryl ketones in moderate to good yields. The approach is tolerant to a wide range of substrates and applicable to library synthesis. A possible reaction mechanism was proposed based on the experimental results.

Key words: isocyanide, carbonylative Suzuki coupling, palladium catalyst, diaryl ketone, insertion reaction

Biaryl ketones are important building blocks in many natural products and pharmaceuticals.[1] It is necessary to explore mild and high regioselective methods for the preparation of diaryl ketones from commercially available simple starting materials. The traditional approach to prepare biaryl ketones involves oxidation of diaryl methanols[2] or Friedel–Crafts acylation of substituted aromatic ring compounds with acyl halides. However, the Friedel–Crafts acylation is incompatible with many functional groups and the regioselectivity is limited to the *para* position.[3] In addition, the transition-metal-catalyzed direct synthesis of biaryl ketones with aryl carboxylic acid or aryl aldehydes as coupling partners has emerged as a useful method. Various transition metals have been used for these transformations, including cobalt,[4] copper,[5] nickel,[6] rhodium,[7] and palladium.[8] Furthermore, an another alternative approach is the carbonylative Suzuki coupling. In 1986, Kojima and co-workers firstly reported the carbonylative coupling of aryl iodides, carbon monoxide (CO) with organoboranes in the presence of $PdCl_2(PPh_3)_2$ as catalyst.[9] Later, Suzuki and co-workers expanded the aryl coupling partner from ArI to ArBr, ArOTf.[10] Recently, many biaryl ketones have been successfully synthesized by carbonylative Suzuki coupling reactions.[11] The common character of these reactions is that CO serves as the carbonyl source. However, CO is a toxic gas usually used in excess and under high pressures. Further, the reaction is heterogeneous. All above drawbacks limits the applications.[12]

Isocyanides are highly versatile reagents which have found widespread applications in organic, medicinal, and combinatorial chemistry. As valuable C1 building blocks, isocyanides represent an important class of reactive species and synthons. This chemistry has seen a surge of interest in recent years.[12,13] Isocyanide is isoelectronic with carbon monoxide and can be considered to replace carbon monoxide in coupling reactions. In addition, isocyanides are easily to handle liquids or solids, which can be used in stoichiometric quantities. So far, a lot of transition-metal-catalyzed coupling reactions via the insertion of isocyanides to form C–N[14,15] and C–O[16] bonds have been investigated. However, reactions via isocyanide insertion to form C–C bonds have been rarely described.[17] For example,[17c] the group of Suzuki reported a protocol for the catalytic reaction between haloarenes, *t*-BuNC and 9-alkyl-9-BBN to synthesize alkyl aryl ketones. However, the required 9-alkyl-9-BBN were prepared in situ and used directly. Recently, our group developed a simple and efficient palladium-catalyzed carbonylative Sonogashira coupling reaction via *tert*-butyl isocyanide insertion, which demonstrated the utility of isocyanides in intermolecular C–C bond construction.[18] Enlightened by the above literatures[12–17] and the finding of our group,[16b,18] we surmised that it might be possible for the insertion of isocyanides into aryliodo and arylboronic acid to construct intermolecular C–C bonds to generate biaryl ketones. To the best of our knowledge, there have been no reports of carbonylative Suzuki coupling from isocyanides to generate biaryl ketones.

In a model experiment, phenylboronic acid and iodobenzene were reacted with *tert*-butyl isocyanide in $Pd(OAc)_2$ and Ph_3P with K_2CO_3 as base. The reaction was firstly performed in dry toluene at 110 °C for four hours, then it was hydrolyzed in HCl–THF, and the desired product benzophenone was formed in 71% yield (Table 1, entry 1). The solvents for the activity of the reaction were examined. To our disappointment, the yields decreased from 4–12% with dioxane or anisole as solvent comparing to toluene, and the yield was 22% with DMSO as solvent (Table 1, entries 2–4); however, only trace of the desired product was isolated with THF as solvent (Table 1, entry 5), and most of the starting materials remained. In comparison with $Pd(OAc)_2$, $PdCl_2$ can slightly increase the yield (Table 1, entry 6). Then we examined the influence of base for the reaction activity. The desired product was not appeared with NaOAc or CsF as base (Table 1, entries 7 and 8). To our delight, the yield was improved to 80% when K_3PO_4 was used (Table 1, entry 9); the side product biphenyl was also isolated, and the yield was 16%. When Cs_2CO_3, KO*t*-Bu, Et_3N, or DBU was used as base, the

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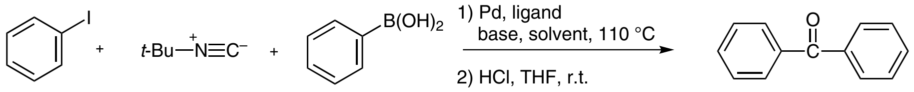
Table 1 Condition Optimizations[a]



Entry	Catalyst	Ligand	Base	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	Ph_3P	K_2CO_3	toluene	71
2	$Pd(OAc)_2$	Ph_3P	K_2CO_3	dioxane	67
3	$Pd(OAc)_2$	Ph_3P	K_2CO_3	anisole	59
4	$Pd(OAc)_2$	Ph_3P	K_2CO_3	DMSO	22
5	$Pd(OAc)_2$	Ph_3P	K_2CO_3	THF	trace
6	$PdCl_2$	Ph_3P	K_2CO_3	toluene	74
7	$PdCl_2$	Ph_3P	NaOAc	toluene	0
8	$PdCl_2$	Ph_3P	CsF	toluene	0
9	$PdCl_2$	Ph_3P	K_3PO_4	toluene	80
10	$PdCl_2$	Ph_3P	Cs_2CO_3	toluene	61
11	$PdCl_2$	Ph_3P	KO*t*-Bu	toluene	52
12	$PdCl_2$	Ph_3P	Et_3N	toluene	0
13	$PdCl_2$	Ph_3P	DBU	toluene	34
14	$PdCl_2$	DPPF	K_3PO_4	toluene	69
15	$PdCl_2$	DPEPhos	K_3PO_4	toluene	65
16	$PdCl_2$	PCy_3	K_3PO_4	toluene	67
17	$PdCl_2$	TFP	K_3PO_4	toluene	72

[a] *Reaction conditions:* All reactions were performed with iodobenzene (1.0 mmol), phenylboronic acid (1.2 mmol), *tert*-butyl isocyanide (1.2 mmol), catalyst (0.03 mmol), ligand (0.06mmol), and base (2.0 mmol) in solvent (4.0 mL) at 110 °C for 4 h, followed by stirring in THF–HCl at r.t. for 2 h. Et_3N = triethylamine; DBU = 1,5-diazabicyclo[5.4.0] undecen-5-ene; dppf = 1,1′-bis(diphenylphosphino)ferrocene; DPEPhos = bis[(2-diphenylphosphino)phenyl]ether; PCy_3 = tricyclohexylphosphine; TFP = tri(2-furyl)phosphine.

[b] Isolated yield.

yield was 61%, 52%, 0%, and 34%, respectively (Table 1, entries 10–13). Other commercially available mono- and bidentate ligands were also tested to further improve the yield. But none of them was compared to Ph_3P (Table 1, entries 14–17). Therefore, the optimal reaction conditions were $PdCl_2$ (3 mol%) and Ph_3P (6 mol%) as the catalyst system, with K_3PO_4 (2 equiv) as the base and with toluene as the solvent.

With optimal reaction conditions established, we turned our focus to the effect of substituents on aryl iodide compounds towards the coupling reaction (Table 2). The model reaction with iodobenzene led to the isolation of benzophenone in 80% yield (Table 2, entry 1). Similarly, 2-, 3-, and 4-iodotoluene were converted into the corresponding products in yields of 63%, 83%, and 81%, respectively (Table 2, entries 2–4). The yield of entry 2 (Table 2) is lower than that of entries 3 and 4 (Table 2) due to the steric hindrance of 2-iodotoluene. 3,5-Dimethyliodobenzene gave a slightly lower yield of 62% (Table 2, entry 5). The presence of the methoxy substituent on the iodobenzene resulted in a decreased yield of 42% (Table 2, entry 6). To our delight, iodobenzenes containing sensitive functional groups such as 4-CN and 4-CO_2Me were all coupled smoothly in moderate yields of 67% and 63%, respectively (Table 2, entries 7 and 8). Hence, the relationship between the nature of the substituent on the aryl ring and the yield is unclear. In addition, thiophenyl and naphthyl iodides afforded the desired biaryl ketones in modest yields by use of the method (Table 2, entries 9 and 10). Furthermore, 1,4-diiodobenzene bearing two iodo substituents could undergo isocyanide insertion twice and produced the target product in 51% yield (Table 2, entry 11).

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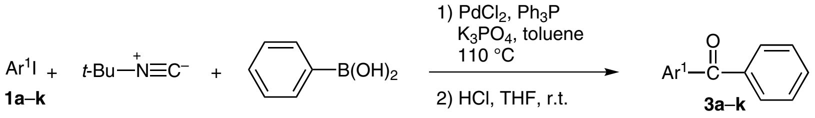
Table 2 Carbonylative Suzuki Coupling of Various Aryl Iodides with Phenylboronic Acid via *tert*-Butyl Isocyanide Insertion[a]



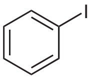
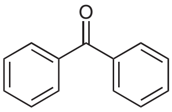
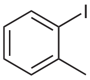
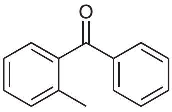
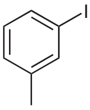
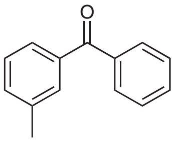
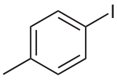
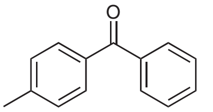
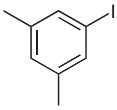
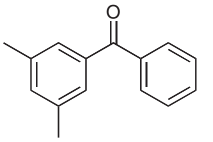
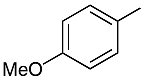
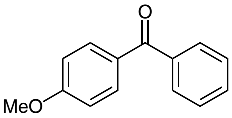
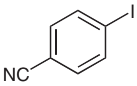
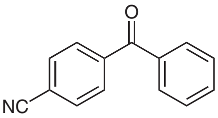
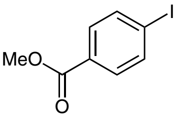
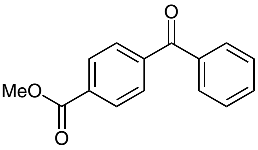
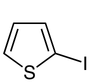
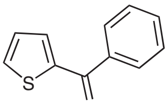
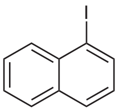
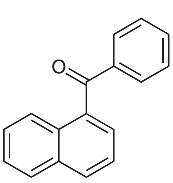
Entry	Substrate		Product		Time (h)	Yield (%)[b]
1		**1a**		**3a**[19]	4	80
2		**1b**		**3b**	22	63
3		**1c**		**3c**	7	83
4		**1d**		**3d**	4	81
5		**1e**		**3e**	5	62
6		**1f**		**3f**	24	42
7		**1g**		**3g**	6	67
8		**1h**		**3h**	22	63
9		**1i**		**3i**	22	64
10		**1j**		**3j**	22	41

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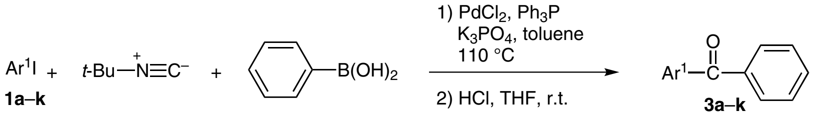
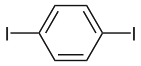
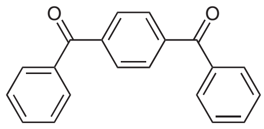
Table 2 Carbonylative Suzuki Coupling of Various Aryl Iodides with Phenylboronic Acid via *tert*-Butyl Isocyanide Insertion[a] (continued)



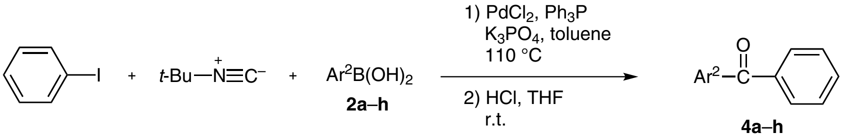
Entry	Substrate		Product		Time (h)	Yield (%)[b]
11		**1k**		**3k**	23	51

[a] *Reaction conditions:* All reactions were performed under on a 1 mmol scale, using aryliodides (1.0 mmol), phenylboronic acid (1.2 mmol), *tert*-butyl isocyanide (1.2 mmol), $PdCl_2$ (0.03 mmol), Ph_3P (0.06 mmol), and K_3PO_4 (2.0 mmol) in toluene at 110 °C for 4–23 h, followed by stirring in THF–HCl at r.t. for 2 h.

[b] Isolated yield.

Next, we examined the effect of substituents on arylboronic acid towards the coupling reaction (Table 3). Electron-rich substituents such as 4-Me, 4-OMe and 4-OBn were tolerated and led to good or modest yields (Table 3, entries 1–3). Besides, phenylboronic acid with electron-withdrawing substituents such as 4-F, 4-Cl, and 4-vinyl reacted smoothly with iodobenzene under our standard conditions and resulted in 62–66% yields (Table 3, entries 4–6). In addition, naphthalen-2-ylboronic acid was successfully coupled with *tert*-butyl isocyanide and iodobenzene in good yield (79%, Table 3, entry **7**). Furthermore, (4-vinylphenyl)boronic acid and methyl 4-(4-vinylbenzoyl)benzoate could couple easily with *tert*-butyl isocyanide and gave the desired product in 64% yield (Table 3, entry 8).

Table 3 Carbonylative Suzuki Coupling of Iodobenzene with Various Arylboronic Acid via *tert*-Butyl Isocyanide Insertion[a]



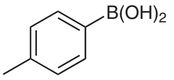
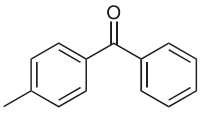
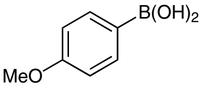
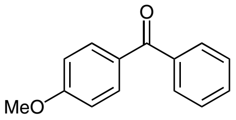
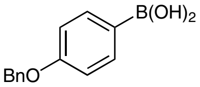
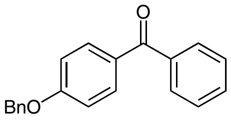
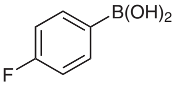
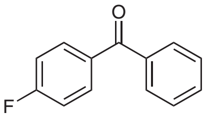
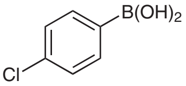
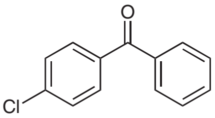
Entry	Substrate		Product		Time (h)	Yield (%)[b]
1		**2a**		**4a**	12	86
2		**2b**		**4b**	12	54
3		**2c**		**4c**	12	61
4		**2d**		**4d**	12	62
5		**2e**		**4e**	12	66

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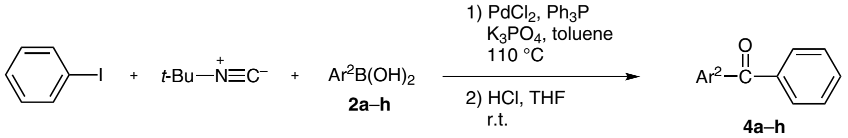
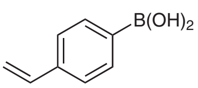
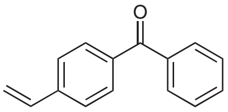
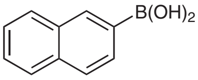
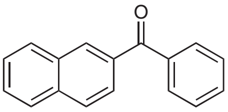
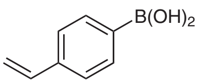
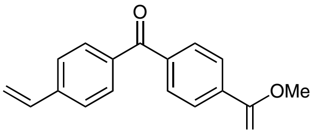
Table 3 Carbonylative Suzuki Coupling of Iodobenzene with Various Arylboronic Acid via *tert*-Butyl Isocyanide Insertion[a] (continued)



Entry	Substrate		Product		Time (h)	Yield (%)[b]
6		**2f**		**4f**	22	64
7		**2g**		**4g**	22	79
8		**2h**		**4h**	22	64[c]

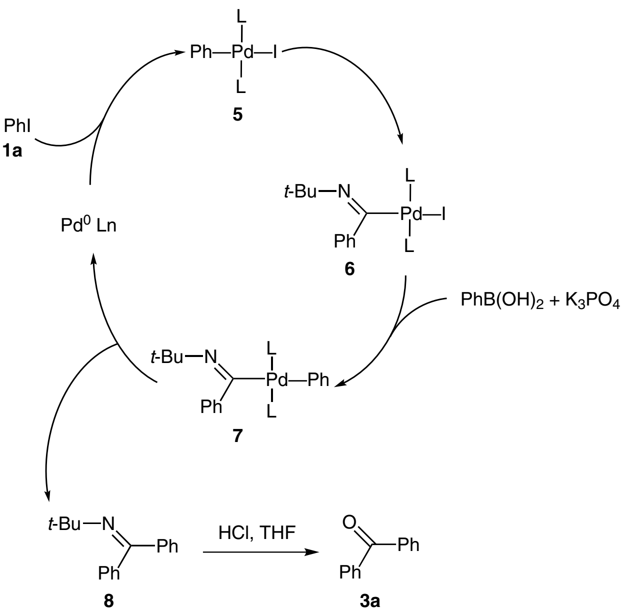
[a] *Reaction conditions:* All reactions were performed on a 1 mmol scale, using iodobenzene (1.0 mmol), arylboronic acid (1.2 mmol), *tert*-butyl isocyanide (1.2 mmol), $PdCl_2$ (0.03mmol), Ph_3P (0.06mmol), and K_3PO_4 (2.0 mmol) in toluene at 110 °C for 12–22 h, followed by stirring in THF–HCl at r.t. for 2 h.

[b] Isolated yield.

[c] One of the coupling partners is methyl 4-iodobenzoate.

A plausible mechanism for this reaction is depicted in Scheme 1. Oxidative addition of **1a** to the palladium(0) catalyst leads to the palladium complex **5**, followed by *tert*-butyl isocyanide insertion to form **6**. With the assistance of K_3PO_4, the iodine is exchanged by phenyl, which leads to the generation of **7**. Reductive elimination of **7** gives the intermediate **8**, which was detected by HRMS in the reaction system.[20] Intermediate **8** yields the target product **3a** by hydrochloric acid catalyzed hydrolysis.

In conclusion, we have developed a simple and efficient palladium-catalyzed carbonylative Suzuki coupling to synthesize diaryl ketones via *tert*-butyl isocyanide insertion and subsequent hydrochloric acid catalyzed hydrolysis. *tert*-Butyl isocyanide serves as carbonyl source in catalytic C–C bond construction. Characterized by mild reaction conditions, wide substrate scope and moderate to good yields (42–86%), this protocol may aid the further development of the isocyanides insertion reactions.



Scheme 1 Plausible mechanism for the synthesis of **3a**

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(19) **General Experimental Procedure**

In a 15 mL sealed tube equipped with a magnetic stirring bar were added iodobenzene (1.0 mmol, 112 μL), phenylboronic acid (1.2 mmol, 146 mg), *tert*-butyl isocyanide (1.2 mmol, 136 μL), $PdCl_2$ (0.03 mmol, 5 mg), Ph_3P (0.06 mmol, 16 mg), K_3PO_4 (2.0 mmol, 424 mg), and anhydrous toluene (4.0 mL). The tube was purged with N_2, and the contents were stirred at 110 °C for 4 h. After completion of the reaction as indicated by TLC, the mixture was filtered through neutral Al_2O_3, and the solvent was removed under vacuum. Then, the residue was stirred in THF (10 mL) and HCl (1 M, 3 mL) for 2 h. Then, the mixture was extracted with EtOAc, dried with Na_2SO_4, and evaporated. The residue was purified on a silica gel column using PE–EtOAc (100:1) as the eluent to give the pure product **3a**.

Benzophenone (3a)

White solid; mp 48–50 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79–7.82 (m, 4 H), 7.55–7.60 (m, 2 H), 7.45–7.49 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7, 137.6, 132.4, 130.1, 128.3. ESI-MS: *m/z* = 183.0 $[M + H]^+$.

(20) **Intermediate 8**

HRMS (CI): *m/z* calcd for $C_{17}H_{19}N$ $[M]^+$: 237.1517; found: 237.1517. HRMS (CI): *m/z* calcd for $C_{13}H_9N$ $[M - C_4H_9]^+$: 180.0813; found: 180.0810.

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