Silver-Catalyzed Direct C–H Arylation of *N*-Iminopyridinium Ylides with Arylboronic Acids

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Abstract: A novel direct C–H arylation of *N*-iminopyridinium ylides with arylboronic acids has been developed. This reaction is performed at ambient temperature using inexpensive reagents: catalytic silver nitrate in the presence of potassium persulfate co-oxidant and give pyridyl arylation derivatives in moderate to good yields.

Key words: silver, *N*-iminopyridinium ylides, arylboronic acids, arylation, room temperature

Pyridine moieties are key structural units and exist widely in a large number of natural products, functional materials, pharmaceuticals, and ligands.[1] As such, there has been significant interest in developing efficient methods for the synthesis of these molecular architectures. These compounds are typically synthesized by cross-coupling reactions between 2-halopyridines and aryl organometallic derivatives[2] or by the reaction of Grignard reagents with pyridine *N*-oxide as described by Almvist and Olsson.[3] More recently, considerable attention has been given to direct arylation reactions as a more efficient approach for aryl–aryl bond formation.[4] In this context, Fagnou, Charette, Hiyama, and other groups have disclosed their pioneering work on transition-metal-catalyzed *ortho* arylation through C–H functionalization of pyridine *N*-oxides[5] or *N*-iminopyridinium ylides.[6] This remarkable progress avoids the utilization of stoichiometric amounts of organometallic reagents and has made 2-aryl pyridine derivatives easily available. However, these transition-metal-catalyzed methods also have some limitations such as need of a large excess of heterocyclic partners, expensive ligands, and harsh reaction conditions.

In a major improvement, Baran et al. recently reported a method[7] for the cross-coupling of electron-deficient arenes and quinines with arylboronic acids under classical Minisci conditions. Recently, Wang et al. developed a cheaper and environmentally friendly catalytic system[8] composed of FeS and $K_2S_2O_8$ for this cross-coupling reaction. Then Vishwakarma et al. developed a new and efficient iron catalyst[9] $Fe(acac)_2$ which was used in a catalytic amount. In order to expand the scope and selectivity of the reaction substrates, Mai et al. used pyridine *N*-oxides as platforms to generate the 2-arylpyridines.[10] Very recently, Wu et al. also developed a new method for the arylation of pyridine *N*-oxides with arylboronic esters.[11] Indeed, although there has been made tremendous progress in this area, new and efficient methods for the arylation of heterocycles are still in demand. Herein we report a new approach for the C–C bond formation of *N*-iminopyridinium ylides which catalyzed by silver salt at room temperature.

Benzoyliminopyridinium ylide and phenylboronic acid using water–dichloromethane co-solvent system to establish the best reaction conditions (Table 1). Regioselectivity on the heterocycle was predominantly for the 2- and 4-positions. However, unlike the literature report,[10] a mixture of C2 and C4 coupling products were obtained together even an excess of the the ylide relative to phenylboronic acid coupling partner was employed. The reaction performed better when excessive phenylboronic acid was used (Table 1, entries 1–4). Using 1.5 equivalents of the phenylboronic acid increased the yield to 60% (Table 1, entry 3). Further increasing the excess to 2.5 equivalents provided only a marginal improvement (62%, Table 1, entry 4), which did not justify the large excess. To know the effective amount of silver salt required for catalysis, experiments with lower amounts (20–10 mol%) as well as higher amounts (20–50 mol%) of $AgNO_3$ did not show any improvement in the coupling reaction (Table 1, entries 5 and 6). In the light of recent advances in this area, evaluation with other metal salts identified $AgNO_3$ as the most efficient catalyst (Table 1, entries 7–12). As the reaction conditions involved two immiscible substances, the addition of a phase-transfer catalyst was tested. With 5 mol% of tetrabutylammonium bromide (TBAB), formation of arylated products increased to 67% (Table 1, entry 13). Moreover, the yield was slightly reduced when $(NH_4)_2S_2O_8$ was used as an oxidant (Table 1, entry 14). The influence of solvents was also examined, and polar solvents were not suitable in this reaction (Table 1, entry 15).

With the optimized conditions in hand, the scope of the reaction was investigated, and all the results are given in Table 2. The reaction worked well even on gram scale, and the yield decreased when phenylboronic acid pinacol ester was used instead of phenylboronic acid (Table 1, entry 1). The use of *N*-iminoquinolinium ylide successfully formed the desired product with a similar acceptable yield (Table 2, entry 2). Other various 2-, 3-, and 4-methyl-substituted *N*-iminopyridinium ylides also gave moderate yields of arylated products, respectively (Table 2, entries 3–5).

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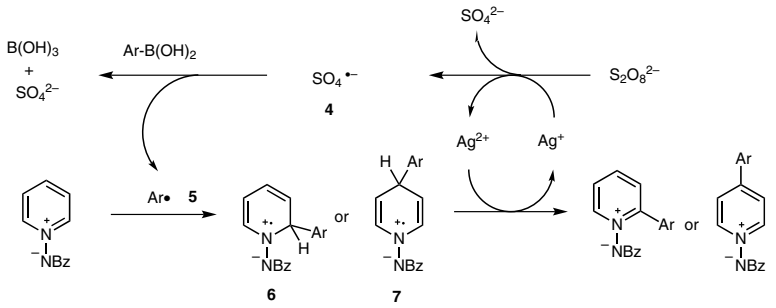
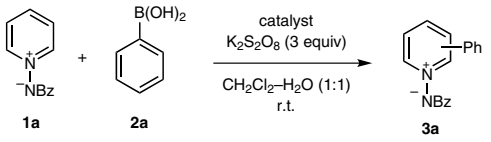


Scheme 1 Proposed mechanism of the arylation

Table 1 Optimization Studies for the Cross-Coupling Reaction[a]



Entry	Ratio (**1a**/**1b**)	Catalyst (mol%)	Yield (%)[b]
1	1:1	$AgNO_3$ (20)	40
2	1.5:1	$AgNO_3$ (20)	34
3	1:1.5	$AgNO_3$ (20)	60
4	1:2.5	$AgNO_3$ (20)	62
5	1:1.5	$AgNO_3$ (10)	40
6	1:1.5	$AgNO_3$ (50)	60
7	1:1.5	AgOAc (20)	56
8	1:1.5	$Fe(acac)_2$ (20)	55
9	1:1.5	$FeSO_4$ (20)	54
10	1:1.5	$FeCl_2$ (20)	52
11	1:1.5	FeS (20)	50
12	1:1.5	CuI (20)	27
13[d]	1:1.5	$AgNO_3$ (20)	67
14[c,d]	1:1.5	$AgNO_3$ (20)	63
15[e]	1:1.5	$AgNO_3$ (20)	trace

[a] Reaction conditions: *N*-iminopyrinium ylide (0.25 mmol), phenylboronic acid (0.375 mmol), CH_2Cl_2–H_2O (2 mL, 1:1), 8 h, under air at r.t.
[b] Yield of two isolated arylated products (C2 and C4).
[c] $(NH_4)_2S_2O_8$ was used instead of $K_2S_2O_8$.
[d] TBAB (5 mol%) was added.
[e] Reactions were performed in some polar solvents (DMF–H_2O, dioxane–H_2O, MeCN/H_2O) instead of CH_2Cl_2/H_2O.

Various *ortho*-, *para*-substituted organoboronic acids on reaction with *N*-iminopyridinium ylide were also explored. Arylboronic acids possessing electron-donating groups at the *para* position smoothly underwent cross-coupling reaction and gave good to excellent yields (Table 2, entries 6 and 7). Similarly, arylboronic acid with electron-withdrawing group also gave the desired product with good yield (Table 2, entry 8). Meanwhile, the use of halogenated phenylboronic acids led to decreased yields (Table 2, entries 9–11). Hindered 2-methyl phenylboronic acid also could work smoothly (Table 2, entry 12) while 1-naphthylboronic acid gave the product in lower yield (Table 2, entry 13). Moreover, vinylic boronic acids such as *trans*-2-phenyl-vinylboronic acid cannot couple with *N*-iminoquinolinium ylide (Table 2, entry 14) while thiophene-yl-2-boronic acid only gave a trace quantity of the desired product (Table 2, entry 15).

A proposed mechanism for the arylation is shown in Scheme 1. Silver salts react with potassium persulfate and generate sulfate radical anion **4**. This radical could react with the boronic acid, providing an aryl radical **5**, which can then add to *N*-iminopyridinium ylide, leading to product through reoxidation by Ag^{2+}. It is worth noting that by using *N*-iminopyridinium ylide to activate the aromatic ring, two mesomeric moments are accessed (**6** and **7**), thereby permitting both 2- and 4-arylated product.

In summary, a novel room-temperature approach to a silver-catalyzed direct arylation of *N*-iminoquinolinium ylide with arylboronic acids has been developed.[12] A broad range of substrates could react smoothly with arylboronic acids to give the desired coupling products with moderate to excellent yields. A supposed reaction mechanism was given. Further studies to improve the regioselectivity and yield of this reaction are under way.

Acknowledgment

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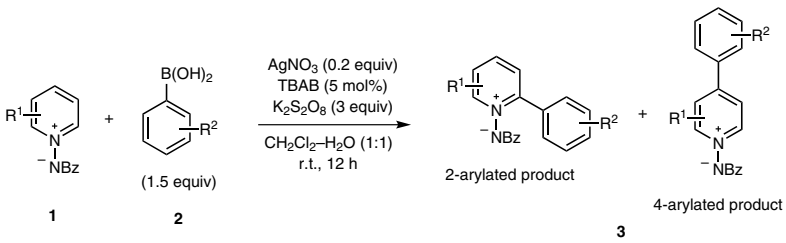
Table 2 Scope of *N*-Iminopyrinium and Boronic Acid Coupling Partners[a]



1 **2** **3**

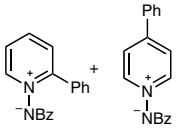
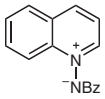
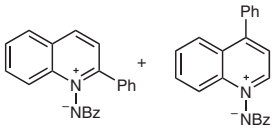
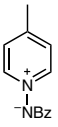
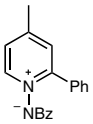
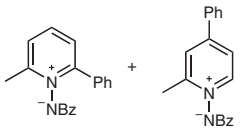
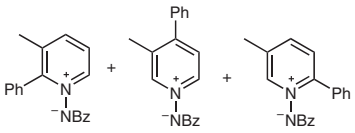
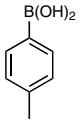
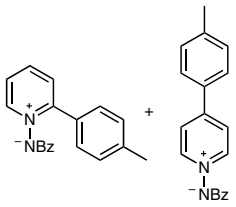
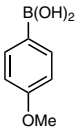
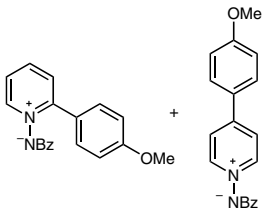
Entry	*N*-Iminoquinolinium ylide **1**	Boronic acid **2**	Product	Yield (%)[b]
1	 **1a**	 **2a**	 **3aa** **3ab**	67 (C2/C4 = 1.7:1) 42 (C2/C4 = 1.2:1)[c] 69 (C2/C4 = 1.7:1)[d]
2	 **1b**	**2a**	 **3ba** **3bb**	62 (C2/C4 = 1.4:1)
3	 **1c**	**2a**	 **3c**	45
4	 **1d**	**2a**	 **3da** **3db**	60 (C2/C4 = 1.2:1)
5	 **1e**	**2a**	 **3ea** **3eb** **3ec**	65 (C2/C4/C6 = 1:1.4:1.1)
6	 **1a**	 **2b**	 **3fa** **3fb**	70 (C2/C4 = 1.7:1)
7	**1a**	 **2c**	 **3ga** **3gb**	89 (C2/C4 = 1.2:1)

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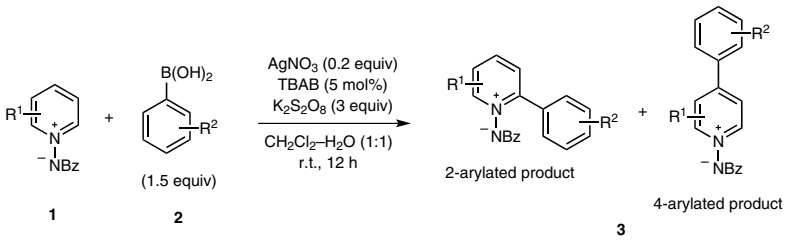
Table 2 Scope of *N*-Iminopyrinium and Boronic Acid Coupling Partners[a] (continued)



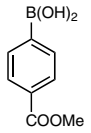
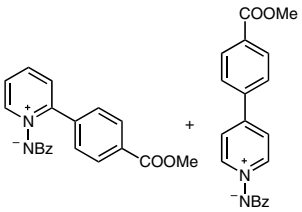
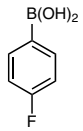
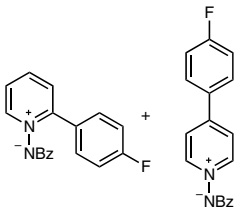
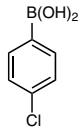
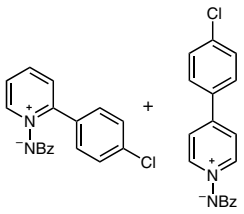
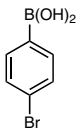
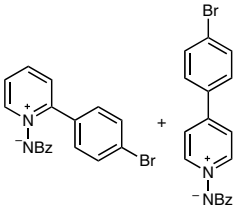
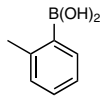
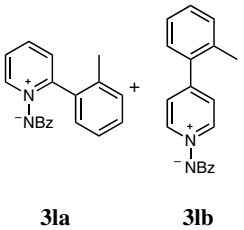
Entry	*N*-Iminoquinolinium ylide **1**	Boronic acid **2**	Product	Yield (%)[b]
8	**1a**	 **2d**	 **3ha** **3hb**	80 (C2/C4 = 1:1)
9	**1a**	 **2e**	 **3ia** **3ib**	58 (C2/C4 = 1.5:1)
10	**1a**	 **2f**	 **3ja** **3jb**	53 (C2/C4 = 1.4:1)
11	**1a**	 **2g**	 **3ka** **3kb**	50 (C2/C4 = 1.4:1)
12	**1a**	 **2h**	 **3la** **3lb**	61 (C2/C4 = 1.5:1)

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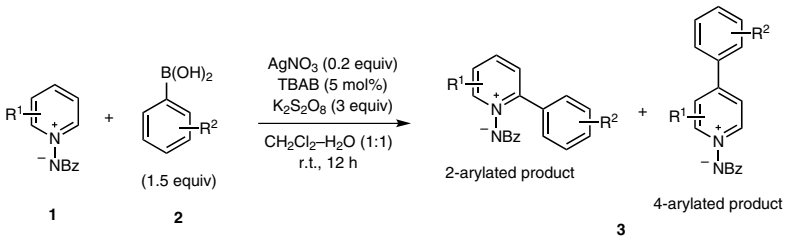
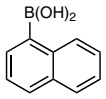
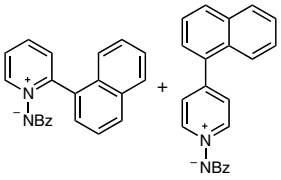
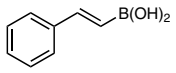
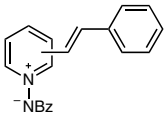
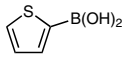
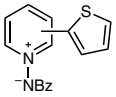
Table 2 Scope of *N*-Iminopyrinium and Boronic Acid Coupling Partners[a] (continued)



Entry	*N*-Iminoquinolinium ylide **1**	Boronic acid **2**	Product	Yield (%)[b]
13	**1a**	 **2i**	 **3ma** **3mb**	45 (C2/C4 = 1.4:1)
14	**1a**	 **2j**	 **3n**	n.d.
15	**1a**	 **2k**	 **3o**	trace

[a] Reaction conditions: *N*-iminopyrinium ylide **1** (0.25 mmol), boronic acid **2** (0.375 mmol), $AgNO_3$ (0.05 mmol), $K_2S_2O_8$ (0.75 mmol), TBAB (5 mol%), CH_2Cl_2/H_2O (2 mL, 1:1), 8 h, under air at r.t.
[b] Yields of isolated products. The ratio of the regioisomers was determined by isolated yield.
[c] Phenylboronic acid pinacol ester was used instead of phenylboronic acid.
[d] Reaction was performed on 1.0 g of *N*-iminopyridinium ylide.

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(12) ***N*-Iminopyrinium and Boronic Acid Cross-Coupling Reaction – General Procedure**

A mixture of *N*-iminopyridinium ylide **1** (0.25 mmol), phenylboronic acid **2** (0.375 mmol), $AgNO_3$ (0.05 mmol), $K_2S_2O_8$ (0.75 mmol), TBAB (5 mol%) in CH_2Cl_2/H_2O (2 mL, 1:1) was stirring at r.t. for 8 h. Then the reaction mixture was filtered (washed with CH_2Cl_2), extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried, then evaporated in vacuum. The resulting residue was purified by silica gel column chromatography to give the pure product.

Compound **3fa**: yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (dd, *J* = 6.4, 1.0 Hz, 1 H), 8.01–7.91 (m, 3 H), 7.72 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.63–7.53 (m, 3 H), 7.40–7.29 (m, 3 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 2.37 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.9, 153.7, 146.4, 140.9, 137.7, 137.3, 130.0, 129.5, 129.1, 128.4, 128.1, 127.8, 124.2, 21.6. ESI-HRMS: *m/z* $[M + H]^+$: *m/z* calcd for $C_{19}H_{17}N_2O$: 289.1335; found: 289.1335.

Compound **3fb**: yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (d, *J* = 7.2 Hz, 2 H), 8.17 (dd, *J* = 7.5, 2.1 Hz, 2 H), 7.81 (d, *J* = 7.2 Hz, 2 H), 7.60 (d, *J* = 8.2 Hz, 2 H), 7.44–7.34 (m, 5 H), 2.45 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.1, 149.6, 143.3, 141.7, 137.4, 132.3, 130.5, 129.5, 128.1, 128.0, 127.2, 123.0, 21.5. ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}N_2O$: 289.1335; found: 289.1341.

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