Cross-Coupling Methods

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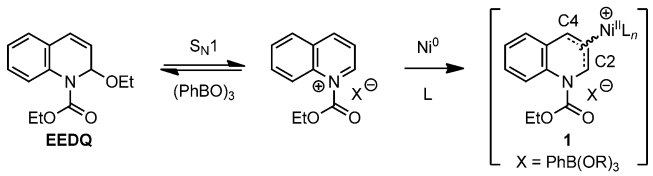
# Nickel-Catalyzed Enantioselective Arylation of Pyridinium Ions: Harnessing an Iminium Ion Activation Mode**

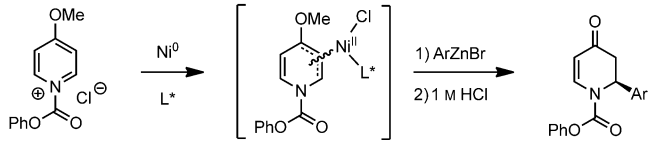
*Stephen T. Chau, J. Patrick Lutz, Kevin Wu, and Abigail G. Doyle**

The ability to engage cationic substrates such as iminium and oxocarbenium ions in transition-metal-catalyzed C–C bond formation is a challenging task that has recently seen successful application.[1] In this context, we reported that a low-valent Ni catalyst facilitates unprecedented Suzuki–Miyaura cross-coupling reactions with allylic *N*,*O*- and *O*,*O*-acetal substrates.[2,3] Mechanistic studies revealed that boronic acids mediate allylic C–O activation, with oxidative addition occurring between the resulting iminium or oxocarbenium ion intermediate and the Ni catalyst (Scheme 1 a).[4]

a) *Prior work: Elucidation of an ionic oxidative addition pathway*




b) *This work: Application to asymmetric cross coupling with pyridinium ions*




***Scheme 1.*** Nickel-catalyzed cross-coupling with iminium ions.

The demonstration that a transition-metal catalyst can oxidatively insert into these prochiral intermediates offers a number of exciting possibilities for reaction design and enantioselective synthesis. Herein, we demonstrate that this activation mode enables the enantioselective synthesis of α-substituted 2,3-dihydro-4-pyridones by Negishi cross-coupling with *N*-acyl pyridinium ions (Scheme 1 b).

α-Substituted piperidines are among the most prevalent scaffolds in biologically active small molecules, and also serve as building blocks for natural product and pharmaceutical synthesis.[5] The stereoselective addition of carbon-centered nucleophiles to activated pyridines is a particularly attractive route to these core structures.[6] Seminal work from the groups of Comins and Charette established the possibility of using stoichiometric chiral acylating agents to control the stereochemical outcome of C–C bond formation.[7,8] However, only two examples have been described for the catalytic enantioselective addition of organometallic reagents to prochiral *N*-acyl/alkyl pyridinium ions.[9] Both of these reactions likely proceed through the addition of a chiral [M]-R species into a prochiral pyridinium salt (M = Cu or Rh). As such, the strategy is limited to reactions with either highly nucleophilic R groups or highly electrophilic pyridinium ions. As the oxidative addition/reductive elimination mechanism that we elucidated for cross-coupling with *N*-acyl quinolinium salts should not be subject to these same limitations, we envisioned that its application to enantioselective cross-coupling with pyridinium ions could provide a complementary approach to these methods. Furthermore, successful development of such a reaction would demonstrate for the first time that iminium ion activation by $Ni^0$ is subject to highly enantioselective C–C bond formation.

One challenge apparent at the outset of our endeavors was potential catalyst poisoning in the presence of free pyridine. To address this issue, we chose to use 4-methoxypyridine as a substrate, because it shows substantial formation of a pyridinium salt with chloroformates at −78 °C.[10] To enable facile transmetalation at low temperature, a Negishi reaction platform was selected.[11] Notably, when we initiated the reaction at −78 °C with warming to RT, the combination of [{(methallyl)NiCl}$_2$] (7.5 mol %) and (*R*)-Monophos (**L1**; 18 mol %) was found to promote arylation of 4-methoxypyridine in the presence of phenyl chloroformate and 4-$FC_6H_4ZnBr$ with low but measurable *ee* (Table 1, entry 1).[12] Commercial phosphoramidite ligands **L2**–**L4**, which bear substituents at the 3 and 3′ positions of the binaphthyl backbone, induced more promising levels of asymmetric induction (up to 91 % *ee*, entries 2–4).[13] Accordingly, an extensive library of 3,3′-substituted ligands was prepared and evaluated, revealing that ligand **L7** was optimal (entry 7). With this ligand, the 2,3-dihydro-4-pyridone product **2a** was obtained in 95 % *ee*, albeit with moderate reaction efficiency.

Upon selection of an optimal ligand (**L7**), we pursued further optimization of the reaction parameters. Among the Ni sources examined, $NiBr_2$·diglyme was most promising, as its use increased the yield of the reaction while maintaining high levels of enantioselectivity (Table 2, entry 2). This result is particularly attractive because $NiBr_2$·diglyme is air stable,

[*] S. T. Chau, J. P. Lutz, K. Wu, Prof. A. G. Doyle
Department of Chemistry, Princeton University
Washington Rd, Princeton, NJ 08544-1009 (USA)
E-mail: agdoyle@princeton.edu
Homepage: http://www.princeton.edu/~doylegrp/

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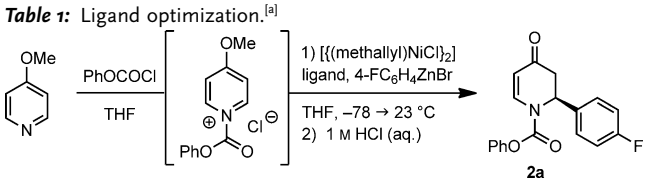
***Table 1:*** Ligand optimization.[a]




| Entry | Ligand | R | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 | **L1** | H | 9 | 18 |
| 2 | **L2**[d] | Me | 11 | −40 |
| 3 | **L3** | Ph | 8 | 79 |
| 4 | **L4** | OMe | 52 | 91 |
| 5 | **L5** | OEt | 54 | 92 |
| 6 | **L6** | O*i*Pr | 61 | 96 |
| 7 | **L7** | O*n*Pr | 64 | 95 |
| 8 | **L8** | O*i*Bu | 57 | 96 |
| 9 | **L9** | – | 8 | −40 |

[a] Reactions run on a 0.05 mmol scale; [{(methallyl)NiCl}$_2$] (7.5 mol%), ligand (18 mol%), 4-FC$_6$H$_4$ZnBr (4 equiv; 0.3 M solution in THF), and phenyl chloroformate (4 equiv). [b] Determined by $^{19}$F NMR spectroscopy with 1,4-difluorobenzene as a quantitative internal standard. [c] Determined by HPLC analysis on a chiral stationary phase. [d] **L2** was derived from (*S*)-1,1′-bi-2-naphthol.

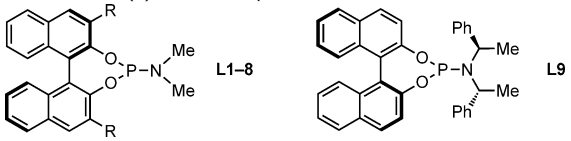
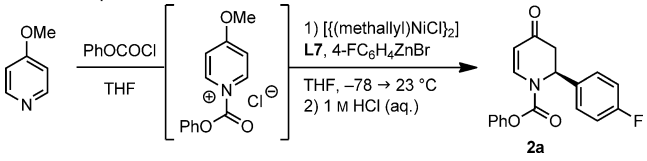



***Table 2:*** Optimization of reaction conditions.[a]

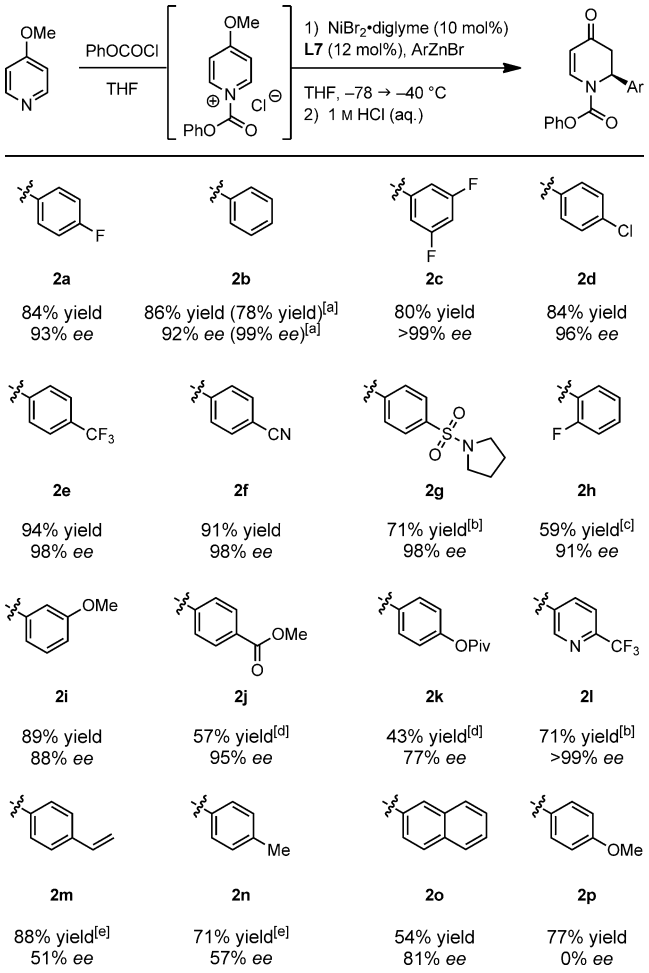



| Entry | Deviation from standard conditions | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|
| 1 | none (standard conditions) | 64 | 95 |
| 2 | $NiBr_2$·diglyme (15 mol%) | 76 | 95 |
| 3 | $NiCl_2$·glyme (15 mol%) | 51 | 89 |
| 4 | [Ni(cod)$_2$] (15 mol%) | 32 | 72 |
| 5 | No nickel or ligand | 23 | 0 |
| 6 | 4-FC$_6$H$_4$ZnBr (2 equiv) | 21 | 91 |
| 7 | benzyl chloroformate | 33 | 90 |
| 8 | ethyl chloroformate | 21 | 73 |
| 9 | $NiBr_2$·diglyme (10 mol%), **L7** (12 mol%) | 88[d] | 93 |
| 10 | $NiBr_2$·diglyme (5 mol%), **L7** (6 mol%) | 73[e] | 93 |

[a] Reactions run on a 0.05 mmol scale; [{(methallyl)NiCl}$_2$] (7.5 mol%), ligand (**L7**; 18 mol%), 4-FC$_6$H$_4$ZnBr (4 equiv; 0.3 M solution in THF), and phenyl chloroformate (4 equiv). [b] Determined by $^{19}$F NMR spectroscopy with 1,4-difluorobenzene as a quantitative internal standard. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Yield of isolated product on a 0.5 mmol scale. [e] Yield of isolated product on a 5 mmol scale with the reaction warmed to −40 °C. cod = 1,5-cyclooctadiene.

thus permitting the reactions to be set up on the benchtop. In the absence of a Ni source, the reaction performs poorly, demonstrating that Ni induces substantial rate acceleration (entry 5). Additional changes to the reaction conditions, such as decreasing the amount of nucleophile or changing the identity of the acylating agent, had a negative effect on reactivity (entries 6–8). On the other hand, decreasing the Ni loading from 15 mol% to 10 mol% provided nearly identical levels of enantioselectivity and reaction efficiency (entry 9). A gram-scale reaction set up on the benchtop using a catalyst loading of 5 mol% delivered **2a** in 73% yield and 93% *ee* (entry 10).

Having identified conditions to prepare **2a** in high yield and enantiomeric excess, a survey of aryl zinc nucleophiles was conducted to evaluate the scope of the reaction (Scheme 2).[14] Phenyl zinc bromide afforded 2,3-dihydro-4-




***Scheme 2.*** Scope of aryl zinc nucleophiles in the reaction. Yields and *ee* values are the average of two runs on a 0.5 mmol scale. [a] Yield and *ee* after recrystallization from ether. [b] Reaction warmed to RT. [c] Reaction warmed to −20 °C. [d] Derived from an ArZnCl solution (0.3 M in THF). [f] Reaction warmed to −50 °C.

pyridone **2b** in 92% *ee*, which could be recrystallized to >99% *ee* in 78% yield. Generally, *ortho*-, *meta*-, and *para*-substituted zinc nucleophiles are well tolerated. Reactions with electron-withdrawing zinc reagents fared exceptionally well, delivering products bearing 3,5-difluoro (**2c**), 4-Cl (**2d**), 4-CF$_3$ (**2e**), 4-cyano (**2f**), and 4-sulfonamide (**2g**) groups in 96–99% *ee*. Notably, zinc reagents substituted with methyl ester and pivaloate groups afforded products (**2j**, **2k**) that are otherwise inaccessible by standard Grignard methods. Moreover, a reaction with a heteroaromatic nucleophile furnished

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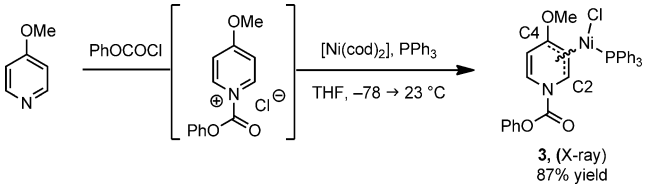
**21** in excellent *ee* and yield, highlighting the potential of this strategy to deliver medicinally relevant products. Whereas electron-neutral aryl zinc nucleophiles such as 4-vinyl (**2m**), 4-Me (**2n**) and 2-naphthyl (**2o**) performed modestly in terms of enantioselectivity, electron-rich nucleophiles such as 4-OMe (**2p**) underwent reaction with no stereoinduction owing to a competitive racemic background reaction (77% yield of isolated product without nickel).[15] An additional limitation is that other electrophile partners, including pyridine, 2-methoxy-pyridine, and 4-dimethylaminopyridine (DMAP), are not competent under the optimized conditions.

To understand the mechanism of this transformation, we studied the stoichiometric reaction of $Ni^0$ with the pyridinium salt derived from 4-methoxypyridine and phenyl chloroformate, which was generated in situ. For simplicity, we chose to conduct our studies with $PPh_3$, as it is a competent ligand for the reaction of interest, providing (±)-**2a** in 87% yield under otherwise standard reaction conditions.[13] In the event, an air-sensitive allyl–$Ni^{II}$ adduct **3** was produced in 87% yield (Scheme 3), the structure of which was confirmed by single




***Scheme 3.*** Stoichiometric reaction between $Ni^0$ and a pyridinium ion.

crystal X-ray diffraction (Figure 1). When subjected to 4-$FC_6H_4ZnBr$, allyl adduct **3** underwent C–C bond formation, providing **2a** in 25% yield [Eq. (1)]. Furthermore, **3** is catalytically competent, providing racemic **2a** in 68% yield at 10 mol% catalyst loading [Eq. (2)]. Taken together, these data provide compelling evidence for a redox mechanism distinct from that typically considered for transition-metal-catalyzed addition reactions to pyridinium ions.

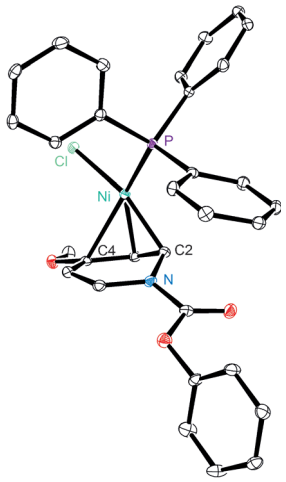
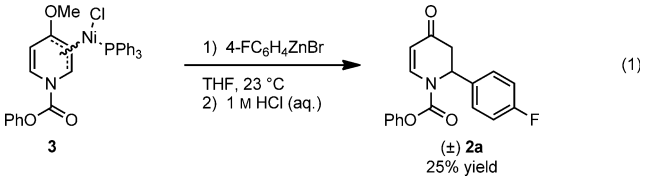
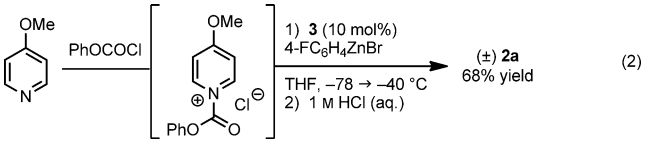



***Figure 1.*** Solid-state structure of allyl $Ni^{II}$ complex **3**. Ellipsoids set at 30% probability. Hydrogen atoms omitted for clarity.

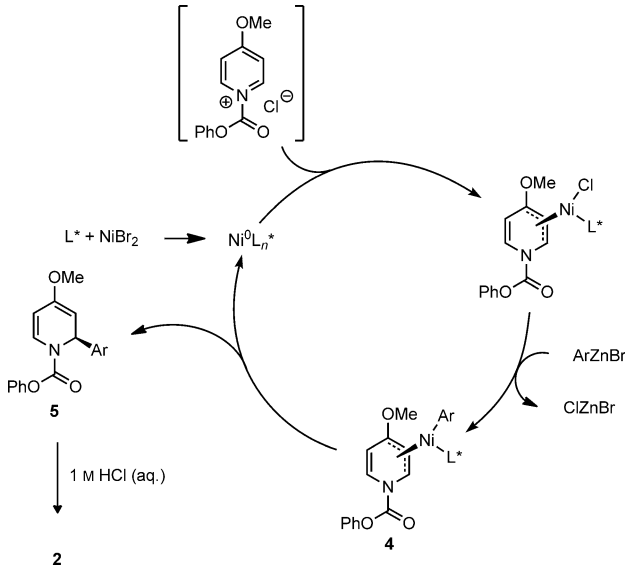



(1)




(2)

With these data in mind, we propose the reaction mechanism shown in Scheme 4. Oxidative addition of $Ni^0$ into the C–N π bond of the pyridinium salt provides a $Ni^{II}$ allyl intermediate analogous to complex **3**.[16] Subsequent




***Scheme 4.*** Proposed catalytic cycle.

transmetalation with ArZnBr gives diorganonickel intermediate **4**, which can undergo reductive elimination to regenerate the $Ni^0$ catalyst and complete the catalytic cycle.[17] The presence of the methoxy substituent at C4 presumably serves as a blocking group, favoring the observed regioisomeric dihydropyridine **5**.[18] Acid hydrolysis of **5** then affords the 2,3-dihydro-4-pyridone product **2**.

In conclusion, we have described a novel nickel-catalyzed enantioselective Negishi cross-coupling reaction of 4-methoxypyridinium salts. A broad range of synthetically valuable enantioenriched 2,3-dihydro-4-pyridones can be obtained from commercially available or readily prepared starting materials and an air-stable, inexpensive $Ni^{II}$ precatalyst. Preliminary mechanistic data support the intermediacy of a $Ni^{II}$ π-allyl intermediate generated upon ionic oxidative addition of $Ni^0$ to the pyridinium electrophile. The study

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provides an exciting indication of the generality of this mode of activation and its amenability to asymmetric catalysis.

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