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Enantioselective, Nickel-Catalyzed Suzuki Cross-Coupling of Quinolinium Ions

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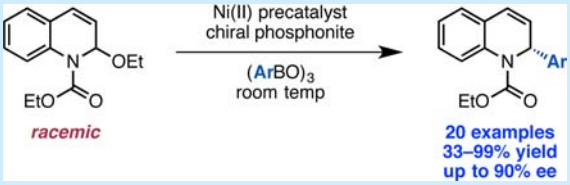
Supporting Information

ABSTRACT: Quinolinium ions are engaged in an asymmetric, Ni-catalyzed Suzuki cross-coupling to yield 2-aryl- and 2-heteroaryl-1,2-dihydroquinolines. Key to the development of this method is the use of a Ni(II) precatalyst that activates without the need for strong reductants or high temperatures. The Ni−iminium activation mode is demonstrated as an exceptionally mild pathway to generate enantioenriched products from racemic starting materials.



Our laboratory recently reported a Ni-catalyzed cross-coupling reaction between arylboroxines and allylic *N,O*-acetals embedded within quinolines (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinolines or EEDQs).[1] This reaction was notable in part because it proceeded in a stereoconvergent manner from enantioenriched EEDQ, whereas previously described coupling reactions with related substrate classes were shown to be stereospecific.[2] Detailed mechanistic studies indicated that stereoconvergency arises from boronate-assisted ionization of the substrate, followed by an unusual ionic oxidative addition of Ni into the resulting prochiral quinolinium intermediate.[3] Accordingly, we were interested in whether a chiral Ni catalyst could be identified that would transform the racemic *N,O*-acetal substrates into single enantiomer products (Figure 1). Such a

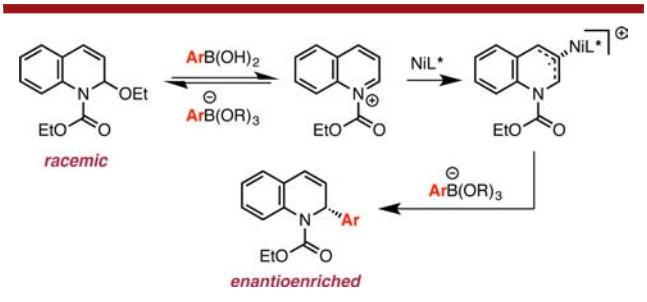


Figure 1. Ni−iminium activation mode for asymmetric catalysis.

transformation would unite the advantages of the Suzuki−Miyaura cross coupling (broad functional group tolerance, low cost and toxicity of boronic acids) with the advantages of asymmetric catalysis (step and atom economy) in a rare example of an enantioselective cross coupling of a racemic electrophile bearing an oxygen leaving group.[4] Herein we describe the successful realization of this goal and our accompanying discovery of a Ni(II) precatalyst that proved critical to the identification of a highly enantioselective process.

In addition to demonstrating the potential of the Ni−iminium activation mode for enantioselective cross coupling,[5] this method allows modular access to enantioenriched 2-substituted dihydroquinoline derivatives, an important pharmaceutical scaffold.[6,7] The catalytic, asymmetric addition of a nucleophile to quinolinium ions represents an underutilized but attractive method to access this motif due to the ready availability of quinolinium precursors.[8,9] Building on seminal studies by Shibasaki using TMSCN as nucleophile,[10] Takemoto and Schaus have described highly enantioselective organocatalytic addition reactions with boronate nucleophiles; however, both methods are restricted to the use of cinnamyl boronates.[11,12] Similar restrictions were encountered by Arndtsen and co-workers in their asymmetric addition of alkynes to quinolines via Cu catalysis.[13] The only successful use of an aryl nucleophile involves the addition of organolithium reagents to quinoline as reported by Alexakis.[14] Unfortunately, this method is quite limited with regard to scope and selectivity, and dependence on the use of (−)-sparteine is prohibitive due to the alkaloid's shortage.

With the aim of developing an enantioselective quinolinium arylation reaction, we began by evaluating a variety of chiral phosphine ligands using $Ni(cod)_2$ as the Ni(0) source according to our previously reported racemic method (Table 1). Monodentate and bidentate phosphines provided poor reactivity, poor enantioselectivity, or both.[15] The phosphoramidite ligand (*R*)-MonoPhos (**L1**) represented the most promising candidate, giving cross-coupled product in 97% yield and 58% ee (entry 2). Unfortunately, an extensive ligand screening effort failed to yield a significant increase in enantioselectivity when $Ni(cod)_2$ was used as precatalyst. For example, substitution at the 3,3′-positions of (*R*)-Monophos decreased the enantioselectivity to 13% ee, (entry 3) and variations at the amine resulted in depressed ee (entries 4 and 5).

During this process, it was found that $Ni(cod)_2$ catalyzed a facile racemic background reaction (Table 1, entry 1).[16] Since this could impede high enantioselectivity in the absence of ligand-accelerated catalysis or rapid and strong ligand binding, we sought to generate cod-free Ni(0) in situ from a Ni(II)

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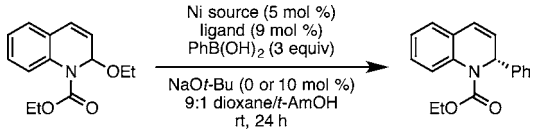
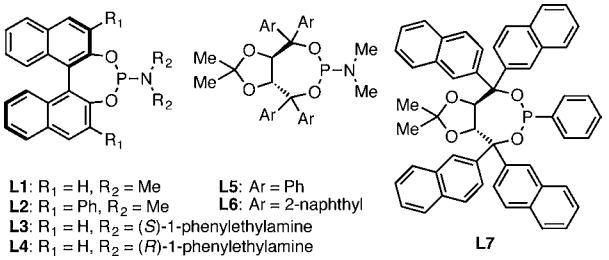
Table 1. Catalyst Development



entry	Ni source[a]	ligand	yield[b,c] (%)	ee[d] (%)
1	$Ni(cod)_2$	none	99	–
2	$Ni(cod)_2$	**L1**	97	58
3	$Ni(cod)_2$	**L2**	62	−13
4	$Ni(cod)_2$	**L3**	94	49
5	$Ni(cod)_2$	**L4**[e]	4	nd
6	$[(methallyl)NiCl]_2$	none	23	–
7	$[(methallyl)NiCl]_2$	**L1**	18	66
8	$[(methallyl)NiCl]_2$	**L2**	17	−39
9	$[(methallyl)NiCl]_2$	**L3**	28	58
10	$[(methallyl)NiCl]_2$	**L4**[e]	56	39
11	$[(methallyl)NiCl]_2$	**L5**	18	60
12	$[(methallyl)NiCl]_2$	**L6**	19	73
13	$[(methallyl)NiCl]_2$	**L7**	15	75
14[f]	$[(methallyl)NiCl]_2$	**L7**	89	75

[a]Base added for $[(methallyl)NiCl]_2$ only; 2.5 mol % dimer. [b]Reactions run on a 0.025 mmol scale at 0.01 M under an N_2 atmosphere. [c]Yields determined by gas chromatography. [d]Enantiomeric excess determined by chiral HPLC. [e]**L4** is sold as the dichloromethane adduct, which poisons the $Ni(cod)_2$ catalyst. [f]5 mol % dimer, 15 mol % **L7**, 0.75 equiv $(PhBO)_3$, 15 mol % $NaOPh{\cdot}3H_2O$.

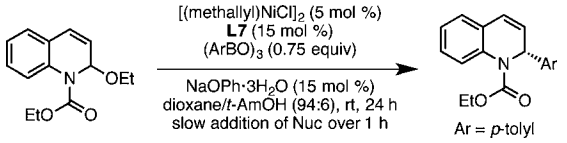


precatalyst.[17,18] In this regard, the use of a Ni(II) salt with a reducing agent such as Zn is well-known.[19] However, we found that the *N,O*-acetal starting material was prone to decomposition in the presence of reducing agents, prohibiting application of these commonly adopted procedures. For this reason, we turned to the mild conditions reported by Nolan for the reduction of a $[(cinnamyl)PdCl]_2$ precatalyst with catalytic alkoxide.[20] We reasoned by analogy that $[(methallyl)NiCl]_2$ could be reduced to Ni(0) by the nucleophilic attack of *tert*-butoxide.[21] A similar pathway may be operative in the activation of [(dppf)Ni(cinnamyl)Cl], a Ni(II) precatalyst for sp^2–sp^2 cross-coupling recently reported by the Hartwig group.[22]

In the event, $[(methallyl)NiCl]_2$ gave product in 18% yield with 66% ee in the presence of (*R*)-MonoPhos and NaO-*t*-Bu (Table 1, entry 7). Notably, a slower racemic background reaction allowed the coordination of hindered ligands such as **L2**–**L4** (entries 8–10), providing product in higher ee than with $Ni(cod)_2$ (Table 1, compare to entries 3–5). More encouragingly, TADDOL-derived ligands provided up to 75% ee when used in conjunction with $[(methallyl)NiCl]_2$, although yields were low (Table 1, entries 11–13).[23]

Having identified a promising catalyst, other parameters were modified. The use of boroxine instead of boronic acid, increased catalyst loading, decreased ligand/metal ratio, and the use of $NaOPh{\cdot}3H_2O$ instead of *tert*-butoxide were found to increase

Table 2. Reaction Optimization



entry	conditions	yield[a,b] (%)	ee[c] (%)
1	no slow addition	70	81
2	standard	85	87
3	NaOPh instead of $NaOPh{\cdot}3H_2O$	48	89
4	NaO-*t*-Bu instead of $NaOPh{\cdot}3H_2O$	45	84
5	$ArB(OH)_2$ instead of $(ArBO)_3$[d]	43	85
6	ArBpin instead of $(ArBO)_3$[d]	0	nd
7	$ArBF_3K$ instead of $(ArBO)_3$[d]	0	nd
8	0.1 M instead of 0.01 M	79	71
9	dioxane only	87	75

[a]Reactions run on a 0.5 mmol scale at 0.01 M under an N_2 atmosphere. [b]Isolated yields. [c]Enantiomeric excess determined by chiral HPLC. [d]2.25 equiv of boronate nucleophile.

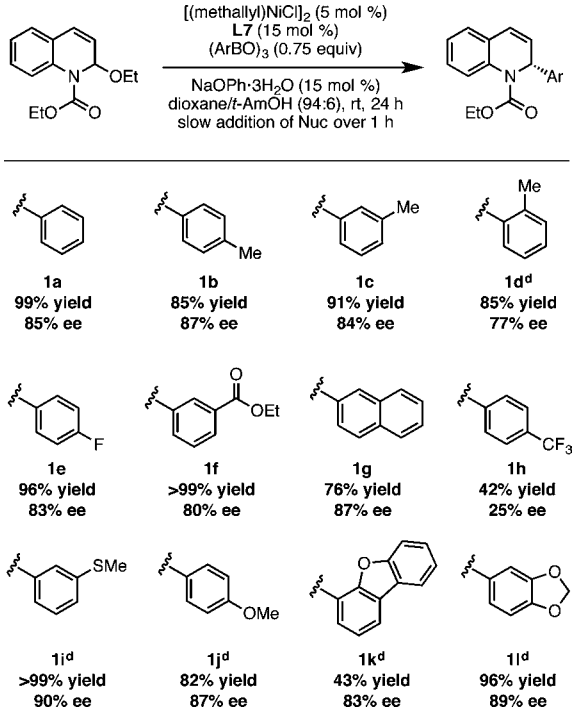


Figure 2. Nucleophile scope. (a) Reactions run on a 0.5 mmol scale at 0.01 M under an N_2 atmosphere. (b) Isolated yields (average of two runs). (c) Enantiomeric excess determined by chiral HPLC (average of two runs). (d) 10 mol % $[(methallyl)NiCl]_2$, 30 mol % **L4**, 30 mol % $NaOPh{\cdot}3H_2O$, 48 h.

yield (Table 1, entry 14, and the Supporting Information). These conditions were then tested on a larger scale using *p*-tolylboroxine to ensure reproducibility (Table 2, entry 1). Slow addition of arylboroxine was found to provide a boost to yield and enantioselectivity (entry 2). Under these optimal conditions, the enantioselective arylation took place with 85% yield and 87% ee at a 0.5 mmol scale. Perturbations to this system decreased yield or enantioselectivity (entries 3–9).

Next, the scope of the reaction was investigated (Figure 2). Substitution at the *meta* and *para* positions of the nucleophile was well-tolerated in the reaction (**1b**,**c**), whereas substitution at the *ortho* position required an increase in catalyst loading and

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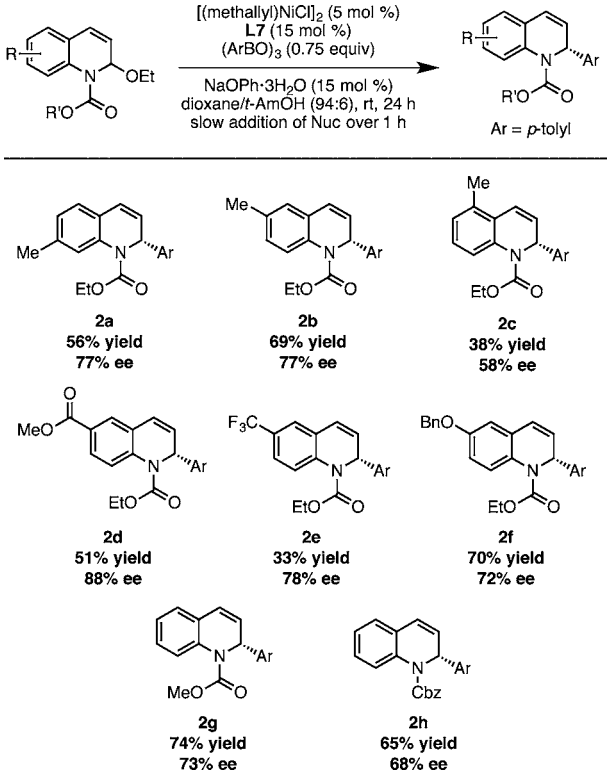

Figure 3. Electrophile scope. (a) Reactions run on a 0.5 mmol scale at 0.01 M under an N_2 atmosphere. (b) Isolated yields (average of two runs). (c) Enantiomeric excess determined by chiral HPLC (average of two runs).

caused a slight decrease in selectivity (**1d**). A variety of electron-neutral nucleophiles performed well (**1a**–**g**), including an ester, which would be incompatible with alternative approaches using aryllithium reagents (**1f**). Electron-deficient nucleophiles provided lower yield and enantioselectivity (**1h**), while electron-rich nucleophiles were the most selective, although they required double catalyst loading to achieve high yields (**1i**–**l**). Notably, a thioether was tolerated, suggesting that the catalyst is resistant to common poisons. Select heterocyclic boroxines were also competent in the reaction (**1k**,**l**). However, sufficiently electron-rich species such as 2-benzofurylboroxine were nucleophilic enough to undergo racemic background reaction.[24]

The scope of the electrophile was also investigated (Figure 3). Unfortunately, both yield and selectivity suffered relative to reactions with unsubstituted EEDQ.[25] Substitution on the quinoline ring was tolerated to a moderate extent at the 5, 6, and 7 positions (**2a**–**c**).[26] Electron-withdrawing groups enhanced selectivity (**2d**,**e**) while electron-donating groups diminished it (**2f**). Lastly, the reaction can be run with different carbamate protecting groups, although ethyl carbamate remained superior (**2g**,**h**).[27]

In conclusion, the Ni–iminium activation mode has enabled the development of an enantioselective arylation of quinolinium ions. This method allows modular access to 2-aryl-1,2-dihydroquinolines with moderate to high levels of selectivity. Furthermore, we employ a Ni(II) precatalyst that delivers Ni(0) under exceptionally mild conditions, an advance that may find general utility in Ni catalysis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Graham, T. J. A.; Shields, J. D.; Doyle, A. G. *Chem. Sci.* **2011**, *2*, 980.
(2) (a) Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7273. (b) Nomura, N.; RajanBabu, T. V. *Tetrahedron: Lett.* **1997**, *38*, 1713.
(3) Sylvester, K. T.; Wu, K.; Doyle, A. G. *J. Am. Chem. Soc.* **2012**, *134*, 16967.
(4) (a) Oelke, A. J.; Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 2966. (b) Do, H.-Q.; Chandrashekar, E. R. R.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 16288.
(5) Chau, S. T.; Lutz, J. P.; Wu, K.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 9153.
(6) (a) Fotie, J.; Kaiser, M.; Delfin, D. A.; Manley, J.; Reid, C. S.; Paris, J.-M.; Wenzler, T.; Maes, L.; Mahasenan, K. V.; Li, C.; Werbovetz, K. A. *J. Med. Chem.* **2010**, *53*, 966. (b) Probst, G.; Aubele, D. L.; Bowers, S.; Dressen, D.; Garofalo, A. W.; Hom, R. K.; Konradi, A. W.; Marugg, J. L.; Mattson, M. N.; Neitzel, M. L.; Semko, C. M.; Sham, H. L.; Smith, J.; Sun, M.; Truong, A. P.; Ye, X. M.; Xu, Y.; Dappen, M. S.; Jagodzinski, J. J.; Keim, P. S.; Peterson, B.; Latimer, L. H.; Quincy, D.; Wu, J.; Goldbach, E.; Ness, D. K.; Quinn, K. P.; Sauer, J.-M.; Wong, K.; Zhang, H.; Zmolek, W.; Brigham, E. F.; Kholodenko, D.; Hu, K.; Kwong, G. T.; Lee, M.; Liao, A.; Motter, R. N.; Sacayon, R.; Santiago, P.; Willits, C.; Bard, F.; Bova, M. P.; Hemphill, S. S.; Nguyen, L.; Ruslim, L.; Tanaka, K.; Tanaka, P.; Wallace, W.; Yednock, T. A.; Basi, G. S. *J. Med. Chem.* **2013**, *56*, 5261. (c) Cracknell, M.; Duriatti, A.; Kirby, N. World Patent 9,805,646, Feb 12, 1998.
(7) 2-Aryl-1,2-dihydroquinolines have also been incorporated in chiral phosphoramidite ligands: Pullmann, T.; Engendahl, B.; Zhang, Z.; Holscher, M.; Zanotti-Gerosa, A.; Dyke, A.; Francio, G.; Leitner, W. *Chem.—Eur. J.* **2010**, *16*, 7517.
(8) Ahamed, M.; Todd, M. H. *Eur. J. Org. Chem.* **2010**, 5935.
(9) Asymmetric hydrogenation of quinolines is well-known; however, such methods cannot terminate at the dihydroquinoline and instead yield tetrahydroquinoline products. To the best of our knowledge, a general and selective oxidation of tetrahydroquinolines to dihydroquinolines is unknown. (a) Wang, T.; Zhuo, L.-G.; Li, Z.; Chen, F.; Ding, Z.; He, Y.; Fan, Q.-H.; Xiang, J.; Yu, Z.-X.; Chan, A. S. C. *J. Am. Chem. Soc.* **2011**, *133*, 9878. (b) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536. (c) Rueping, M.; Antonchick, A. P.; Theissman, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683.
(10) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327.
(11) Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686.

(12) Kodama, T.; Moquist, P. N.; Schaus, S. E. *Org. Lett.* **2011**, *13*, 6316.
(13) Black, D. L.; Beveridge, R. E.; Arndtsen, B. A. *J. Org. Chem.* **2008**, *73*, 1906.
(14) Cointeaux, L.; Alexakis, A. *Tetrahedron: Asymmetry* **2005**, *16*, 925.
(15) See the Supporting Information for details.
(16) For another example of $Ni(cod)_2$ interfering in catalysis, see: Standley, E. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2013**, *135*, 1585.
(17) Tolman, C. A.; Reutter, D. W.; Seidel, W. C. *J. Organomet. Chem.* **1976**, *117*, C30.
(18) Cornella, J.; Gomez-Bengoa, E.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997.
(19) Zembayashi, M.; Tamao, K.; Yoshida, J.-I.; Kumada, M. *Tetrahedron Lett.* **1977**, *18*, 4089.
(20) (a) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470. (b) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053.
(21) For an example of an alkoxide nucleophile attacking a putative $L_nNi(allyl)$ intermediate, see: Yatsumonji, Y.; Ishida, Y.; Tsubochi, A.; Takeda, T. *Org. Lett.* **2007**, *9*, 4603.
(22) Ge, S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 12837.
(23) (a) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92. (b) Alexakis, A.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; van den Heuvel, A.; Leveque, J.-M.; Maze, F.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011.
(24) Chang, Y. M.; Lee, S. H.; Nam, M. H.; Cho, M. Y.; Park, Y. S.; Yoon, C. M. *Tetrahedron: Lett.* **2006**, *46*, 3053.
(25) We hypothesize that π-coordination of the catalyst may serve as a recognition element, accounting for the ee dependence on substrate srtucture. Furthermore, electron withdrawing substituents and those proximal to the π-allyl may adversely effect yield by deterring ionization or oxidative addition, respectively.
(26) Substitution at the 3- and 4-positions was not tolerated; 2- and 8-substituted quinolines were too sterically hindered to generate the *N*,*O*-acetal starting material.
(27) A Cbz-protected product was hydrogenated to yield the free 2-aryltetrahydroquinoline, which is known in the literature. This was used to assign the absolute stereochemistry of the products by analogy. See the Supporting Information for details.

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