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EDGE ARTICLE

# Transition metal-catalyzed cross coupling with *N*-acyliminium ions derived from quinolines and isoquinolines†

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A Ni(0) catalyst facilitates efficient C–C bond formation between a wide range of  $\pi$ -neutral and  $\pi$ -deficient aryl boronic acids and *N*-acyliminium precursors derived from quinoline and isoquinoline. The reaction proceeds under mild conditions and is tolerant of common organic functional groups. In addition, a simple one-pot protocol amenable to the direct use of substituted quinolines is described. Consistent with preliminary data revealing a mild, organoboronate-mediated racemization of enantioenriched *N*-acyliminium precursors, initial results indicate that a chiral phosphoramidite-ligated nickel catalyst promotes enantioselective arylation of racemic substrate with no evidence of a kinetic resolution during catalysis.

## Introduction

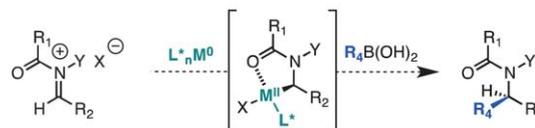
The intermolecular addition of carbon-centered nucleophiles to iminium and *N*-acyliminium ions is a powerful strategy for the synthesis of substituted amines that has found widespread use in the rapid assembly of alkaloids and active pharmaceutical ingredients.<sup>1</sup> Classically, this transformation has been achieved with strongly nucleophilic organometallic reagents (RMgX, RLi, R<sub>2</sub>Zn),  $\pi$ -rich arenes (Friedel–Crafts reaction), allyl silanes and stannanes, as well as enolates and their synthetic equivalents (Mannich reaction).<sup>2</sup> The seminal work of Petasis expanded the scope of the Mannich reaction by demonstrating that vinyl boronic acids undergo 1,2-addition to iminium ions as part of a three-component coupling.<sup>3</sup> Subsequent studies have demonstrated that  $\pi$ -rich aryl and heteroaryl boronic acids also participate in the reaction, but  $\pi$ -neutral and  $\pi$ -deficient aryl boronic acids show little or no reactivity in the absence of directing groups on the substrate.<sup>4</sup> Herein, we report a distinct strategy to effect catalytic C–C bond formation with *N*-acyliminium ions and organoboronates.

As a first example, we document a Ni(0)-catalyzed Petasis-like transformation between  $\pi$ -neutral and  $\pi$ -deficient aryl boronic acids and quinoline-derived *N,O*-acetals. Application of this strategy to the three-component coupling of azaaromatics, chloroformates, and aryl boronic acids provides a general route

**Petasis reaction:** confined to  $\pi$ -rich and vinyl boronic acids



**Transition metal catalysis:** amenable to  $\pi$ -neutral and  $\pi$ -deficient boronic acids



for the construction of 2-arylated dihydroquinolines and 1-arylated dihydroisoquinolines that comprise the core of numerous bioactive agents.<sup>5</sup>

Pioneering studies by Beller and Arntdsen have documented the ability of coordinatively unsaturated transition metal catalysts to oxidatively insert into *N*-acyliminium ion precursors.<sup>6</sup> Subsequent reports by Arntdsen established that the resulting cyclometalated adducts undergo C–C bond formation with vinyl stannanes as well as carbonylative coupling reactions with vinyl and aryl stannanes.<sup>7</sup> Given the intriguing reactivity profile of such complexes, we proposed that *N*-acyliminium-derived metallacycles might function as intermediates in Suzuki–Miyaura reactions with appropriate organoboronate partners. In contrast to the Petasis reaction, transition metal-catalyzed cross-coupling methodologies have progressed to such a degree that high efficiency is achieved nearly independently of the electronic nature and structure of the organometallic reagent. Consequently, we envisioned that this approach would expand conventional iminium additions to those previously inaccessible by Friedel–Crafts

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chemistry, allowing stable and widely available aryl, vinyl, and alkyl boronates to function as competent nucleophiles under mild and functional group-tolerant conditions.<sup>8</sup> In addition, this approach could provide a common mechanism amenable to the development of catalyst-controlled enantioselective C–C bond-forming reactions, and in so doing, represents a strategic alternative for the asymmetric catalytic synthesis of nitrogen-containing heterocycles.<sup>9</sup>

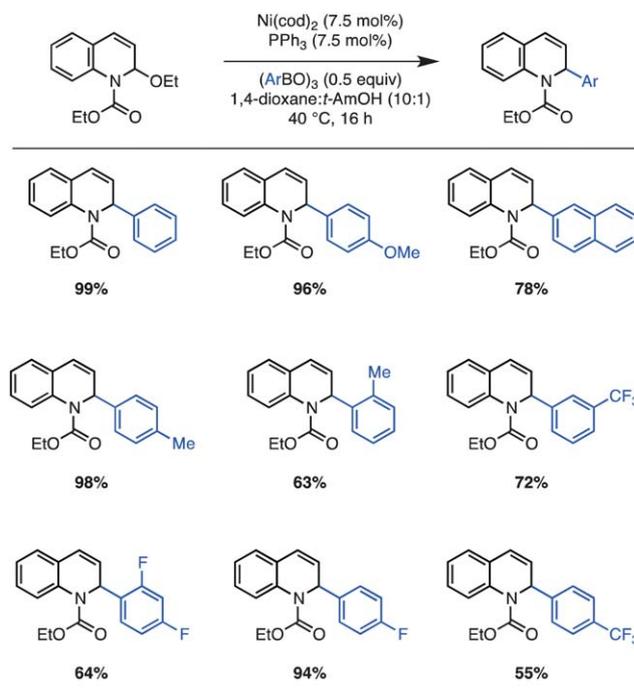
## Results and discussion

To test this proposal, commercially available 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) was selected as a substrate for initial catalyst screening studies.<sup>10</sup> *N,O*-Acetals such as EEDQ serve as convenient *N*-acyliminium ion precursors that can be revealed by mild Lewis or Brønsted acid additives.<sup>1</sup> We surmised that the Lewis acidic nature of the boronic acids<sup>11</sup> might be sufficient to (1) facilitate oxidative addition<sup>12</sup> of a low valent metal to the *N,O*-acetal substrate and (2) simultaneously activate the boronic acid toward transmetalation *via* formation of an ate complex.<sup>13</sup>

Transition-metal complexes typically employed in imine arylation<sup>14</sup> and Suzuki cross coupling<sup>15</sup> were evaluated for their ability to promote C–C bond formation between EEDQ and *p*-fluorophenyl boronic acid (*p*-F-PhB(OH)<sub>2</sub>) at 40 °C (Table 1). Notably, less than 5% product was formed in the absence of a transition metal catalyst after 16 h, unambiguously demonstrating the limitations of the traditional Petasis borono–Mannich reaction (Table 1, entry 1). In keeping with the ability of [Rh]–Ar and [Ir]–Ar intermediates to undergo efficient conjugate addition,<sup>16</sup> reactions with [Rh(cod)Cl]<sub>2</sub> and [Ir(cod)Cl]<sub>2</sub> gave the undesired 1,4-dihydroquinoline regioisomer in >20 : 1 rr,<sup>17</sup> albeit in low yield (Table 1, entries 2 and 3). In contrast, a Pd(0) catalyst provided the dihydroquinoline product in an improved 52% yield and with high 1,2-regioselectivity, consistent with the intermediacy of a chelated intermediate (Table 1, entry 4). Among the other transition metal catalysts examined, Ni(cod)<sub>2</sub> with equimolar PPh<sub>3</sub> (7.5 mol% each) proved optimal (Table 1, entry 6).<sup>18</sup> With this catalyst system, the desired product was isolated in 94% yield and >20 : 1 rr when the cyclic anhydride of the boronic

acid (aryl boroxine = (ArBO)<sub>3</sub>) was employed (Table 1, entry 7).<sup>19</sup> Since EEDQ is susceptible to decomposition by hydrolysis,<sup>20</sup> use of the boroxine leads to higher reaction efficiency at least in part by minimizing the amount of H<sub>2</sub>O introduced to the reaction.

These optimized conditions are general for aryl-boroxines containing substitution at the *ortho*, *meta*, and *para* positions (Scheme 1). In the case of  $\pi$ -neutral aryl-boroxines, near-quantitative yields are obtained for the cross coupling. Perhaps most important, the reaction proceeds well with electron-deficient boronic acids that are traditionally inert to Petasis conditions



**Scheme 1** Ni(0)-catalyzed arylation of EEDQ: scope. Isolated yields after column chromatography for reactions run on 0.50 mmol scale (average of two runs).

**Table 1** Evaluation of transition metals for the catalytic addition of boronic acids to *N*-acyliminium precursor EEDQ<sup>d</sup>

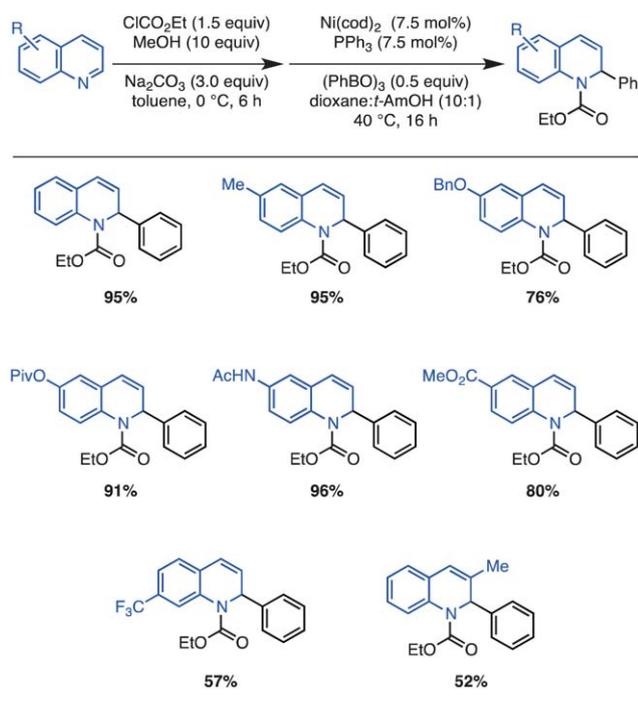
Entry	Catalyst	Nucleophile	Yield (%)	rr <sup>b</sup>
1	None	<i>p</i> -F-PhB(OH) <sub>2</sub>	<5 <sup>c</sup>	—
2	[Rh(cod)Cl] <sub>2</sub>	<i>p</i> -F-PhB(OH) <sub>2</sub>	24	1 : >20
3	[Ir(cod)Cl] <sub>2</sub>	<i>p</i> -F-PhB(OH) <sub>2</sub>	9	1 : >20
4	Pd <sub>2</sub> (dba) <sub>3</sub> /PPh <sub>3</sub> (1 : 1)	<i>p</i> -F-PhB(OH) <sub>2</sub>	52	>20 : 1
5	Ni(PPH <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	<i>p</i> -F-PhB(OH) <sub>2</sub>	<5	—
6	Ni(cod) <sub>2</sub> /PPh <sub>3</sub> (1 : 1)	<i>p</i> -F-PhB(OH) <sub>2</sub>	74 <sup>d</sup>	>20 : 1
7	Ni(cod) <sub>2</sub> /PPh <sub>3</sub> (1 : 1)	( <i>p</i> -F-PhBO) <sub>3</sub> <sup>e</sup>	94 <sup>d</sup>	>20 : 1

<sup>a</sup> See supporting information for details. † Yields determined by <sup>19</sup>F NMR using PhCF<sub>3</sub> as a quantitative internal standard. <sup>b</sup> 1,2 : 1,4 regioisomeric ratio; determined by <sup>19</sup>F NMR analysis of the crude reaction mixture. <sup>c</sup> Reactions run at 60 °C, 80 °C, and 100 °C provide similar results. <sup>d</sup> Isolated yield after column chromatography. <sup>e</sup> Using 0.5 equiv of (*p*-F-PhBO)<sub>3</sub>.

(Scheme 1, 55–95% yield). Hindered boronic acids are also competent reaction partners, although C–C bond formation takes place with reduced efficiency (*e.g.* *o*-tolyl boroxine: 63% yield). On the other hand, our initial attempts using  $\pi$ -deficient heteroaryl boroxines (*e.g.* 3-pyridyl boroxine), challenging partners for  $C_{sp^2}$ – $C_{sp^2}$  Suzuki cross couplings,<sup>21</sup> led to no reaction. In all cases, exclusion of the Ni(0) catalyst provides minimal product (<5%).

Considering the value of quinoline-derived intermediates in complex target and bioactive molecule synthesis,<sup>22</sup> we sought a simple, one-pot protocol amenable to the direct use of substituted quinolines (Scheme 2). Treatment of quinoline with excess ethyl chloroformate, MeOH, and  $Na_2CO_3$ ,<sup>23</sup> followed by exposure to the optimized nickel-catalyzed conditions, provided the dihydroquinoline cross-coupling product in 95% yield (Scheme 2; compared with 99% from EEDQ in Scheme 1).<sup>24</sup>

A survey of the scope of this *in situ* protocol was conducted, revealing that quinolines substituted with common functional groups at the 6-position are well tolerated (Scheme 2). However, quinolines substituted at the 7-position with strong electron-withdrawing groups or at the 3-position with alkyl groups react with reduced efficiency. The efficient formation of dihydroquinolines bearing amides and esters is worthy of direct mention since their preparation using strongly nucleophilic organomagnesium or organolithium reagents would likely not be successful. Notably, in all cases, the dihydroquinoline products are obtained in >20:1 regioselectivity whereas mixtures of regioisomers typically result from uncatalyzed reactions with stronger nucleophiles.

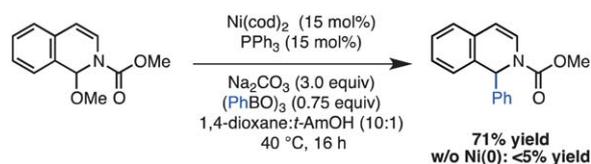


**Scheme 2** One-pot *N,O*-acetal formation and Ni(0)-catalyzed arylation of substituted quinolines: scope. Isolated yields after column chromatography for reactions run on 0.50 mmol scale (average of two runs).

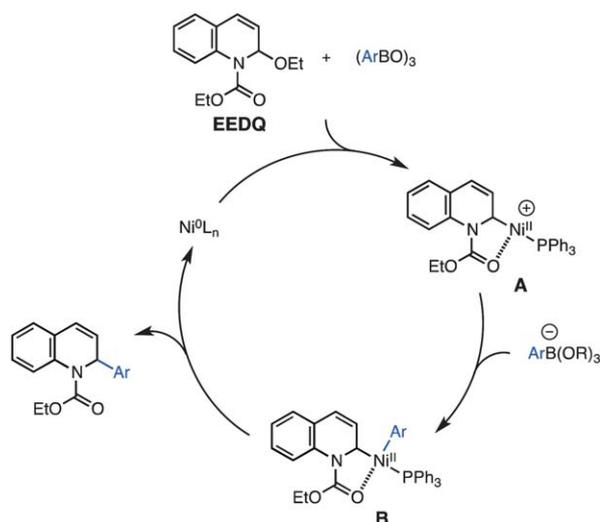
We next tested whether the reaction could be extended to the arylation of other azaaromatic substrates. Although it was necessary to increase the catalyst loading (15 mol%) and equivalents of phenyl boroxine (0.75 equiv), the reaction with an isoquinoline-derived *N,O*-acetal proceeded in a promising 71% yield (Scheme 3). This result provides a preliminary indication of the utility of the catalytic strategy to effect addition reactions with an array of *N*-acyliminium ion precursors.

A preliminary proposal for the mechanism of the nickel-catalyzed coupling is presented in Scheme 4. As a working hypothesis, we suggest that the boroxine coupling partner facilitates addition of Ni(0) to EEDQ through ionization of the *N,O*-acetal, affording a Ni(II) complex **A**,<sup>25,26</sup> analogous to the palladium complexes characterized by Arndtsen.<sup>6d</sup> According to a traditional cross-coupling cycle, transmetalation between **A** and the boronic acid ate complex to give **B**, followed by reductive elimination, would deliver the arylated product and complete catalyst turnover. An alternative mechanism in which the nickel catalyst undergoes direct oxidative addition to the allylic ether of EEDQ and the benzylic ether of the isoquinoline *N,O*-acetal (Scheme 3) is also plausible in light of related studies on nickel-catalyzed substitutions with allylic ethers.<sup>27</sup> However, a few pieces of information suggest a role for the boroxine as a Lewis acid activator of the C–O bond of the *N,O*-acetal. The use of phenyl boronate esters and phenyl trifluoroborate<sup>28</sup> as nucleophiles in place of phenyl boroxine/boronic acid led to no reaction, consistent with their reduced Lewis acidity. In addition, preliminary NMR experiments have shown that the nickel catalyst does not undergo oxidative addition to EEDQ in the absence of additives.

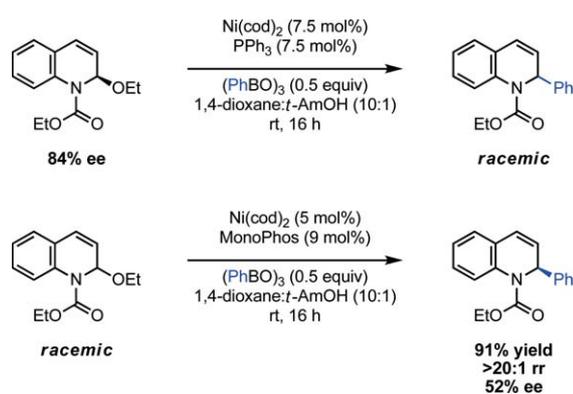
To further test this proposed mechanism, enantioenriched EEDQ (84% ee) was subjected to the nickel-catalyzed cross-coupling conditions with phenyl boroxine; in accord with the intermediacy of an *N*-acyliminium ion and/or a configurationally unstable organonickel complex, the dihydroquinoline product was formed as a racemic mixture. Similarly, exposure of EEDQ (84% ee)<sup>29</sup> to phenyl boroxine in the absence of the nickel catalyst led to racemization of EEDQ over 5 h. Importantly, these observations suggest that attempts at rendering the coupling reaction enantioselective will not be complicated by kinetic resolution of the racemic starting material. Indeed, we have obtained promising preliminary evidence that a chiral catalyst imparts modest levels of asymmetry within the coupling protocol (Scheme 5). Use of the chiral phosphoramidite ligand, Monophos, in place of PPh<sub>3</sub> led to the efficient room temperature coupling of phenyl boroxine and EEDQ in 52% ee.<sup>29</sup> Notably, this example constitutes the first reported catalytic asymmetric arylation of *N*-acylquinolinium ions.<sup>9a</sup>



**Scheme 3** Application of Ni(0)-catalyzed arylation to an isoquinoline derived *N,O*-acetal.



Scheme 4 Proposed mechanism.



Scheme 5 Asymmetric Ni(0)-catalyzed arylation of EEDQ.

## Conclusions

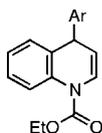
In summary, we have developed a Ni(0)-catalyzed reaction that facilitates efficient coupling between a wide range of  $\pi$ -neutral and  $\pi$ -deficient aryl boronic acids and *N*-acyliminium precursors derived from quinoline and isoquinoline. Preliminary studies indicate a mechanism involving organoboronate-mediated activation of EEDQ and support the viability of rendering the process enantioselective. Application of the protocol to related substrate classes and further development of an enantioselective method are ongoing and will be reported in due course.

## Acknowledgements

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- 29 The absolute stereochemistry has not been confirmed at this time.