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A versatile method for the synthesis of diaryl and alkyl aryl ketones via palladium-catalysed cross-coupling reaction of arylboronic acids with acyl chlorides

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An efficient catalytic system using 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride and $PdCl_2$ was developed for the cross-coupling reaction of arylboronic acids with acyl chlorides. The catalytic amount of this homogeneous catalytic system affords the corresponding diaryl and alkyl aryl ketones in good to excellent yields under mild reaction conditions. Copyright © 2015 John Wiley & Sons, Ltd.

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Keywords: palladium catalyst; cross-coupling reaction; arylboronic acid; aryl ketone

Introduction

Aryl ketones constitute the key components of various commercial compounds, including natural products, biologically active compounds, pharmaceuticals, cosmetics, dyes, fragrances, agrochemicals and functional materials.[1–5] A traditional method for the preparation of aryl ketones is Friedel–Crafts acylation, which suffers from low regioselectivity, difficulty of regioisomer separation, release of large amounts of waste, harsh reaction conditions and incompatibility with electron-deficient functional groups.[6]

The acylation of carbon nucleophiles of organometallic reagents such as magnesium, lithium, zinc, copper, tin, cadmium or bismuth with carboxylic acids and their derivatives is an important C–C bond-forming reaction for the preparation of aryl ketones.[7–12] In 1983 Rapoport and co-workers reported the formation of α-amino ketones from various α-*N*-acylated amino acids and organolithium or organomagnesium reagents.[13] In 1998 Fukuyama and co-workers described an efficient methodology for the palladium-catalysed synthesis of ketones from reaction of thiol esters and organozinc reagents.[14] However, these methods have typical disadvantages including usage of toxic reagents, high temperature and long reaction time, low yields due to the formation of tertiary alcohols as side products and inferior tolerance of functional groups.[15,16]

Recently, palladium-catalysed cross-coupling of boronic acids with carboxylic derivatives has been developed as a powerful protocol for the regioselective synthesis of aromatic ketones.[17–26] This approach is superior to the previous methods in terms of reaction conditions, selectivity, efficiency and functional group compatibility and also non-toxicity, thermal, air and moisture stability and commercial availability of organoboron compounds as starting materials. Liebeskind and Srogl in 2000 developed a mild and general method for the palladium-catalysed, copper-mediated coupling of thiol esters and boronic acids under base-free conditions.[27] The first developments of palladium-catalysed cross-coupling of anhydrides with boronic acids have been investigated by Yamamoto and co-workers[28,29] and Gooßen and Ghosh[25] independently. Gooßen and co-workers reported efficient procedures for the coupling of arylboronic acids with carboxylic acids using pivalic anhydride,[26] disuccinimidyl carbonate[30] and dimethyl dicarbonate as activating agents.[31]

Bumagin and co-workers described the synthesis of aromatic ketones via ligandless and phosphine-free palladium-catalysed coupling of acyl chlorides with arylboronic acids in aqueous acetone.[32] There are several alternative procedures for this cross-coupling reaction under various conditions, such as in aqueous media,[33,34] anhydrous reaction[35–37] and solvent-free conditions.[38]

Generally, the combination of palladium catalysts with phosphine and carbene ligands results in high efficiency in coupling reactions. However, most phosphine ligands are air-sensitive, expensive and require an inert environment and high catalyst loading of palladium source in carrying out the reaction. Although carbene ligands are more stable than phosphines, they must be synthesized through multi-step processes.[39] Thus the development of efficient phosphine-free palladium catalytic systems remains a potentially promising field in organic synthesis.[40]

Results and Discussion

In continuation of our recent investigations on the synthesis and applications of the palladium complex of 1-benzyl-4-aza-1-

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azoniabicyclo[2.2.2]octane chloride with palladium chloride ($(BeDABCO)_2Pd_2Cl_6$),[41–44] we now report the extension of this complex as an efficient and highly active homogeneous catalyst for the cross-coupling reaction of various acyl chlorides with phenylboronic acid under phosphine-free conditions (Scheme 1).

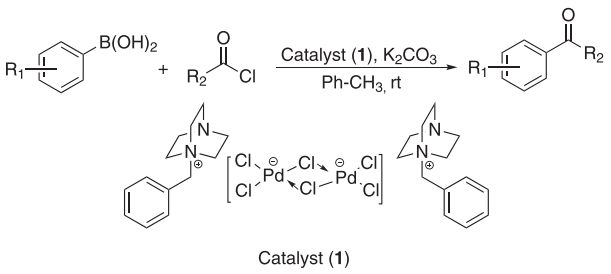
In order to search for better experimental conditions, the cross-coupling of phenylboronic acid and benzoyl chloride was chosen as a model reaction to optimize the effects of solvent, base, temperature and amount of catalyst (Table 1).

As evident from Table 1, K_2CO_3 as base, toluene as solvent and 0.4 mol% of catalyst give the best results for enhanced selectivity toward benzophenone and for preventing the formation of undesirable biaryl by-products. Biphenyls can be produced using two pathways: the homocoupling of phenylboronic acids and the decarbonylative coupling between acyl chloride and phenylboronic acid.[45] Several solvents, namely *N*-methyl-2-pyrrolidone (NMP), *N*,*N*-dimethylformamide (DMF), methanol, dioxane, toluene and water, were examined. When DMF is used as a polar solvent, the selectivity for aryl ketone is decreased and leads to the formation of biphenyl. When methanol is used as solvent, methyl benzoate is obtained in significant amounts. A lower yield of benzophenone is produced in aqueous solvents and water due to the partial hydrolysis of benzoyl chloride and formation of significant amounts of benzylic anhydride and benzoic acid as by-products.[46] Moderate yields are afforded using the bases Cs_2CO_3, Na_2CO_3, $NaHCO_3$, K_3PO_4 and *t*-BuOK. No desired product is observed when Et_3N is used in this coupling reaction. Decreasing the amount of base leads to a decrease in the yield of benzophenone.

Increasing the reaction temperature in this cross-coupling reaction results in a small increase in yield. Although an increase of temperature from 60 to 80 °C has a positive effect on the conversion in shorter reaction time, more biphenyl by-product is observed.

A low palladium concentration usually leads to a long period of reaction. Increasing the amount of palladium catalyst shortens the reaction time, but does not increase the yield of benzophenone. There is no reaction in the absence of catalyst.

With the optimized reaction conditions in hand, we extended the scope to a variety of acid chlorides with phenylboronic acids. The results are shown in Table 2. Under the optimized reaction conditions, a variety of aryl ketones are obtained in high yields and the competitive hydrolysis for most of the acyl chlorides and biaryl formation appear to be minimized. Benzoyl chlorides with both electron-releasing and electron-withdrawing substituents can be converted into the corresponding ketones in good to excellent yields. However, acyl chlorides bearing electron-donating groups are reacted in longer times due to a slower reductive elimination step.

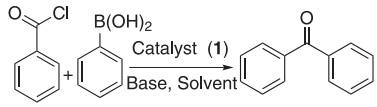


Scheme 1. Cross-coupling reaction of acyl halides with phenylboronic acids using catalyst (**1**).

2-Thenoyl chloride and 2-furoyl chloride as heteroaromatic acyl chlorides (Table 2, entries 8 and 9), acetyl chloride and phenylacetyl chloride as aliphatic acyl chlorides (Table 2, entries 11 and 12 and 16–18) and also cinamoyl chlorides (Table 2, entries 20–22) couple with arylboronic acids in good yields. Cross-coupling reactions of acyl chlorides with electron-donating arylboronic acids such as 4-methoxy and 4-methylphenylboronic acid give higher yields with shorter reaction times. Also thiophen-2-ylboronic acid as a heteroarylboronic acid couples with benzoyl chlorides in good yields (Table 2, entries 10 and 19).

A general catalytic cycle for this cross-coupling reaction is presented in Scheme 2.[18] Potassium carbonate as a co-catalyst facilitates the reduction of palladium(II) species and has a positive effect on the reaction.[47] Also a negatively charged base, such as potassium carbonate, is needed in different cross-coupling reactions of organoboronic acids. It is found that the base accelerates the transmetallation rate. The negatively charged base coordinates to the boron atom thus increasing its nucleophilicity.[48] The effect of tetraalkylammonium salts on the activity and stability of palladium catalysts has been described by Jeffery.[49] BeDABCO quaternary ammonium in this catalyst stabilizes the Pd(0) species by preventing the formation of unreactive palladium black.

Table 1. Optimization of reaction conditions for Suzuki-type cross-coupling reaction[a]



Entry	Solvent	Base	Temp. (°C)	Catalyst (mol%)	Time (min)	Conversion (%)	
						Product	By-product[b]
1	DMF	K_2CO_3	rt	0.4	60	10	74
2	NMP	K_2CO_3	rt	0.4	60	12	70
3[c]	MeOH	K_2CO_3	rt	0.4	60	—	98
4	Dioxane	K_2CO_3	rt	0.4	60	24	43
5[d]	H_2O	K_2CO_3	rt	0.4	60	30	65
6	Toluene	K_2CO_3	rt	0.4	60	98	2
7	Toluene	t-BuOK	rt	0.4	60	50	30
8	Toluene	Cs_2CO_3	rt	0.4	60	78	20
9	Toluene	Na_2CO_3	rt	0.4	60	57	34
10	Toluene	$NaHCO_3$	rt	0.4	60	69	20
11	Toluene	NEt_3	rt	0.4	60	—	10
12	Toluene	K_3PO_4	rt	0.4	60	52	18
13[e]	Toluene	K_2CO_3	rt	0.4	60	90	10
14	Toluene	K_2CO_3	rt	—	60	—	—
15	Toluene	K_2CO_3	rt	0.3	60	83	8
16	Toluene	K_2CO_3	rt	0.5	60	98	2
17	Toluene	K_2CO_3	60	0.4	50	98	2
18	Toluene	K_2CO_3	80	0.4	30	90	10
19[f]	Toluene	K_2CO_3	rt	0.4	70	42	7

[a]Reaction conditions: benzoyl chloride (0.75 mmol), phenylboronic acid (0.6 mmol), base (1 mmol), solvent (2 ml), catalyst **1**, room temperature (rt).

[b]By-product was biphenyl.

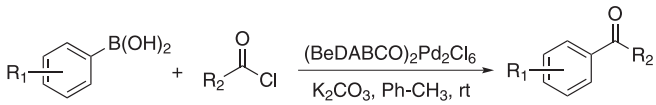
[c]By-products were biphenyl and methyl benzoate.

[d]By-products were biphenyl and benzoic acid.

[e]Base (0.6 mmol).

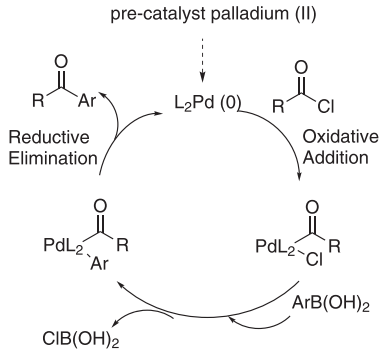
[f]$PdCl_2$/BeDABCO (in 1:1 ratio) was used as catalyst.

Table 2. Suzuki-type cross-coupling reaction of acyl chlorides using catalyst **1**[a]



Entry	RCOCl	$ArB(OH)_2$	Time (min)	Yield (%)[b]
1	PhCOCl	$PhB(OH)_2$	60	96
2	*p*-O_2N-C_6H_4-COCl	$PhB(OH)_2$	20	92
3	*m*-MeO-C_6H_4-COCl	$PhB(OH)_2$	70	90
4	*p*-MeO-C_6H_4-COCl	$PhB(OH)_2$	80	94
5	*p*-Me-C_6H_4-COCl	$PhB(OH)_2$	65	90
6	*p*-Cl-C_6H_4-COCl	$PhB(OH)_2$	35	89
7	*p*-MeOC-C_6H_4-COCl	$PhB(OH)_2$	45	86
8	2-Thenoyl chloride	$PhB(OH)_2$	40	90
9	2-Furoyl chloride	$PhB(OH)_2$	35	85
10	PhCOCl	2-Thiophen-$B(OH)_2$	60	90
11	CH_3COCl	$PhB(OH)_2$	70	91
12	$PhCH_2COCl$	$PhB(OH)_2$	40	92
13	PhCOCl	*p*-MeO-C_6H_4-$B(OH)_2$	20	95
14	PhCOCl	*p*-Me-C_6H_4-$B(OH)_2$	30	92
15	*p*-MeO-C_6H_4-COCl	*p*-MeO-C_6H_4-$B(OH)_2$	45	90
16	CH_3COCl	*p*-MeO-C_6H_4-$B(OH)_2$	30	93
17	CH_3COCl	*p*-Me-C_6H_4-$B(OH)_2$	40	90
18	$PhCH_2COCl$	*p*-MeO-C_6H_4-$B(OH)_2$	35	91
19	*p*-Me-C_6H_4-COCl	2-Thiophen-$B(OH)_2$	60	87
20	PhCH=CHCOCl	$PhB(OH)_2$	60	90
21	PhCH=CHCOCl	*p*-MeO-C_6H_4-$B(OH)_2$	40	92
22	PhCH=CHCOCl	*p*-Me-C_6H_4-$B(OH)_2$	50	90

[a]Reaction conditions: acyl chloride (0.75 mmol), phenylboronic acid (0.6 mmol), K_2CO_3 (1 mmol), toluene (2 ml), catalyst (0.4 mol%).
[b]Isolated yield after column chromatography.



Scheme 2. Proposed mechanism for the coupling of acyl halides with phenylboronic acids.

Conclusions

In this investigation, a general protocol was applied for the Suzuki-type reaction of various acyl chlorides with phenylboronic acids using catalytic amounts of $(BeDABCO)_2Pd_2Cl_6$ complex to obtain aryl ketones in good to excellent yields.

Experimental

General

^1H NMR and ^{13}C NMR spectra were recorded using 400 MHz with samples in $CDCl_3$ solutions at room temperature (tetramethylsilane was used as an internal standard) with a Bruker Avance 500 instrument (Rheinstetten, Germany) and a Varian 400 NMR. FT-IR spectra were recorded with a Jasco-680 (Japan) spectrophotometer. Spectra of solids were obtained using KBr pellets. Vibrational transition frequencies are reported in wavenumber (cm^{-1}). We used GC (Agilent 6890 N) for examination of reaction completion and yields. Palladium chloride, acyl chlorides and all chemicals were purchased from Merck or Aldrich and were used as received. $(BeDABCO)_2Pd_2Cl_6$ complex was synthesized according to our previous work.[27]

General Procedure for Cross-Coupling of Acyl Halides with Phenylboronic Acids

In a typical experiment, an oven-dried round-bottom flask was charged with phenylboronic acid (0.6 mmol), benzoyl chloride (0.75 mmol), K_2CO_3 (1 mmol), toluene (2 ml) and $(BeDABCO)_2Pd_2Cl_6$ (0.4 mol%). The reaction mixture was stirred at room temperature for the required time and progress of the reaction monitored using both TLC and GC. After the reaction was completed, the solution was extracted with water and ethyl acetate. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure using a rotary evaporator. The residue was purified by silica gel column chromatography (ethyl acetate–hexane, 1:9).

All products are known compounds and were characterized by comparing their m.p. and FT-IR, ^1H NMR and ^{13}C NMR spectra with those found in the literature.[16,50–52]

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