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Palladium-Catalyzed Cross-Coupling Reactions of Carboxylic Anhydrides with Organozinc Reagents

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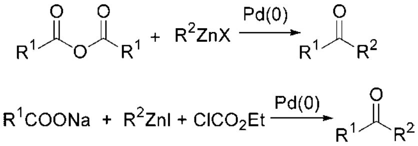
ABSTRACT



Negishi-type cross-coupling reaction was effected by employing organozincs and anhydrides or mixed anhydrides that formed in situ from sodium salts of the corresponding acids and ethyl chloroformate under the catalysis of palladium(0). A general method for preparing symmetrical/unsymmetrical ketones was developed.

Ketones occupy pivotal positions as intermediates as well as final products in the synthesis of natural products and pharmaceutical compounds. The traditional oxidations of secondary alcohols are extensively employed to obtain ketones; however, stoichiometric amounts of oxidizing reagents are required with concomitant formation of undesired byproducts.[1] The Friedel−Crafts acylation reaction is another powerful method for the synthesis of aromatic ketones, but the utilization of more than a stoichiometric amount of Lewis acid causes poor functional group compatibility and untunable regioselectivity, which limit its application.[2] Carboxylic acid derivatives can also be transformed into the corresponding ketones by treatment with lithium, magnesium, or aluminum reagents as nucleophiles;[3] however, the reactions have to be carried out at low temperature to avoid the formation of tertiary alcohols.

In the past three decades, palladium-catalyzed reactions have been developed into a broadly used protocol in organic synthesis. Some complementary methods for the ketone synthesis catalyzed by palladium have been disclosed. Ketones can be obtained by palladium-catalyzed oxidation of olefins[4] (Wacker process) or by palladium-catalyzed cross-coupling reactions between organoboron compounds and haloarene[5] or acyl halides[6] (Suzuki−Miyaura reaction). Recently, Yamamoto and Goossen reported independently a new method for obtaining ketones under mild reaction conditions based on the cleavage of C−O bond of carboxylic anhydrides in the presence of palladium(0) catalysts (Scheme 1).[7] This method is superior to the previous methods in terms

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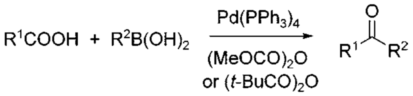
Scheme 1



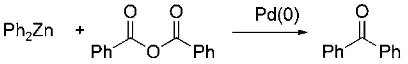
of its reaction conditions, efficiency, and functional group compatibility.

Negishi-type coupling that uses organozinc reagents is an important process in palladium-catalyzed cross-coupling reactions.[8] Recently, organozinc reagents have been used to realize nickel-catalyzed alkylative desymmetrization of *meso* anhydrides and paladium-catalyzed coupling reactions with thioesters to achieve ketones.[9] Herein we report a new method for preparing various symmetrical/unsymmetrical ketones from carboxylic anhydrides or corresponding in situ-generated mixed anhydrides and organozinc reagents in the presence of palladium(0) catalysts.

Treatment of benzoic anhydride (1 mmol) with Ph$_2$Zn (1.2 mmol) in THF at 80 °C in the presence of 5 mol % Pd(OAc)$_2$ and 10 mol % PPh$_3$ for 20 h gave benzophenone in 55% yield (entry 1, Table 1). Various catalysts and reaction conditions were examined as shown in Table 1. Pd(PPh$_3$)$_4$ proved to be the most efficient when THF or 1,4-dioxane was employed as a solvent (entries 7, 17, 18, Table 1). Use of Pd(OAc)$_2$ in combination with 2 or 4 mol amounts of PPh$_3$ per mol of Pd(OAc)$_2$ gave benzophenone with moderate yields (entries 1, 8, Table 1). In the case of employing Pd$_2$(dba)$_3$•CHCl$_3$ itself or in combination with various tertiary phosphines as the catalysts, only low yields were observed (entries 2−5, Table 1); palladacycle species gave similar results (entry 9, Table 1).[10] Among all of the solvents screened, THF proved to be the best (entries 6−8 vs 10−18, Table 1).

To study the scope and limitation of this transformation, various organozinc reagents and anhydrides were examined, and the results are summarized in Table 2. Aromatic carboxylic anhydrides bearing either an electron-donating or electron-withdrawing substituent at the para position of the aromatic ring could be smoothly converted into the corresponding ketones in good yields (entries 1−7, Table 2); anhydrides with either an ortho or meta substituent could also react with Ph$_2$Zn to give comparable yields (entries

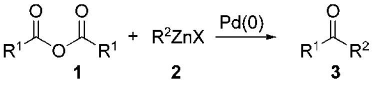
Table 1. Cross-Coupling of Benzoic Anhydride with Ph$_2$Zn[a]



entry	Pd catalyst	solvent	yield (%)[b]
1	Pd(OAc)$_2$ + 2 PPh$_3$	THF	55
2	Pd$_2$(dba)$_3$CHCl$_3$ + 2 PCy$_3$	THF	40
3	Pd$_2$(dba)$_3$CHCl$_3$ + 1 DPPE	THF	46
4	Pd$_2$(dba)$_3$CHCl$_3$ + 1 BINAP	THF	30
5	Pd$_2$(dba)$_3$CHCl$_3$	THF	3
6	Pd$_2$(dba)$_3$CHCl$_3$+ 2 ^{i}PrNPPh$_2$	THF	58
7	Pd(PPh$_3$)$_4$	THF	85
8	Pd(OAc)$_2$ + 4 PPh$_3$	THF	68
9	Pd(OAc)$_2$ + P(*o*-MeC$_6$H$_4$)$_3$	THF	32
10[c]	Pd(PPh$_3$)$_4$	CH$_2$Cl$_2$	43
11	Pd(PPh$_3$)$_4$	acetone	16
12	Pd(PPh$_3$)$_4$	DMF	14
13	Pd(PPh$_3$)$_4$	octane	trace
14	Pd(PPh$_3$)$_4$	CHCl$_3$	33
15	Pd(PPh$_3$)$_4$	CH$_3$CN	42
16	Pd(PPh$_3$)$_4$	toluene	22
17	Pd(PPh$_3$)$_4$	1,4-dioxane	53
18	Pd(PPh$_3$)$_4$	1,4-dioxane	51

[a] All reactions were run with benzoic anhydride (1 mmol), Ph$_2$Zn (1.2 mmol), and palladium catalyst (0.05 mmol) in dry solvent (3 mL) under argon in an oil bath of 80 °C for 18 h. [b] Determined by GC using dibenzyl ether as the internal standard. [c] Oil bath temperature was 45 °C.

Table 2. Ketones from Anhydrides and Organozincs[a]



entry	**1**, R^1	**2**	**3**	yield (%)[b]
1	C$_6$H$_5$	**2a**	**3a**	85
2	*p*-MeC$_6$H$_4$	**2a**	**3b**	70
3	*p*-MeOC$_6$H$_4$	**2a**	**3c**	65
4	*p*-CF$_3$C$_6$H$_4$	**2a**	**3d**	71
5	C$_6$H$_5$	**2b**	**3e**	73
6	*p*-MeOC$_6$H$_4$	**2b**	**3f**	79
7	*p*-CF$_3$C$_6$H$_4$	**2b**	**3g**	68
8	*o*-MeC$_6$H$_4$	**2a**	**3h**	64
9	*o*-MeOC$_6$H$_4$	**2a**	**3i**	62
10	*m*-MeC$_6$H$_4$	**2a**	**3r**	71
11	*m*-MeOC$_6$H$_4$	**2a**	**3s**	65
12	C$_6$H$_5$	**2c**	**3t**	86
13	C$_6$H$_5$	**2d**	**3u**	76
14	C$_6$H$_5$	**2e**	**3v**	74
15[c]	**1X**	**2a**	**3a**	78

[a] All reactions were run with aromatic acid anhydride (1 mmol), organozincs (1.2 mmol; **2a**, Ph$_2$Zn; **2b**, 4-CF$_3$C$_6$H$_4$ZnBr; **2c**, *n*-BuZnI; **2d**, *i*-PrZnI; **2e**, EtZnI) and Pd(PPh$_3$)$_4$ (0.05 mmol) in dry THF (3 mL) at reflux under argon for 15−20 h. [b] Isolated yields. [c] Mixed anhydride C$_6$H$_5$CO$_2$CO$_2$C$_2$H$_5$ (**1X**) was used.

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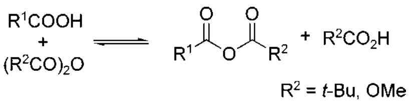
8−11, Table 2). Furthermore, the mixed anhydride was converted into ketones regioselectively in decent yield (entry 15, Table 2).

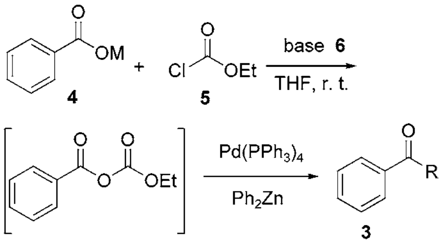
Yamamoto and Goossen have reported the preparation of ketones directly from carboxylic acids in the presence of dimethyl dicarbonate or pivalic anhydride catalyzed by Pd(0) (Scheme 1).[7c,e,f,11] However, this method is not applicable to the organozinc reagents, since the reaction generates carboxylic acids (Scheme 2).

Scheme 2



Since the anhydride can be generated in situ from the reaction of carboxylic acid with ethyl chloroformate in the presence of a base, a more convenient access to ketones can be envisioned by the method shown in Table 3.

Table 3. Reaction of Ph_2Zn with Mixed Anhydride Formed in Situ[a]



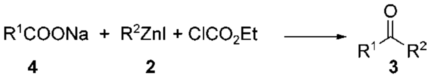
entry	M	base **6**	**4**:**5**:**6** (mol)	yield (%)[b]
1	H	Et_3N	1:1:1	17
2	H	Et_3N	1:3:1	31
3	H	Et_3N	1:3:3	40
4[c]	H		1:2:0	24
5[d]	H		1:3:0	trace
6[e]	H	Et_3N	1:3:3	54
7	H	K_2CO_3	1:1.5:0.5	37
8	H	K_2CO_3	1:3:1	15
9	Na		1:3:0	70
10[f]	Na		1:1.2:0	30
11[g]	Na		1:1.2:0	78
12[g]	Na		1:3:0	95

[a] Benzoic acid (or sodium benzoate) (1 mmol), ethyl chloroformate, and a base were mixed in THF (3 mL) under argon and stirred for 15 min at room temperature before Ph_2Zn (1.2 mmol) and $Pd(PPh_3)_4$ were added. Then, the temperature of the oil bath was raised to 80 °C for 16 h. [b] Determined by GC using dibenzyl ether as an internal standard. [c] Reaction mixture was evacuated to dryness to remove ethyl chloroformate and HCl before Ph_2Zn and catalyst were introduced. [d] Reaction mixture was bubbled with argon to remove ethyl chloroformate and HCl before Ph_2Zn and the catalyst were introduced. [e] $Et_3N{\cdot}HCl$ was filtered off before Ph_2Zn and catalyst were introduced. [f] Oil bath temperature was 110 °C. [g] Oil bath temperature was 70 °C.

Employing benzoic acid and Ph_2Zn as substrates and Et_3N or inorganic salts as the bases resulted in low yields of ketones (entries 1−3, 7, 8, Table 3), and increasing the amount of ethyl chloroformate and Et_3N or K_2CO_3 made little improvement (entries 2, 3, 8, Table 3). We have tried to remove HCl by direct evacuation of the reaction system instead of using Et_3N as a base or filtering the $Et_3N{\cdot}HCl$ salt before the catalyst and Ph_2Zn were added; however, the yields of the product were still low (entries 4−6, Table 3). When sodium benzoate was used instead of the corresponding acid in the absence of a base, the yield increased remarkably (entry 9, Table 3). It was further found that at a lower reaction temperature, good to excellent yields could be achieved (entries 11, 12, Table 3).

Therefore, we chose the conditions in Table 3, entry 12 as the optimum reaction conditions for the coupling reaction. The scope of the reaction was investigated by employing different combinations of sodium carboxylates and organozinc reagents, and the results are summarized in Table 4.

Table 4. Synthesis of Ketones from Sodium Carboxylates and Organozincs[a]



entry	R^1	R^2	**3**	yield (%)[b]
1	Ph	Ph	**3a**	95
2	p-MeC_6H_4	Ph	**3b**	89
3	p-$MeOC_6H_4$	Ph	**3c**	82
4	o-MeC_6H_4	Ph	**3h**	83
5	o-$MeOC_6H_4$	Ph	**3i**	69
6	p-ClC_6H_4	Ph	**3j**	86
7	p-$O_2NC_6H_4$	Ph	**3k**	90
8	2-naphthyl	Ph	**3l**	89
9	2-furanyl	Ph	**3m**	76
10	$PhCH_2CH_2$	Ph	**3n**	79
11	$PhOCH_2$	Ph	**3o**	77
12	trans-PhCH=CH	Ph	**3p**	93
13	n-C_8H_{17}	Ph	**3q**	99
14	m-MeC_6H_4	Ph	**3r**	87
15	m-$MeOC_6H_4$	Ph	**3s**	73
16	Ph	n-Bu	**3t**	85
17	Ph	i-Pr	**3u**	83
18	Ph	Et	**3v**	78
19	$PhCH_2CH_2$	n-Bu	**3w**	58[c]

[a] Typical conditions: a mixture of sodium carboxylate (2 mmol) and ethyl chloroformate (6 mmol) in dry THF (5 mL) was stirred for 15 min at room temperature under argon, after which $Pd(PPh_3)_4$ (0.1 mmol) and organozinc reagents (2.4 mmol) were added. Then, the oil bath temperature was raised to 70 °C and kept at this temperature for 14 h. [b] Isolated yields. [c] Contaminated with ethyl phenylpropionate.

A wide spectrum of sodium salts of aromatic acids are suitable substrates for the coupling reaction with PhZnI. Good to excellent yields were obtained (entries 1−9, 14, 15, Table 4). Sodium salts of aliphatic acids could also react smoothly with PhZnI to give the corresponding ketones (entries 10−13, Table 4), and no decarbonylation product was detected. Alkyl zinc reagents are also applicable in the

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reaction with sodium salts of both aromatic and aliphatic acids, and good to excellent yields were observed (entries 16−19, Table 4). However, when sodium phenylpropionate and *n*-butylzinc iodide were employed as starting materials, the decomposed product of the in situ-generated mixed anhydride,[12] ethyl phenyl propionate, was also detected (32% yield), which may account for the low yield of the desired ketone product (**3w**). Nevertheless, this could not easily be accomplished by palladium-catalyzed cross-coupling between anhydride and alkyl boronic acid.

Therefore, aromatic−aromatic ketones, aromatic−aliphatic ketones, and aliphatic−aliphatic ketones could be prepared straightforwardly from the sodium salts of corresponding acids and organozinc reagents via this method. Another important characteristic of this reaction is that organozinc reagents in this reaction are unlike the Grignard reagents in Kumada coupling reactions:[13] no isomerization product was formed.

In summary, we have developed an efficient method for accessing symmetrical and unsymmetrical ketones from organozinc reagents and anhydrides or mixed anhydrides under the catalysis of palladium(0). The employment of mixed anhydrides that are generated in situ from corresponding carboxylic acids or their sodium salts and ethyl chloroformate is especially of significance, since it makes the direct synthesis of ketones from carboxylic acids and their sodium salts practical.

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Supporting Information Available: Experimental details and analytical data for **3**, as well as selected spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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