Communication

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Nickel-Catalyzed Asymmetric Reductive Cross-Coupling between Heteroaryl Iodides and α-Chloronitriles.

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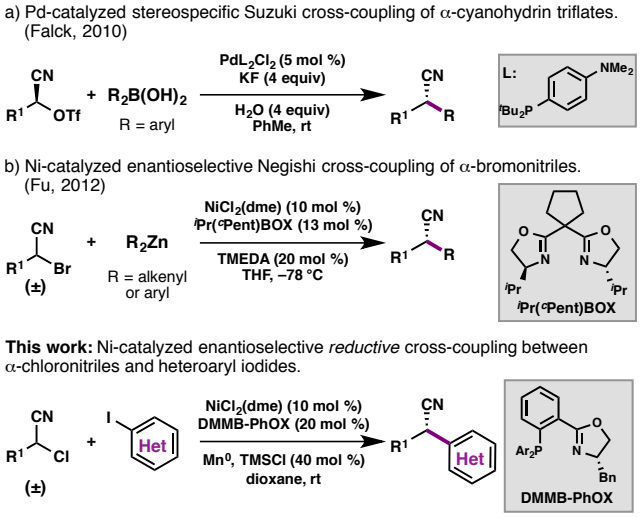
Supporting Information Placeholder

ABSTRACT: A Ni-catalyzed asymmetric reductive cross-coupling of heteroaryl iodides and α-chloronitriles has been developed. This method furnishes enantioenriched α,α-disubstituted nitriles from simple organohalide building blocks. The reaction tolerates a variety of heterocyclic coupling partners, including pyridines, pyrimidines, quinolines, thiophenes, and piperidines. The reaction proceeds under mild conditions at room temperature, and precludes the need to pre-generate organometallic nucleophiles.

In recent years, Ni-catalyzed reductive cross-coupling reactions have experienced a surge of development.[1] These transformations forge C–C bonds between two organic electrophiles, employing a stoichiometric reductant (usually Zn^0 or Mn^0) to turn over the Ni catalyst. An appealing aspect of this chemistry is that *sec*-alkyl electrophiles are competent reaction partners,[2] and in some cases, these reactions can be rendered enantioselective by use of an appropriate chiral ligand.[3] However, the scope of C(sp^3) electrophiles used in these asymmetric transformations has so far been limited to α-substituted benzyl chlorides. Moreover, the asymmetric cross-coupling of heteroaryl electrophiles – a substrate class that would be of high value for medicinal chemists[4] – has proven challenging.[5] In this communication, we report the Ni-catalyzed asymmetric reductive cross-coupling between α-chloronitriles and heteroaryl iodides, a reaction that provides access to a variety of enantioenriched heterocyclic products.

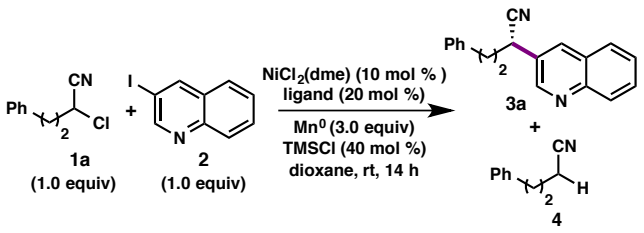
In considering the development of new C(sp^3) electrophiles for Ni-catalyzed reductive cross-coupling reactions, we became interested in the use of α-chloronitriles. Nitriles are valuable synthetic intermediates that serve as precursors to amines, carboxylic acids, carboxamides, aldehydes, ketones, and alcohols.[6] The cyano group is also found in a number of natural products and medicinal compounds.[7] However, there are few transition metal-catalyzed cross-coupling methods to directly prepare enantioenriched α,α-disubstituted nitriles. In 2010, Falck and coworkers published a Pd-catalyzed stereospecific Suzuki cross-coupling of α-cyanohydrin triflates.[8] Two years later, Fu and Choi reported a highly enantioselective Ni-catalyzed Negishi coupling between racemic α-bromonitriles and arylzinc reagents.[9,10] However, neither report included heteroaryl nucleophiles as part of their substrate studies.

Scheme 1. Transition metal-catalyzed cross-coupling reactions of α-cyano electrophiles.



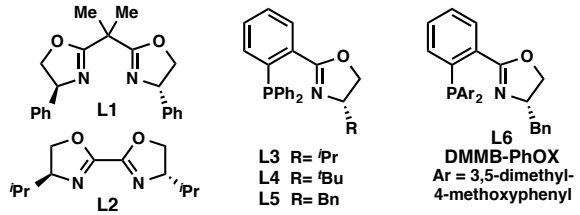
We envisioned that a Ni-catalyzed asymmetric *reductive* cross-coupling between α-chloronitriles and heteroaryl halides could provide access to a complementary scope of synthetically useful products. Furthermore, α-chloronitriles have not been developed as C(sp^3) electrophiles for Ni-catalyzed reductive cross-coupling reactions (even in the racemic sense).[11] Thus, the successful development of this transformation would expand the scope of reductive cross-coupling reactions to new and synthetically versatile classes of electrophiles.

Table 1. Optimization of reaction conditions.[a]



Entry[a]	Ligand	Deviation from Standard Conditions	Yield **3** (%)[b]	Yield **4** (%)[b]	ee **3** (%)[c]
1	**L6**	None	78	20	84
2	**L1**	DMA instead of dioxane	0	62	--
3	**L1**	--	<5	32	38
4	**L2**	--	17	22	9
5	**L3**	--	25	40	83
6	**L4**	--	0	32	--
7	**L5**	--	52	35	77
8	**L6**	No Ni	0	0	--
9	**L6**	No Mn^0	0	0	--
10	**L6**	No TMSCl	<5	<5	82
11	--	No Ligand	4	23	0
12	**L6**	Zn^0 instead of Mn^0	25	32	10
13	**L6**	TFA (0.4 equiv)	48	37	78
14	**L6**	$NaBF_4$ (1.0 equiv)	76	24	90
15	**L6**	NaI (0.25 equiv)	71	29	84
16	**L6**	RBrCN (**5**) instead of **1**	9	36	84

[a] Reactions conducted under inert atmosphere on 0.1 mmol scale for 14 h. [b] Determined by ^1H NMR versus an internal standard. [c]Determined by SFC using chiral stationary phase.



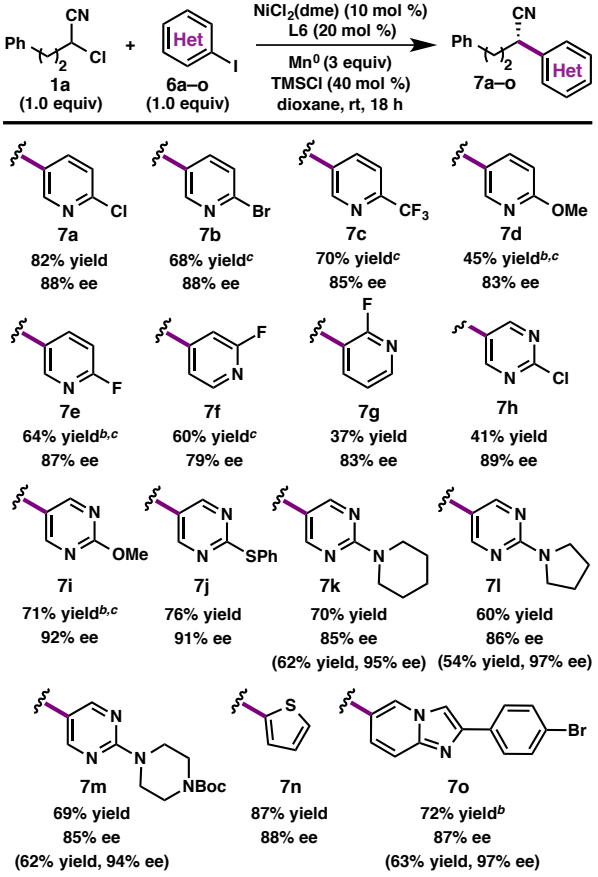
We began our investigations with the coupling between α-chloronitrile **1a** and 3-iodoquinoline (**2**). When the reaction was conducted in DMA with chiral BOX ligand **L1** and TMSCl to activate Mn^0, no product was formed (Table 1, entry 2). Rather, the α-chloronitrile was rapidly consumed, generating the hydrodehalogenation product 4-phenylbutyronitrile (**4**). A solvent screen revealed that **3a** forms in trace yield and 38% ee when dioxane is used as solvent (entry 3); chiral BiOX ligand **L2** provided slightly improved yield (entry 4). We hypothesized that more electron-rich ligands might accelerate the rate of oxidative addition of **2** to a LNi(0) complex, relative to the rate of hydrodehalogenation and decomposition reactions of **1**, thereby improving the yield of **3a**.[12] Consistent with this hypothesis, phosphino-oxazoline (PhOX) ligands were found to provide improved reactivity, with BnPhOX **L5** furnishing **3a** in 52% yield and 77% ee (entry 7). Further ligand optimization identified DMMB-PhOX **L6** as providing the best combination of yield and selectivity (entry 1). A study of additional reaction parameters revealed that: 1) use of Zn^0 instead of Mn^0 provides the product in lower yield and ee (entry 12), and 2) 2-bromo-4-phenylbutanenitrile (**5**) suffers from facile hydrodehalogenation and elimination under the reaction conditions, providing **3a** in only 9% yield and 84% ee (entry 16). Additives that have been shown to improve the yields of reductive cross-electrophile coupling were also investigated (entries 13–15).[3a, 5a] The addition of $NaBF_4$ provided **3** in comparable yield and improved selectivity (entry 14); however, further studies revealed that for many substrates, $NaBF_4$ provides no added benefits. Erring toward the use of fewer reagents, $NaBF_4$ was only added for the cross-coupling of certain more challenging substrates, as indicated in the following Tables. The exact role of $NaBF_4$ in these transformations is unknown at this time.[5a]

Having optimized the reaction parameters for the coupling between **1a** and **2**, we sought to probe the scope of the heteroaryl partner (Table 2). We were pleased to find that a variety of heteroaryl iodides undergo cross-coupling to furnish the α,α-disubstituted nitriles in good yields and with high enantioinduction. The reaction demonstrates good chemoselectivity, with no coupling observed at the 2-position of 2-bromo- or 2-chloro-5-iodopyridine (see products **7a** and **7b**).[13] Whereas substitution *meta* to the iodide was tolerated (**7f**), a decrease in yield was observed when the substituent was *ortho* to the iodide (**7g**). Iodo-pyridines or -pyrimidines lacking substitution at C2 were poor substrates, presumably due to the increased Lewis basicity of the nitrogen. A variety of C2-substituted pyrimidines, as well as 2-iodothiophene and a 6-imidazopyridine also undergo cross-coupling, delivering products in good yield and with high enantioinduction (**7h**–**7o**). Importantly, many of the products were easily recrystallized to afford highly enantioenriched (>95% ee) material with excellent recovery. For less-reactive heteroaryl iodides, competitive hydrodehalogenation of **1a** resulted in decreased yields; this could be mitigated in most cases by using two equivalents of the iodide partner.[14]

We also investigated the scope of the α-chloronitrile (**1**). In general, less sterically-encumbered substrates provide products in good yield and modest enantioselectivity, while more bulky substrates provide the product with good enantioselectivity and slightly more modest yields. Nonetheless, the reaction exhibits notable functional group tolerance, including carbamates (**3h** and **3i**), esters (**3f**) and a primary alkyl chloride (**3g**). Recrystallization of nitrile **3e** provided

crystals suitable for X-ray diffraction analysis, which allowed us to assign the stereochemistry as the (*S*)-configuration.[15]

Table 2. Scope of heteroaryl iodide.[a]

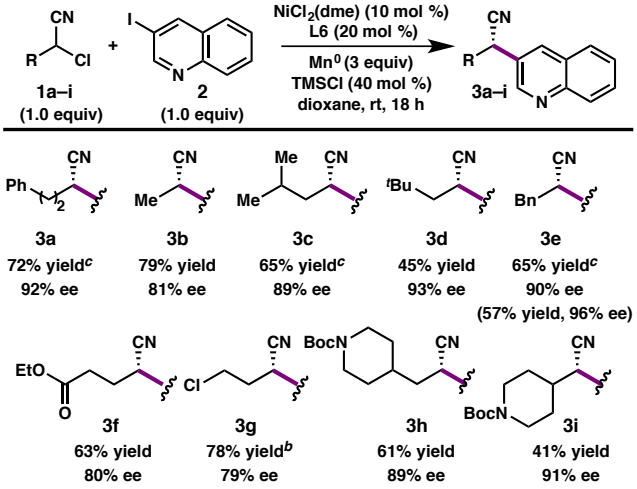


[a] Reaction conducted on 0.2 mmol scale. Isolated yields are provided; ee is determined by SFC using chiral stationary phase. Values in parentheses are yield and ee following a single recrystallization of the product. [b] 2.0 equiv heteroaryl iodide used. [c] 1.0 equiv $NaBF_4$ added.

The enantioenriched α,α-disubstituted nitriles produced in this reaction serve as versatile synthetic intermediates. For example, hydrogenation of 2-piperidyl-pyrimidine **7k** under standard conditions provides phenethylamine **8** in excellent yield and with no erosion of ee (Scheme 2). The two step sequence involving cross-coupling and hydrogenation represents an straightforward approach to the synthesis of this bioactive class of molecule. The same substrate can be subjected to Pt-catalyzed hydrolysis[16] to afford carboxamide **9** in high yield and with complete stereoretention. Alternatively, reduction of thiophene-containing nitrile **7n** with DIBAL-H furnished the enantioenriched aldehyde **10** in excellent yield and with minor erosion of ee.

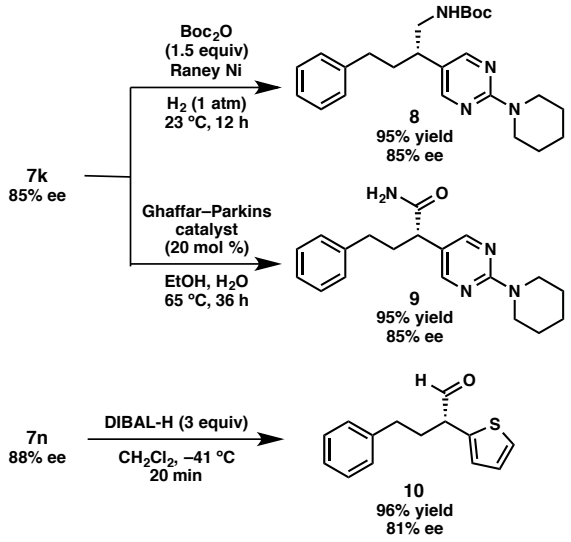
Several experiments were conducted to interrogate the potential mechanism of this transformation. To probe whether the oxidative addition of the α-chloronitrile proceeds by a radical pathway, cyclopropyl-containing substrate **11** was prepared and subjected to the reaction conditions (Scheme 3). Ring-opened coupling product **12** was obtained in 21% yield as a 1:1 mixture of *cis* and *trans* isomers, consistent with a radical intermediate.[17] None of the corresponding cyclopropane-containing product was observed. Despite this evidence for a radical intermediate, the reaction proceeds with comparable efficiency in the presence of 50 mol % of common radical inhibitors, such as 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT) or dihydroanthracene (DHA).[18] The latter finding is inconsistent with cage-escaped radicals expected in a radical chain mechanism, although more studies are needed to fully elucidate the reaction pathway.[19]

Table 3. Scope of α-chloronitriles.[a]



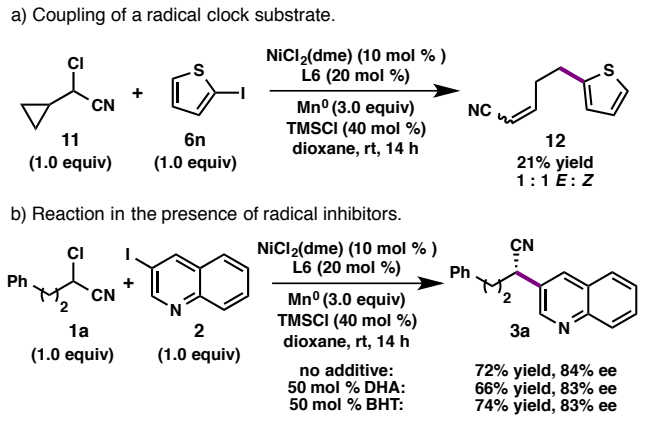
[a] Reaction conducted on 0.2 mmol scale. Isolated yields are provided; ee is determined by SFC using chiral stationary phase. Values in parentheses are yield and ee following a single recrystallization of the product. [b] 2.0 equiv heteroaryl iodide used. [c] 1 equiv $NaBF_4$ added.

Scheme 2. Derivatization of α,α-disubstituted nitriles.



In conclusion, a Ni-catalyzed asymmetric reductive cross-coupling between α-chloronitriles and heteroaryl iodides has been developed. A new chiral PHOX ligand was identified that provides α,α-disubstituted nitriles in good yields and with high enantioinduction. This is the first example of a Ni-catalyzed asymmetric reductive cross-coupling reaction that tolerates *N*- and *S*- heterocyclic coupling partners, and demonstrates the feasibility of developing related transformations of electrophiles containing Lewis basic functional groups. The development of new asymmetric reductive cross-coupling reactions as well as mechanistic investigations are the subject of ongoing research in our laboratory.

Scheme 3. Mechanistic experiments.



ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, compound characterization data, ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The *asymmetric* Ni-catalyzed reductive cross-coupling of (*E*)-2-(2-bromovinyl)furan is the only previously reported example of a heterocyclic substrate (see ref. 3b). For examples of non-asymmetric Ni-catalyzed reductive cross-coupling of heterocyclic electrophiles, see: (a) Molander, G. A.; Traister, K. M.; O'Neill, B. T. *J. Org. Chem.* **2014**, *79*, 5771; (b) Molander, G. A.; Traister, K. M.; O'Neill, B. T. *J. Org. Chem.* **2015**, *80*, 2907; (c) Wang, S.; Qian, Q.; Gong, H. *Org. Lett.* **2012**, *14*, 3352; (d) Molander, G. A.; Wisniewski, S. R.; Traister, K. M. *Org. Lett* **2014**, *16*, 3692.

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(10) MacMillan and coworkers recently reported an enantioselective cross-coupling of primary α-bromonitriles with aldehydes under photoredox organocatalysis. Welin, E. R.; Warkentin, A. A.; Conrad, J. C.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* DOI: 10.1002/anie.201503789

(11) For a single example of a Ni-catalyzed electrochemical cross-coupling of 2-chloropropanenitrile and (*E*)-(2-bromovinyl)benzene, see: Cannes, C.; Condon, S.; Durandetti, M.; Perichon, J.; Nedelec, J.-Y. *J. Org. Chem.* **2000**, *65*, 4575.

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(13) This chemoselectivity is notable given these prior reports of Ni-catalyzed reductive cross-couplings of 2-chloropyridines: (a) Gosmini, C.; Bassene-Ernst, C.; Durandetti, M. *Tetrahedron.* **2009**, *65*, 6141; (b) Everson, D. A.; Buonomo, J. A.; Weix, D. J. *Synlett.* **2014**, *25*, 233.

(14) Electron deficient (non-hetero) aryl iodides are also competent coupling partners, providing the products in good yields but more modest enantioselectivity. For example, 1-iodo-4-(trifluoromethyl)benzene couples to **3a** in 76% yield and 70 % ee.

(15) See Supporting Information.

(16) (a) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657; (b) Ghaffar, T.; Parkins, A. W. *J. Mol. Catal. A: Chem.* **2000**, *160*, 249.

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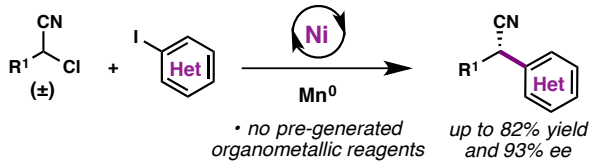
(18) Addition of TEMPO to the reaction mixture results in poor conversion, presumably from catalyst inhibition. There is no evidence of trapping of carbon-based radicals.

(19) For mechanistic investigations of related Ni-catalyzed reactions, see: (a) Ren, Q.; Jiang, F.; Gong, H. *J. Organomet. Chem.* **2014**, *770*, 130; (b) Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192; (c) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 4896.


CN
R1
Cl
(±)
+
I
Het
Ni
Mn0
• no pre-generated organometallic reagents
CN
R1
Het
up to 82% yield and 93% ee