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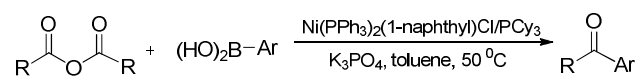
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A nickel-based catalyst was employed in the cross-coupling of carboxylic anhydrides with arylboronic acids, and various products were achieved in good yields under mild conditions.



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Nickel-catalyzed cross-coupling of carboxylic anhydrides with arylboronic acids

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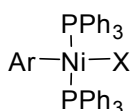
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A nickel-based catalyst was employed in the cross-coupling of carboxylic anhydrides with arylboronic acids, and the reaction was carried out under mild conditions. This new protocol provides an efficient, cheap and convenient alternative to synthesizing aromatic ketones.

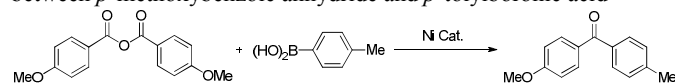
Major advantages of the Suzuki–Miyaura cross-coupling reaction in carbon–carbon bond-forming reactions encourage synthetic chemists to continuously expand its scope and enrich its content.^{1,2} Accordingly, the utility of carboxylic acid derivatives as electrophilic substrates in the Suzuki–Miyaura reaction for ketone synthesis has drawn intensive attention.³ Over the past decade, transition metal-catalyzed coupling reactions of boronic acids with carboxylic acid derivatives, including acid chlorides,⁴ anhydrides,^{5,6} thioesters,⁷ 2-pyridyl esters,⁸ and even carboxylic acids,^{5a,9} have been investigated. This Suzuki–Miyaura type acylation represents a highly valuable alternative to such classic procedures as the Friedel–Crafts acylation¹⁰ and nucleophilic addition of organometallics to carboxylic acid derivatives¹¹ because of its pronounced advantages such as mild conditions, the ease of manipulation, regioselectivity, and high yields, etc.

From economic and practical points of view, the development of cheap metal catalysts for replacing precious metal-based systems is highly desirable in transition metal-catalyzed reactions. To date, however, Suzuki–Miyaura type acylation reactions have largely depended on noble metal-based catalysts (particularly palladium).^{4–9} In striking contrast, much cheaper nickel, being a well-established counterpart of palladium in Suzuki–Miyaura reactions,^{2,12} remains missing in the special Suzuki–Miyaura acylation.¹³ Thus, it was of strong interest to us to explore the application of nickel-based catalysts in cross-couplings of boronic acids with carboxylic acid derivatives. Herein, we wish to disclose our new findings concerning nickel-catalyzed Suzuki–Miyaura acylation reactions.

Figure 1 Ni^{II}–(σ-aryl) complexes

The cross-coupling of *p*-methoxybenzoic anhydride with *p*-tolylboronic acid was used as a model reaction to screen reaction conditions (Table 1). Initially, we selected a Ni^{II}–aryl complex (C-1) as pre-catalyst. This is because we have successfully used Ni^{II}–(σ-aryl) complexes, *trans*-haloarylbis(triphenylphosphane)nickel(II) (Figure 1), as catalyst precursors in the Suzuki–Miyaura reaction.^{12d,l,m} These Ni^{II}–aryl complexes are easily prepared from cheap and commercially available starting materials¹⁴ and conveniently used due to their stability to air and moisture.

Table 1 Screening of conditions for nickel-catalyzed cross-coupling between *p*-methoxybenzoic anhydride and *p*-tolylboronic acid^a



Entry	[Ni(II)] (mol%)	Ligand (mol%)	Base	Solvent	Temp. (°C)	Yield ^b (%)
1	C-1 ^c (5)	none	K ₃ PO ₄	toluene	50	trace
2	C-1 (5)	PPh ₃ (10)	K ₃ PO ₄	toluene	50	trace
3	C-1 (5)	PCy ₃ (10)	K ₃ PO ₄	toluene	50	85
4	C-1 (5)	PCy ₃ (7.5)	K ₃ PO ₄	toluene	50	71
5	C-1 (5)	PCy ₃ (5)	K ₃ PO ₄	toluene	50	57
6	C-2 ^d (5)	PCy ₃ (10)	K ₃ PO ₄	toluene	50	0
7	C-3 ^e (5)	PCy ₃ (10)	K ₃ PO ₄	toluene	50	0
8	C-4 ^f (5)	PCy ₃ (10)	K ₃ PO ₄	toluene	50	0
9	C-1 (5)	DPPE (5)	K ₃ PO ₄	toluene	50	trace
10	C-1 (5)	DPPP (5)	K ₃ PO ₄	toluene	50	trace
11	C-1 (5)	DPPF (5)	K ₃ PO ₄	toluene	50	7
12	C-1 (2.5)	PCy ₃ (5)	K ₃ PO ₄	toluene	50	39
13	C-1 (5)	PCy ₃ (10)	K ₂ CO ₃	toluene	50	trace
14	C-1 (5)	PCy ₃ (10)	Na ₂ CO ₃	toluene	50	0
15	C-1 (5)	PCy ₃ (10)	K ₃ PO ₄	toluene	50	33 ^g
16	C-1 (5)	PCy ₃ (10)	K ₃ PO ₄	dioxane	50	12

17	C-1 (5)	PCy ₃ (10)	K ₃ PO ₄	THF	50	trace
18	C-1 (5)	PCy ₃ (10)	K ₃ PO ₄	toluene	30	46
19	C-1 (5)	PCy ₃ (10)	K ₃ PO ₄	toluene	70	67

^a Conditions: *p*-methoxybenzoic anhydride (1.0 mmol), *p*-tolylboronic acid (1.5 mmol), base (3.0 mmol), 5.0 mL of solvent, 12 h. ^b Isolated yields. ^c C-1: Ni(PPh₃)₂(1-naphthyl)Cl, ^d C-2: NiCl₂·6H₂O, ^e C-3: NiCl₂(PPh₃)₂, ^f C-4: Ni(acac)₂. ^g 1.5 mmol of K₃PO₄ used.

As shown in Table 1, although C-1 alone or with common ligands such as PPh₃ did not mediate this coupling reaction (Table 1, entries 1 and 2), a combination of C-1 and electron-rich, bulky PCy₃ ligand is a very effective catalytic system, giving the desired product in 85% yield (entry 3). And the role of ligand PCy₃ was confirmed by the following observations: the yield decreases gradually as the ratio of PCy₃ to Ni is reduced (entries 4 and 5). The use of common nickel(II) compounds, such as NiCl₂·6H₂O, Ni(PPh₃)₂Cl₂ and Ni(acac)₂, afforded no ketone product at all (entries 6–8). The reason should be that these Ni^{II} precursors are not able to produce the catalytically active Ni⁰ species in the current reaction system.^{12d} Furthermore, bidentate phosphine ligands, such as DPPE, DPPP and DPPF, appeared to be ineffective ligands (entries 9–11). An attempt to reduce loading amounts of the catalyst led to a substantially reduced yield (entry 12). For the bases used, weaker K₂CO₃ (entry 13) and Na₂CO₃ (entry 14) did not work at all; moreover, the reaction was sluggish without the use of excess amounts of base K₃PO₄ (entry 15). Toluene appeared to be the solvent of choice for the reaction and far superior to ethereal solvents such as dioxane (entry 16) and THF (entry 17). Reaction temperatures were essential for this transformation as well. For example, lower reaction temperatures caused a slower conversion (entry 18), but elevating reaction temperatures did not bring about a positive effect (entry 19), possibly because the competitive hydrolysis of the anhydride would be aggravated at higher temperatures. Finally, our standard conditions were set up as entry 3 in Table 1.

Under the optimized conditions, the scope and limitations of this cross-coupling reaction were investigated, and the results were summarized in Table 2. Generally, electron-neutral (entries 1–6), -rich (entries 9–14) and -poor (entries 17–19) anhydrides were all viable electrophilic substrates for the reaction. Further, we noticed an interesting tendency in the anhydride reactivity that the yield would decrease in the order: electron-rich > -neutral > -poor (e.g., entry 9 vs. 1 vs. 17; entry 11 vs. 3 vs. 18; and entry 13 vs. 5 vs. 19). This phenomenon appeared contrary to usual metal-catalyzed cross-couplings. The reason may be that a competitive hydrolysis side-reaction of anhydrides occurs in the reaction system, and thus the more electron rich the anhydride is, the more substantially its hydrolysis is suppressed. Neither aliphatic carboxylic anhydrides nor aliphatic boronic acids were suitable for this reaction and no coupled product was obtained (entries 21 and 22).

On the part of arylboronic acids, electron-rich and -neutral ones showed excellent reactivity and delivered the products in good yields (Table 2, entries 1–6, and 9–14); but electron-deficient boronic acid performed poorly (entries 8 and 16). Several heteroaryl boronic acids were also examined under the reaction conditions. Thiophen-3-ylboronic acid could be used in this reaction with appreciable yields (entries 23–25), while thiophen-2-ylboronic acid and 3-pyridinylboronic acid were ineffective (entries 26 and 27).

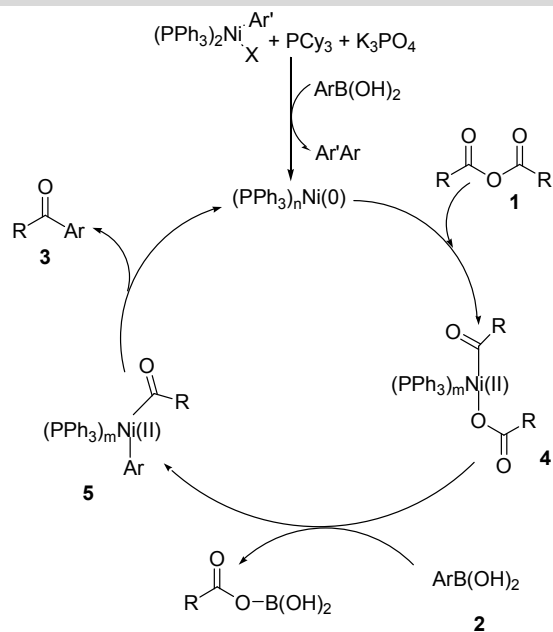
Additionally, this coupling reaction seemed to be very sensitive to the steric effects of both types of substrates. For example, slightly bulky 1-naphthyl boronic acid gave a relatively lower yield than the phenyl one did (Table 2, entry 6 vs. 5; entry 14 vs. 13), and the steric

Table 2 Ni-catalyzed cross-couplings of carboxylic anhydrides with arylboronic acids^a

Entry	Acid anhydride	Boronic acid	Product	Yield (%) ^b
1				81
2				70
3				74
4				77
5				71
6				68
7				0
8				33
9				88
10				76
11				85
12				84
13				81
14				75
15				0
16				39
17				67
18				61

19				56
20				0
21				0
22				0
23				69
24				69
25				66
26				0
27				0

^a Reagents: carboxylic anhydride (1.0 mmol), arylboronic acid (1.5 mmol), K_3PO_4 (3.0 mmol), C-1 (0.05 mmol), PCy_3 (0.1 mmol), toluene (5.0 mL).
^b Isolated yields.



Scheme 1 A possible mechanistic pathway for the Ni-catalyzed Suzuki–Miyaura acylation.

effects of both types of substrates completely retarded the reaction (entries 7, 15, and 20).

Based on our previous studies,^{12d,l,m} we believed that the catalytically active Ni^0 might be in-situ generated in the reaction system by the reaction of $Ni(PPh_3)_2(1\text{-naphthyl})Cl$ and an arylboronic acid under basic conditions, which is consistent with our experimental observations: (i) very small amounts of biaryl were detected in almost all cases; (ii) a deep red colour, usually as an indicator implying the presence of Ni^0 species in solutions, occurred in the reaction mixture at the initial stage of the reaction. Therefore, a possible mechanism for the nickel-

catalyzed acylation reaction is proposed (Scheme 1): oxidative addition of the aromatic carboxylic anhydride **1** to the Ni^0 species generates an acylnickel(II) complex **4**; subsequent transmetalation of the organic group on an arylboronic acid **2** onto Ni^{II} complex **4** takes places at the $Ni-O$ bond; and finally, reductive elimination of an aromatic ketone **3** from the Ni^{II} complex **5** and regenerates the Ni^0 species, and then the next cycle starts again.

In summary, we have for the first time demonstrated the feasibility for Ni-catalyzed acylation of arylboronic acids with carboxylic anhydrides. This protocol provides an efficient, cheap and convenient route to synthesizing aromatic ketones. A possible mechanism for this reaction was proposed. Further work to expand the scope of substrates and elucidate the mechanistic details is currently underway in our lab.

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