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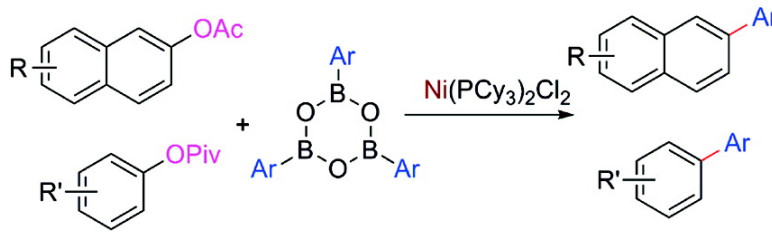

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Biaryl Construction via Ni-Catalyzed C−O Activation of Phenolic Carboxylates

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The industrially important cross-coupling of aromatic compounds meets the requirement of the scientific and commercial valuable biaryl compounds, which are as ubiquitous in molecules as biaryl scaffolds and structural units and broadly used in agrochemicals, pharmaceuticals, and materials fields.[1] In the past, the Suzuki−Miyaura coupling of aryl halides with nucleophilic arylboronic reagents has become a common and reliable method for both laboratorial and industrial applications and has almost completely replaced classical methods for constructing such biaryl units.[2] This is evidenced by numerous publications and patents on the development, improvement and application of this transformation.[3]

Extensive efforts have been made toward the use of less expensive aryl chlorides in cross-coupling reactions, and successes have been achieved.[4] However, several important improvements are still challenging and are yet to be realized. Aryl chlorides are not necessarily ideal starting materials for certain transformations, with some not readily available. In many cases, direct use of ubiquitous ester moieties in cross-coupling could be a synthetically ideal route that is more environmentally friendly (Scheme 1). In addition, the replacement of Pd catalysts with first row transition metal ions would significantly lower cost.[5] Here we present an efficient method to utilize phenolic carboxylates for the Suzuki coupling reaction. For the first time, a broad range of aryl ester substrates can be employed for the formation of C−C bonds in cross-coupling reactions mediated by a Ni-based catalyst.

Direct transformation of simple aryl esters to aryl−aryl products is a very useful synthetic method. In many cases, aryl esters are desired starting materials to replace aryl halides. Some aryl acetates are also much less expensive than aryl halides or aryl sulfonates in large scale productions.[6] Aryl esters may also offer orthogonal groups to aryl halides on a molecule that can be functionalized, which facilitates synthesis of natural or synthetic compounds.[1] However, due to the intrinsic properties of carboxylates, they have only been employed as leaving groups in Tsuji−Trost alkylation of allyl acetates.[7] Use of simple aryl esters such as aryl acetate presents several challenges. The most significant one is to selectively activate the C−OAc bond in the presence of a much more reactive carbonyl C−O bond (Scheme 1).[8,9] If this problem can be solved, starting from simple phenol or its derivatives, the acetate or other types of carboxylate moieties can be readily produced and employed in cross-coupling reactions. Potentially different carboxylic groups with varying steric/electronic properties may be installed to facilitate the coupling selectivity in the future.

Many studies have revealed the unique and efficient catalytic potential of Ni-based compounds to activate aryl and benzyl C−O bonds of the ethers.[10] Compared to aryl methyl ethers, aryl carboxylates are much more affordable. Our ongoing work in Ni-catalyzed C−O activation led us to believe that the crucial inversion of the reactivity of related chemical bonds for cross-coupling of aryl carboxylates is an achievable goal. Our evaluation of the reaction system was initiated from 2-naphthyl acetate (Table 1). $Ni(PCy_3)_2Cl_2$ was the first choice as a catalyst on the basis of our preliminary studies. $Ni(PCy_3)_2Cl_2$ was indeed found to be the best catalyst among the tested Ni and Pd complexes. Different bases were further screened, and K_3PO_4, a common inorganic base in Suzuki coupling, showed the best efficiency for this transformation.[2] Importantly the amount of water played a vital role in promoting this transformation. With the use of completely dried K_3PO_4, the relationship between the amount of water and the efficiency of the C−C bond formation reaction was carefully studied. We found that 0.88 equiv of water (based on the acetate) is the optimal amount for this coupling (73% isolated yield was obtained in a test reaction of 2-phenylnaphthalene). With 0.44 equiv of water the reaction only gave 58% yield with an incomplete conversion, and 1.76 equiv

Scheme 1. New Design on Activation of Aryl Carboxylate

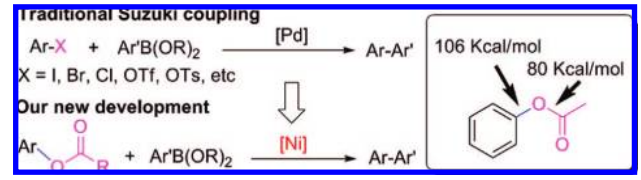
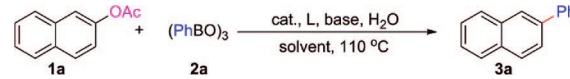


Table 1. Cross-Coupling between 2-Naphthyl Acetate and Phenylboroxine under Different Conditions[a]



1a 2a 3a

entry	cat. (10 mol%)	L (20 mol%)	base (2.0 equiv)	H_2O (mg)	solvent	yield[b] (%)
1	$Co(PCy_3)_2Cl_2$	PCy_3	K_3PO_4	4	dioxane	<5
2	$Cu(PCy_3)_2Cl_2$	PCy_3	K_3PO_4	4	dioxane	<5
3	$Pd(PCy_3)_2Cl_2$	PCy_3	K_3PO_4	4	dioxane	<5
4	$Fe(PCy_3)_2Cl_2$	PCy_3	K_3PO_4	4	dioxane	<5
5	$Ni(PCy_3)_2Cl_2$	−	K_3PO_4	4	dioxane	73[c]
6	$Ni(PCy_3)_2Cl_2$	−	KOH	4	dioxane	9
7	$Ni(PCy_3)_2Cl_2$	−	KO^{t}Bu	4	dioxane	<5
8	$Ni(PCy_3)_2Cl_2$	−	K_2CO_3	4	dioxane	29
9	$Ni(PCy_3)_2Cl_2$	−	Na_2CO_3	4	dioxane	20
10	$Ni(PCy_3)_2Cl_2$	−	K_3PO_4	0	dioxane	23
11	$Ni(PCy_3)_2Cl_2$	−	K_3PO_4	2	dioxane	58
12	$Ni(PCy_3)_2Cl_2$	−	K_3PO_4	6	dioxane	46
13	$NiCl_2\cdot 6H_2O$	PCy_3	K_3PO_4	0	dioxane	51
14	$NiCl_2\cdot 6H_2O$	PPh_3	K_3PO_4	0	dioxane	<5
15	$NiCl_2\cdot 6H_2O$	dppf	K_3PO_4	0	dioxane	<5
16	$NiCl_2\cdot 6H_2O$	PBu^n_3	K_3PO_4	0	dioxane	6
17	$NiCl_2\cdot 6H_2O$	PBu^t_3	K_3PO_4	0	dioxane	27
18	$NiCl_2\cdot 6H_2O$	$P(OMe)_3$	K_3PO_4	0	dioxane	17
19	$Ni(PCy_3)_2Cl_2$	−	K_3PO_4	4	toluene	45
20[d]	$Ni(PCy_3)_2Cl_2$	−	K_3PO_4	4	DCE	<5
21	$Ni(PCy_3)_2Cl_2$	−	K_3PO_4	4	DMF	<5
22[e]	$Ni(PCy_3)_2Cl_2$	−	K_3PO_4	4	dioxane	51

[a] Run using with 0.25 mmol of ester **1a** and 0.30 mmol of phenylboroxine **2a** at 110 °C for 12 h. [b] GC yields using *n*-dodecane as an internal standard. [c] Isolated yield. [d] Reaction carried out under reflux. [e] $PhB(OH)_2$ (1.5 equiv) was used.

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[‡] Chinese Academy of Sciences.

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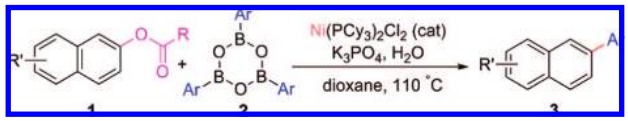
Table 2. Cross-Coupling between Various Substituted Naphthyl Carboxylates **1** and Different Arylboroxines **2**[a]



entry	R′	R	Ar	product **3**	yield[b] (%)
1	H	Me	Ph	**3a**	73
2	H	Et	Ph	**3a**	60
3	H	*i*-Pr	Ph	**3a**	51
4	H	*t*-Bu	Ph	**3a**	38
5	H	CF_3	Ph	**3a**	<5
6	H	Ph	Ph	**3a**	69
7	H	pyridin-2-yl	Ph	**3a**	<5
8	H	2,4,6-$Me_3C_6H_2$	Ph	**3a**	58
9	H	2,6-$Cl_2C_6H_3$	Ph	**3a**	36
10	H	Me	*p*-tolyl	**3b**	77
11	H	Me	*m*-tolyl	**3c**	81
12	H	Me	*o*-tolyl	**3d**	75
13	H	Me	4-BuC_6H_4	**3e**	61
14	H	Me	4-$MeOC_6H_4$	**3f**	75
15	H	Me	4-FC_6H_4	**3g**	70
16	H	Me	3,5-$(MeO)_2C_6H_3$	**3h**	64
17	H	Me	3,5-$Me_2C_6H_3$	**3i**	57
18	6-COMe	Me	Ph	**3j**	76
19	6-CH_2OMe	Me	Ph	**3k**	83
20	6-COOMe	Me	Ph	**3l**	70
21	6-OMOM	Me	Ph	**3m**	73
22	6-OMe	Me	Ph	**3n**	67
23	6-OH	Me	Ph	**3o**	42
24	5-CH_2OMe-6-OMe	Me	Ph	**3p**	61
25[c]	6-Ph	Me	4-BuC_6H_4	**3q**	73
26[c]	6-4-$MeOC_6H_4$	Me	4-BuC_6H_4	**3r**	72
27[c,d]	6-OAc	Me	4-BuC_6H_4	**3s**	56
28	naphthalen-1-yl	acetate	Ph	**3t**	68

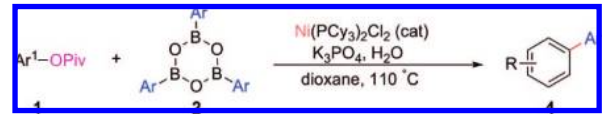
[a] Conditions: 0.25 mmol of ester **1**, 0.30 mmol of boroxine **2**, 0.025 mmol of $Ni(PCy_3)_2Cl_2$, 0.22 mmol H_2O, 0.50 mmol of K_3PO_4, and 2 mL of dioxine, 110 °C, 12 h. [b] Yields of entries 2−9 determined by GC using *n*-dodecane as an internal standard, and isolated yields of entries 10−29 were reported here. [c] Reactions carried out with (4-^{n}BuPhBO)$_3$ to increase the solubility of the products. [d] 2,6-Naphth-diol diacetate was used as starting material, and diarylated product was obtained.

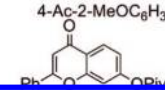
of water led to 46% yield with the hydrolyzed 2-naphthol as a byproduct. Furthermore, different ligands were examined, and PCy_3 was the most efficient. Other than dioxane, toluene is also a proper solvent for this transformation.

During this catalytic transformation, a trace amount of 2-naphthol as a hydrolyzed byproduct was observed, which may arise from the stability of the acetate under the reaction conditions. Many different esters were tested (entries 1−9, Table 2). As predicted, the more labile trifluoroacetate is not suitable for this transformation and only the hydrolyzed 2-naphthol was isolated. The more stable and sterically hindered aliphatic carboxylates showed lower efficiencies, but the hydrolysis side reaction was completely inhibited. Benzoate is also a suitable substrate, and the desired product was isolated in a comparable yield. Starting from 2-pyridinyl carboxylic ester, which could form a five-membered chelated Ni complex,[11] the coupling was completely inhibited as expected. Similar to the pivalyl group, sterically hindered 2,4,6-trimethylbenzoate and 2,6-dichlorobenzoate are beneficial for this transformation with slightly lower isolated yields.

Different boroxines were also explored (entries 10−17, Table 2). The steric hindrance did not affect the efficiency, and all the *para*-, *meta*-, and *ortho*-substituted aryl boroxines showed comparable reactivities. Importantly 4-methoxylphenyl boroxine showed very good reactivity, giving a good opportunity to further functionalize the obtained product with the developed methods.[10] Electron-deficient C−F was also compatible with this transformation. However, low efficiency indicated that C−Cl did not survive well, arising from its

Table 3. C−C Bond Formation via Ni-catalyzed Coupling between Various Pivalates **1** and Arylboroxines **2**[a]



entry	Ar^1	Ar	Product **4**	Yield (%)[b]
1	4-$MeO_2CC_6H_4$	4-$MeOC_6H_4$	**4a**	80
2	4-$MeO_2CC_6H_4$	4-MeC_6H_4	**4b**	75
3	4-$MeO_2CC_6H_4$	2-MeC_6H_4	**4c**	72
4	4-$MeO_2CC_6H_4$	Ph	**4d**	68
5	4-$MeO_2CC_6H_4$	4-FC_6H_4	**4e**	75
6	4-$MeO_2CC_6H_4$	3,5-$Me_2C_6H_3$	**4f**	60
7	4-AcC_6H_4	4-$MeOC_6H_4$	**4g**	75
8	4-AcC_6H_4	Ph	**4h**	64
9	4-FC_6H_4	4-$MeOC_6H_4$	**4i**	68
10	3-$CF_3C_6H_4$	4-$MeOC_6H_4$	**4j**	50
11	4-$MeOC_6H_4$	Ph	**4k**	47
12	4-$MeOC_6H_4$	4-MeC_6H_4	**4l**	48
13	4-PhC_6H_4	4-MeC_6H_4	**4m**	60
14	Ph	4-MeC_6H_4	**4n**	61[c]
15	4-Ac-2-$MeOC_6H_3$	4-$MeOC_6H_4$	**4o**	72
16		4-$MeOC_6H_4$	**4p**	78

[a] Conditions: 0.25 mmol of ester **1**, 0.33 mmol of boroxine **2**, 0.025 mmol of $Ni(PCy_3)_2Cl_2$, 0.05 mmol of PCy_3, 1.0 mmol of K_3PO_4, 0.22 mmol of water, and 3 mL of dioxane, 110 °C, 12 h. [b] Isolated yield. [c] GC yields using *n*-dodecane as an internal standard.

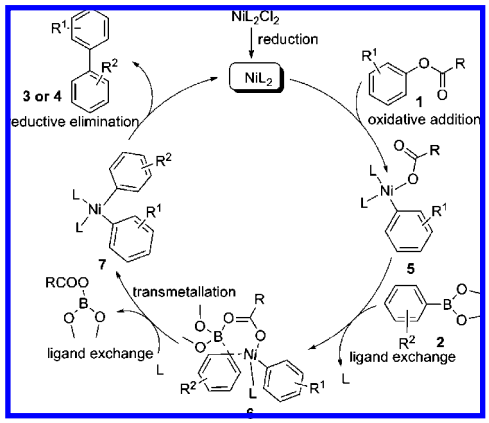
high reactivity under the coupling conditions. Moreover, polysubstituted arylboroxines also exhibited excellent reactivities to facilitate this transformation.

The group compatibility on naphthyl acetate was systematically studied (entries 18−27, Table 2). Generally, functional groups such as alkyl and aryl survived well under the reaction conditions. Carbonyl groups, such as esters, were compatible with this transformation. It is noteworthy that the protected hydroxyl groups with methyl and MOM survived well, which could be further functionalized based on our developed method to perform the subsequent selective coupling in the synthesis of complex molecules. Diphenylation of 2,6-naphthyl diacetate also occurred in good yield. The substrate with a free hydroxyl group was also applied to the reaction to find that the desired phenylated product was obtained in a moderate isolated yield (41%). Polysubstituted naphthyl acetates with methoxyl groups both at the benzyl position and on the phenyl ring were tested and the desired products were isolated in good efficiency, leaving both methoxyl groups untouched.

This transformation was further applied to the direct arylation of phenol derivatives (Table 3). Importantly substituted phenyl acetates were not efficient substrates and hydrolyzed phenols were observed as major products. However, the replacement of the acetate by the pivalate made this transformation applicable. The optimal reaction was achieved with an additional PCy_3 ligand, and the desired product was isolated in good yields (Table S1). The installation of an electron-withdrawing group on aryl pivalates is highly beneficial for this transformation. In contrast, electron-donating substituents slightly lowered the reaction efficiency, but the reaction still furnished the corresponding arylated products in moderate to good yields. Similarly, different substituents on aryl boroxines survived well under this condition. The electron-donating groups, such as a methoxyl group, obviously enhanced the efficiency of this transformation. It is noteworthy that the natural flavor derivative[12] could easily be functionalized in a good efficiency (entry 16, Table 3).

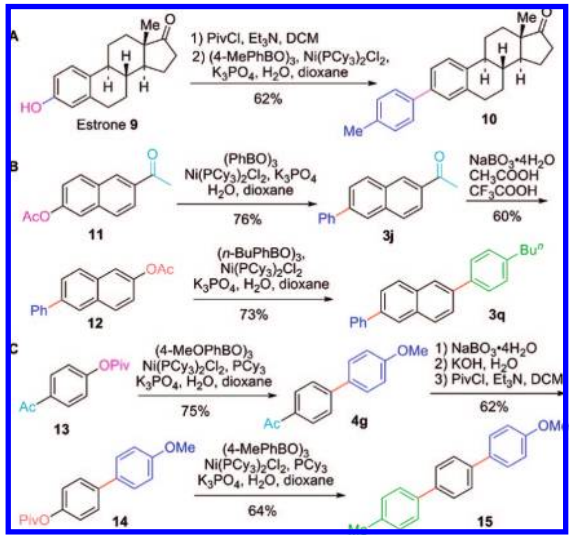
The mechanism of this reaction is proposed as shown in Scheme 2. First, $Ni(PCy_3)_2Cl_2$ was reduced in the presence of arylboroxines and K_3PO_4 to produce the active catalytic species Ni(0) (Supporting

Scheme 2. Proposed Mechanism for Biaryl Synthesis Starting from Aryl Carboxylates[a]



[a] L can be phosphine.

Scheme 3. Application of Cross Coupling via Ni-Catalyzation between Aryl Carboxylates and Arylboroxines



Information, Figure S1), which further underwent oxidative addition by aryl carboxylates to afford a key intermediate **5**. After the dissociation of PCy_3, the transmetalation between aryl boroxine and Ni complexes took place to produce key intermediate **6**, which may be promoted by both base and water. Reductive elimination facilitated the catalytic cycle by regenerating Ni(0) as a catalytic active species, and the desired biaryl was produced. Further studies to clearly understand this reaction pathway is underway.

To further explore the application of this methodology, we applied our method to constructing complicated organic scaffolds (Scheme 3). Starting from a natural product Estrone **9**,[13] the aryl group was introduced to afford the final product **10** through the newly developed coupling. This illustrated a straightforward way to modify the natural product. Furthermore, starting from 6-aceto-2-naphthyl acetate **11**, a phenyl group was introduced into **3j** through this new coupling. After Baeyer−Villiger oxidation to afford acetate **12**, our cross coupling was applied once again to construct the biaryl scaffold, giving **3q**. The new method also provided an efficient manner of accessing linear polyphenyls, which were broadly used in the materials field. From readily available 4-acetophenyl pivalate **13**, the new cross-coupling led to the corresponding substituted biphenyl **4g**. After the sequence of Baeyer−Villiger oxidation, hydration and pivalation to produce compound **14**, the cross-coupling was repeated to give linear terphenyl **15**, which could be further functionalized to yield longer linear polyphenyls.[10]

In summary, we developed a new class of homogeneous Ni-based catalysis to construct biaryl scaffolds by activation of aryl carboxylates with aryl boroxines. Our observation not only offers a new synthetic tool for constructing C−C bonds from simple aryl esters for the synthesis of industrially and medicinally important biaryl molecules but also shows the power of transition metal mediated catalysis to manipulate traditionally "inert" bonds. Aryl esters may be applied to other cross-couplings based on the results shown here.

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Supporting Information Available: Experimental details, spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Price from Alfa Aesar: 2-Bromonnaphthalene (98%, $802 for 100 g); 2-chloronaphthalene is not commercial available; 2-naphthyl acetate (99%, $582 for 250 g); starting material for 2-naphthyl acetate: 2-naphthol (>98%, $262 for 5 kg) and acetic anhydride: (>99%, $105 for 2.5 kg).

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