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Construction of Polysubstituted Olefins through Ni-Catalyzed Direct Activation of Alkenyl C−O of Substituted Alkenyl Acetates

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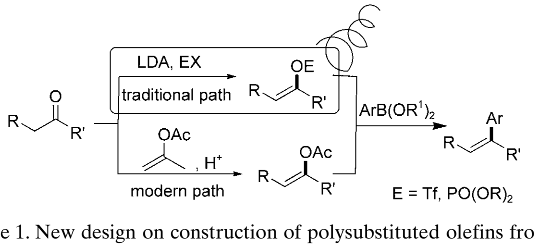
In memory of Professor Xian Huang

Polysubstituted olefins broadly exist in natural and synthetic compounds, which can be constructed through various pathways,[1] such as Wittig reaction, Julia–Lythgoe olefination, as well as coupling reactions.[2] Among coupling reactions, the Suzuki–Miyaura coupling is one of the most efficient choices for alkenyl halides and their derivatives.[3] However, due to the limited availability, high cost and low reactivity of the coupling partners, this method is not ideal. Although recent advances have promoted novel synthetic methods to construct such structural units from alkenyl methyl ethers via Ni-catalyzed Kumada cross-coupling, the difficulty to obtain starting materials and the poor compatibility of substituents, which arises from the use of Grignard reagents, limited its applications.[4]

Recently, the cleavage of "inert" aryl C–OMe, followed by cross-coupling with arylboronic acid derivatives, has been reported by Chatani and Kakiuchi with and without directing groups via Ru and Ni catalysis.[5] Very recently, our group and Garg independently reported that aryl carboxylates could couple with arylboronic acid derivatives via Ni catalysis.[6] Following studies indicated that coupling of aryl pivalates with organozinc reagents and alkyl Grignard reagents could take place under even milder conditions.[7] This transformation was further expanded to alkenyl pivalates to afford styrene derivatives. However, to the best of our knowledge, there is no example to perform the Suzuki–Miyaura coupling starting from alkenyl acetates and arylboronic acid derivatives, although benzyl and allyl acetates have been applied in the corresponding coupling reactions via Pd catalysis.[8] Herein, we reported for the first time a useful synthetic method to construct polysubstituted alkenes from easily available alkenyl acetates through Ni-catalyzed Suzuki–Miyaura coupling with arylboroxines.

Generally, cross-coupling to afford aryl alkenes proceeded between aryl organoboron reagents and alkenyl triflates or phosphates due to their relatively high reactivities, which could be generated easily from carbonyl compounds with triflic anhydride or a chlorophosphate.[9,10] However, the high cost, atomic economic waste, and relative difficulty of handling those chemicals limits this method. Compared with such a process, applying alkenyl acetates to the corresponding coupling reaction should be more general and easily controllable since alkenyl acetates could be easily produced through ester exchange (Scheme 1).[11] Additionally, as reported previously, the methoxy group might react with organoboron compounds in the presence of Ni complexes,[5b] so the tolerance of methoxy group is also questionable in the



Scheme 1. New design on construction of polysubstituted olefins from ketones.

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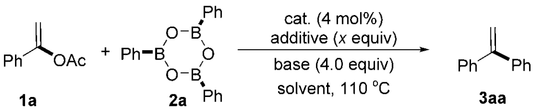
designed transformation. Our studies to achieve this goal initiated from the reaction of 1-phenylvinyl acetate (**1a**) with different organoboron reagents.

Table 1. Cross-coupling between 1-phenylvinyl acetate (**1a**) with phenylboroxine (**2a**) under different conditions.[a]



Entry	Catalyst	Additive (equiv)	Base	Solvent	**3aa** [%][b]
1	$[Ni(PCy_3)_2Cl_2]$	H_2O (1.0)	K_3PO_4	THF	72
2	$[Ni(PCy_3)_2Cl_2]$	H_2O (1.0)	K_3PO_4	DMF	0
3	$[Ni(PCy_3)_2Cl_2]$	H_2O (1.0)	K_3PO_4	toluene	51
4	$[Ni(PCy_3)_2Cl_2]$	H_2O (1.0)	K_3PO_4	dioxane	36
5	$[Ni(PCy_3)_2Cl_2]$	H_2O (1.0)	K_3PO_4	toluene/dioxane 1:1	99 (88)[c]
6	$[Ni(PPh_3)_2Cl_2]$	H_2O (1.0)	K_3PO_4	toluene/dioxane 1:1	0
7	$[Ni(dppe)Cl_2]$	H_2O (1.0)	K_3PO_4	toluene/dioxane 1:1	35
8	$[Ni(dppp)Cl_2]$	H_2O (1.0)	K_3PO_4	toluene/dioxane 1:1	77
9	$[Ni(dppf)Cl_2]$	H_2O (1.0)	K_3PO_4	toluene/dioxane 1:1	72
10	$[Ni(cod)_2]$	H_2O (1.0)	K_3PO_4	toluene/dioxane 1:1	0
11	$[Pd(PPh_3)_2Cl_2]$	H_2O (1.0)	K_3PO_4	toluene/dioxane 1:1	0
12	$[Pd(PPh_3)_4]$	H_2O (1.0)	K_3PO_4	toluene/dioxane 1:1	0
13	–	H_2O (1.0)	K_3PO_4	toluene/dioxane 1:1	0
14	$[Ni(PCy_3)_2Cl_2]$	–	K_3PO_4	toluene/dioxane 1:1	18
15	$[Ni(PCy_3)_2Cl_2]$	H_2O (0.5)	K_3PO_4	toluene/dioxane 1:1	52
16	$[Ni(PCy_3)_2Cl_2]$	H_2O (1.5)	K_3PO_4	toluene/dioxane 1:1	66
17	$[Ni(PCy_3)_2Cl_2]$	H_2O (2.0)	K_3PO_4	toluene/dioxane 1:1	65
18	$[Ni(PCy_3)_2Cl_2]$	H_2O (1.0)	K_2CO_3	toluene/dioxane 1:1	79
19	$[Ni(PCy_3)_2Cl_2]$	H_2O (1.0)	Cs_2CO_3	toluene/dioxane 1:1	0
20	$[Ni(PCy_3)_2Cl_2]$	H_2O (1.0)	CsF	toluene/dioxane 1:1	0
21	$[Ni(PCy_3)_2Cl_2]$	H_2O (1.0)	KO*t*Bu	toluene/dioxane 1:1	0
22	$[Ni(PCy_3)_2Cl_2]$	H_2O (1.0)	–	toluene/dioxane 1:1	0
23	$[Ni(PCy_3)_2Cl_2]$	H_2O (0.5)	K_3PO_4	toluene/dioxane 1:1	70[d]

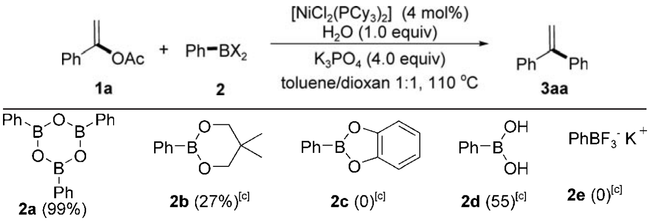
[a] All the reactions were carried out in the scale of 0.2 mmol of **1a** and 0.2 mmol of **2a** in the presence of catalyst and additive in 2 mL solvent. [b] GC yields with the use of *n*-dodecane as an internal standard. [c] Isolated yield in parenthesis. [d] The reaction was carried out in the scale of 2.0 mmol at 0.05 M.

Previous research indicated that Ni complexes were the best catalysts to cleave aryl/alkenyl C–O bonds of alkenyl ethers and carboxylates.[4–6] We first tested the exact reaction conditions, which were successfully applied in the previous system (entries 3 and 4, Table 1).[6a] The designed coupling took place but in low efficiency. Further exploration indicated that the mixed solvent system (dioxane/toluene 1:1) gave higher yields (entry 5, Table 1). Among various Ni complexes, $[Ni(PCy_3)_2Cl_2]$ was the most efficient and the loading of catalyst could be decreased to 4.0 mol %. Under these conditions, the homo-coupling of phenylboroxine was sufficiently suppressed.

Compared with Ni catalysts, Pd complexes failed to give the same coupling results (entries 11 and 12, Table 1). Different bases were also investigated and K_3PO_4 gave the best results (entries 18–22, Table 1). It is important to note that the amount of water was very critical in the transformation (compare entry 5 to entries 14–17, Table 1). We proposed that water might play an important role in facilitating the transmetalation between boroxine and Ni complex.[12] However, alkenyl acetates would hydrolyze in the presence of excess water under such basic and harsh conditions. Furthermore, to expand the application of this method, a 2.0 mmol scale reaction was carried out under the slightly modified conditions and the desired product was isolated in 70 % yield (entry 23, Table 1).

Compared with phenylboroxine **2a**, other phenylboronic acid derivatives showed different reactivities. Arylboronic ester **2b** could react with **1a** but in lower yields. Catecholborane derivative **2c**, however, failed. Phenylboronic acid **2d** facilitated this transformation in moderate yields. The hydrolysis of alkenyl acetate **1a** induced by such an acid may diminished the efficiency. Potassium phenyltrifluoroborate (**2e**) was also tested but no desired product was detected (Table 2). Notably, 3.0 equivalents of aryl boronic reagent related to **1a** are necessary due to the protonation of boronic reagents.

Table 2. Cross-coupling between **1a** and various organoboron reagents.[a;b]

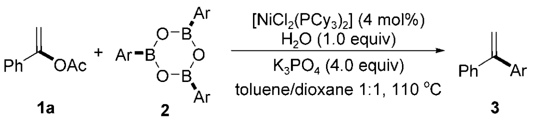


[a] All the reactions were carried out in the scale of 0.2 mmol of **1a** and stirred for 20 h. [b] The yields were determined by GC with *n*-dodecane as an internal standard. [c] The organoboron reagents were added in 3.0 equiv.

To expand the application of this method, we further tested other arylboroxines (Table 3). We found that 1) electron-donating groups were beneficial for the cross-coupling (**3ab**, **3ac**, **3ae**, and **3af**); however, the protonation of boroxines also produced the corresponding arenes as byproducts, which may arise from the high reactivity of organoboron reagents; 2) in contrast, electron-withdrawing groups decreased the rate, but the high efficiency can be achieved by simply lengthening the reaction time (**3ag**–**3aj**); 3) the steric hindrance also played an important role. When steric hindered substrate was used, the product was observed only in a very low yield (**3ad**); 4) 4-biphenylyl and 1-naphthyl boroxines worked well (**3ak** and **3al**).

The reactivity of different carboxylates was further investigated (Table 4). We found that sterically hindered carboxy-

Table 3. Cross-coupling between **1a** and various arylboroxines **2**.[a]

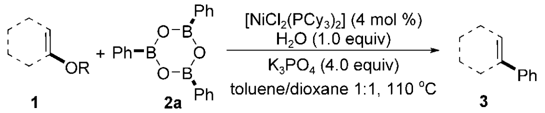


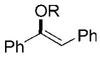
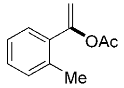
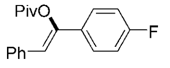
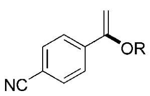
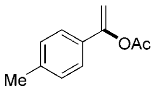
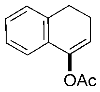
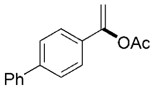
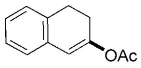
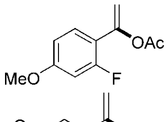
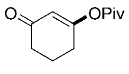
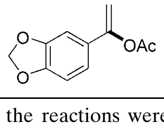
Entry	Ar	**3** [%][b]	Entry	Ar	**3** [%][b]
1	C_6H_5	**3aa** (88)	7	4-ClC_6H_4	**3ag** (60)
2	4-MeC_6H_4	**3ab** (76)	8	4-FC_6H_4	**3ah** (75)
3	3-MeC_6H_4	**3ac** (72)	9	3-$O_2NC_6H_4$	**3ai** (92)
4	2-MeC_6H_4	**3ad** (< 10)	10	3-$CF_3OC_6H_4$	**3aj** (83)
5	4-*t*BuC_6H_4	**3ae** (72)	11	4-PhC_6H_4	**3ak** (93)
6	4-$MeOC_6H_4$	**3af** (95)	12	1-$C_{10}H_7$	**3al** (78)

[a] All the reactions were carried out in the scale of 0.2 mmol of **1a** and all the arylboroxines were added in 1.0 equiv and the reactions were quenched after 20 h. [b] Isolated yields.

lates increased the stability of alkenyl carboxylates and prevented the hydrolysis of the substrates, but also decreased the rate of cross-coupling to lengthen the reaction time (entry 3). However, better leaving groups made the substrates more liable and the hydrolysis prevailed over the corresponding cross-coupling. For example, alkenyl trifluoroacetate completely failed in this transformation under the same reaction conditions (entry 4, Table 4).

Table 4. Cross-coupling between different alkenyl acetates **1** and arylboroxine.[a,b]

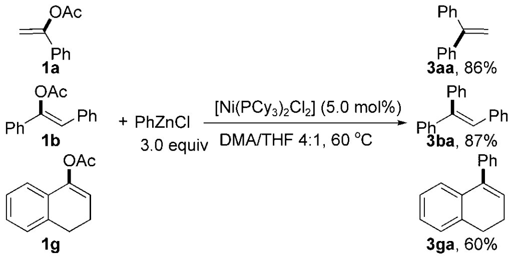


Entry	**1**	**3** [%][c]	Entry	**1**	**3** [%][c]
1		R = Ac, **3ba** (85)	9		**3ad** (< 5)
2		**3bf** (93)[d]	10		**3ea** (56)
3		Piv, **3ba** (89)	11		R = Ac, **3fa** (< 5)
4		TFA, **3ba** (< 5)	12		R = Piv, **3fa** (< 5)
5		**3ab** (92)	13		**3ga** (70)
6		**3al** (79)	14		**3ha** (46)
7		**3ca** (72)	15		**3ia** (60)
8		**3da** (89)			

[a] All the reactions were carried out in the scale of 0.2 mmol of **1** and the reactions were quenched after 20 h. [b] The arylboroxines were added in 1.0 euqiv. [c] Isolated yields. [d] (*p*-Methoxyphenyl)boroxine was used.

The generality of alkenyl acetates was also explored (Table 4). When different groups were added on the phenyl ring, we observed that the electron-donating groups were generally beneficial to this transformation (entries 5 and 8). Many other functional groups survived well, such as alkoxyl, aryl, and fluoro groups (entries 6–8). Notably, the steric effect similarly decreased the efficiency (entry 9). The electron-withdrawing group decreased the efficiency because of the lower stability of substrates (entry 10). The 4-cyano-substituted styryl acetate and pivalate did not afford the product and hydrolyzed to form corresponding ketone (entries 11 and 12). Trisubstituted alkenyl acetates underwent this transformation with lower efficiency than the disubstituted alkenyl acetates (entries 13 and 14). Interestingly, with the fused 1, 2-dihydronaphthyl derivative, 4-alkenyl acetate was much more efficient in this transformation (entries 13 and 14). Moreover, alkenyl pivalates with conjugated carbonyl group showed acceptable reactivity (entry 15).

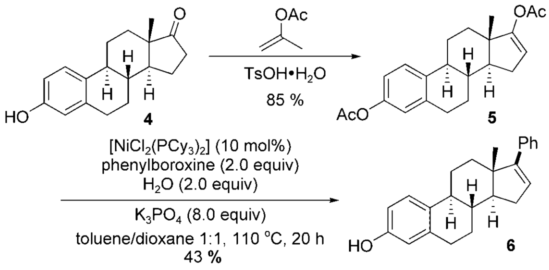
Although the Negishi coupling of vinyl pivalates has been reported before,[7a] the cross-coupling of vinyl acetates with more reactive organozinc reagents remain challenging due to their high instability. To our satisfaction, vinyl acetate could also be applied as an electrophilic partner to couple with phenyl zinc reagents under milder conditions (Scheme 2). It is important to note that a mixed solvent system is required to promote the efficiency. However, aromatic substituents at the α-position of vinyl acetates are necessary to retain their high reactivity. Moreover, α,β-unsaturated vinyl carboxylate **3i** was not a suitable substrate for this transformation, which may arise from the instability of this compound under the reaction conditions. Thus, the reported Suzuki coupling here is a complimentary method to carry out the arylation of those substrates.



Scheme 2. Negishi coupling with vinyl acetate via Ni catalysis.[a]

Supposedly, a reaction mechanism was proposed for the cross-coupling between aryl carboxylates and arylboroxines/aryl zinc reagents. Under such conditions, either arylboroxines or aryl zinc reagents played a key role in reducing Ni^{II} to Ni^0, which underwent oxidative addition of alkenyl acetates. After transmetalation with arylboroxines/ArZnCl, the reductive elimination occurred to produce the desired products under regeneration of Ni^0 to fulfill the catalytic cycle.

With this method, different acetates could well be differentiated in the same molecule. Through simple ester exchange with 2-propenyl acetate, estrone **4** was transformed into diacetates **5**. As predicted, the corresponding cross-coupling only took place at the alkenyl position in acceptable yields, leaving aryl C–OAc untouched and then hydrolyzed to hydroxyl group in a one-pot reaction, which allowed further functionalization of the phenyl ring to build different derivatives (Scheme 3). Further efforts to expand the application of this methodology are currently underway.



Scheme 3. Differentiation of the alkenyl acetate from aryl acetate.

In summary, we comprehensively demonstrated the Suzuki–Miyaura coupling between alkenyl carboxylates and arylboronic acid derivatives, which offered a new strategy to construct polysubstituted styrenes.[13] Alkenyl C–OAc and aryl C–OAc can be well differentiated under these conditions. This method provides a useful and reliable protocol to functionalize various compounds. Further studies to expand the substrate scope and promote the efficiency of this transformation are under investigation.

Experimental Section

General procedure for Ni-catalyzed cross-coupling of alkenyl acetates 1 with arylboroxines 2: The reactions were carried out in Schlenk tubes, which were dried by heating under vacuum. [Ni(PCy$_3$)$_2$Cl$_2$] (4 mol %, 0.04 mmol), boroxines (1.0 equiv, 0.2 mmol) and K$_3$PO$_4$ (4.0 equiv, 0.8 mmol) were added into tubes in glove box under dry N$_2$ atmosphere. Then the solutions of alkenyl acetates (1.0 equiv, 0.2 mmol) and H$_2$O (1.0 equiv, 0.2 mmol) in toluene (1.0 mL)/dioxane (1.0 mL) were added to the tubes (0.2 mmol, 3.6 μL H$_2$O was added in the mixed solvent by microscale syringe). The tubes were degassed in liquid N$_2$ and refilled with N$_2$ three times. Then the mixtures were stirred and heated at 110 °C for 20 h. After cooling down to room temperature, the reaction mixture was extracted by Et$_2$O and washed with water. The organic layer was dried by MgSO$_4$ and then concentrated under vacuum to afford a liquid or solid residue. The desired product was purified by chromatography on silica gel with petroleum ether as the eluent.

Acknowledgements

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Keywords: alkenyl acetate · arylboroxines · C–O activation · cross-coupling · nickel

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