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Nickel-Catalyzed Enantioselective Reductive Cross-Coupling of Styrenyl Aziridines

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Supporting Information

ABSTRACT: A Ni-catalyzed reductive cross-coupling of styrenyl aziridines with aryl iodides is reported. This reaction proceeds by a stereoconvergent mechanism and is thus amenable to asymmetric catalysis using a chiral bioxazoline ligand for Ni. The process allows facile access to highly enantioenriched 2-arylphenethylamines from racemic aziridines. Multivariate analysis revealed that ligand polarizability, among other features, influences the observed enantioselectivity, shedding light on the success of this emerging ligand class for enantioselective Ni catalysis.

Aziridines are versatile synthetic intermediates for the preparation of bioactive targets.[1] Similar to epoxides, aziridines experience significant ring strain that enhances their susceptibility to ring opening with a wide array of nucleophiles.[2] Because these reactions are typically stereospecific, the enantioselective synthesis of amines from aziridines is reliant on the availability of enantioenriched aziridines. However, methods for asymmetric catalytic aziridination typically suffer from modest scope and product enantioselectivity, significantly lagging behind methods for asymmetric catalytic epoxidation.[3] Alternative preparations of enantioenriched aziridines require multistep routes originating from either the chiral pool (amino acids) or chiral building blocks (aminoalcohols, epoxides).[4] Therefore, catalytic strategies that permit the conversion of racemic aziridines to enantioenriched amine products in high yield would represent an attractive alternative.[5]

In 2012, the Doyle lab introduced the catalytic cross-coupling of aziridines with organozinc partners (Figure 1a),[6] building on seminal stoichiometric precedent from Hillhouse[7] and Wolfe.[8] Use of an electron-deficient olefin (EDO) as a ligand for Ni proved critical to achieving high selectivity for C−C bond formation over competitive β-H elimination. Subsequently, the groups of Michael,[9] Minakata,[10] and Jamison[11] described unique and complementary systems for cross-coupling with aziridines.[12] However, these systems, as well as the stoichiometric precedent from Hillhouse and Wolfe, share one feature in common: the reactions are stereospecific.[13] For example, Minakata demonstrated that enantioenriched phenethylamine products can be obtained by stereospecific cross-coupling with enantioenriched styrenyl aziridines. By contrast, stereochemical studies of our Ni/EDO system revealed that C−C bond formation is stereoablative, presumably via an open shell intermediate.[14]

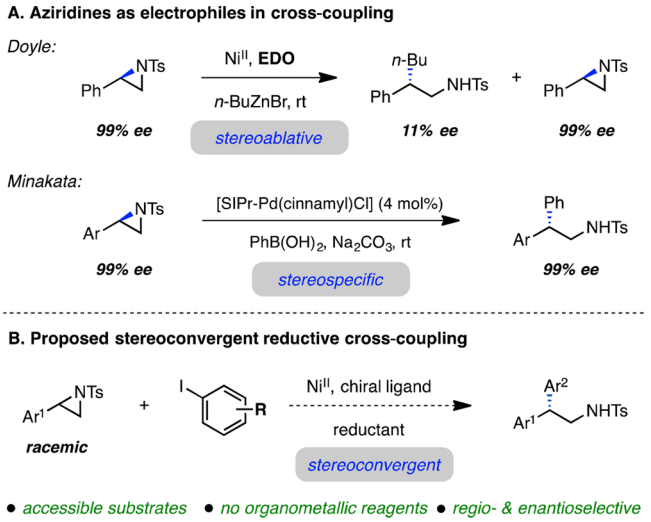

Figure 1. Cross-coupling of aziridines.

In light of this stereochemical outcome, we were intrigued that a stereoconvergent synthesis of enantioenriched 2-arylphenethylamines might be possible from racemic styrenyl aziridines. These products have seen important biological applications as dopamine receptor agonists[15] and have been generally prepared by asymmetric catalytic conjugate additions of organometallic reagents to nitroolefins.[16] Although enabling, this approach requires two steps and organometallic reagents. Our approach would be complementary as the products could be accessed through a single operation using readily accessible coupling partners as well as a simple chiral catalyst.

While we were able to obtain proof-of-concept using our Ni/EDO system, efforts directed at the design of a chiral EDO ligand were met with limited success.[17] As an alternative, we envisioned that a Ni-catalyzed asymmetric reductive cross-coupling reaction could deliver stereoconvergent C−C bond formation with racemic aziridines. Reductive cross-coupling has come to define an important class of reactions wherein two organic electrophiles are combined using both a metal catalyst and stoichiometric reductant. Although a reductive cross-

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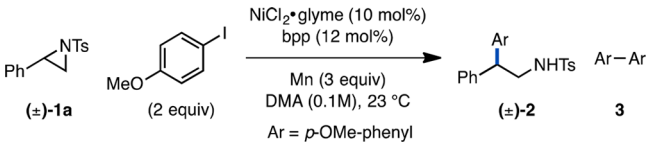
coupling of aziridines has yet to be developed, a number of features of a reductive cross-coupling approach suggested its application to the goal at hand. First, efficient coupling has been demonstrated with secondary alkyl electrophiles.[18] Amine- and imine-based ligands, of which numerous chiral variants are available, are generally most effective for these transformations. Finally, it has been possible to render some reductive coupling reactions of alkyl electrophiles stereoconvergent, as they presumably occur via open shell intermediates.[19] In seminal studies, the Reisman lab demonstrated that chiral bisoxazoline and phosphinooxazoline ligands can be applied in asymmetric reductive coupling of secondary benzylic halides with acid chlorides, and secondary allylic halides with aryl halides.[20] Using a chiral titanocene catalyst in combination with an achiral nickel catalyst, the Weix lab reported an enantioselective cross-coupling of *meso*- epoxides with aryl bromides.[21] Herein we describe the development of a racemic and enantioselective reductive cross-coupling of aryl iodides and styrenyl aziridines. Investigation into ligand structure enantioselectivity trends shed light on nonintuitive factors of chiral BiOx substitution that influence asymmetric catalysis.

We first set out to probe the feasibility of a reductive cross electrophile coupling with aziridines in racemic fashion. Initial reaction optimization was conducted with 2-phenyl-*N*-tosylaziridine **1a** and 4-iodoanisole (2 equiv) using 10 mol % $NiCl_2$·glyme and Mn(0) as the stoichiometric reductant (Table 1). A broad range of ligands were evaluated to achieve

Table 1. Reaction Optimization



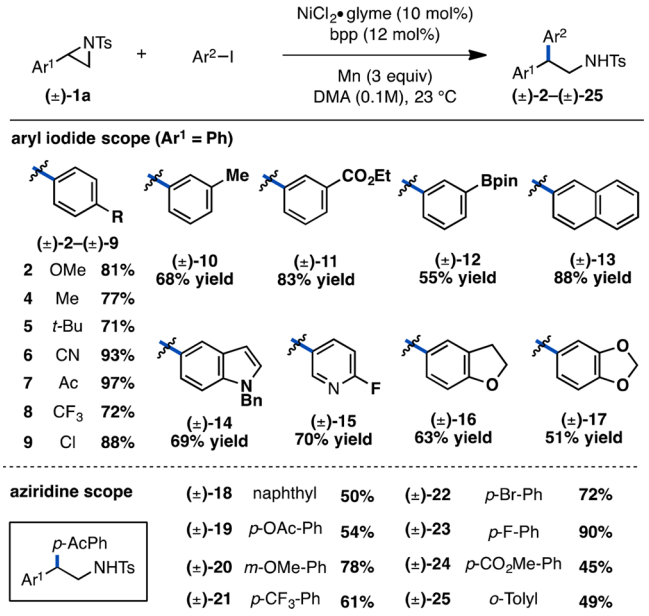
entry	deviation from standard conditions	yield (±)-**2**[a] (%)	yield **3**[a] (%)
1	none	80	57
2	5 mol % Ni, 6 mol % L	35	7
3	1 equiv of ArI	55	20
4	Zn instead of Mn	86	52
5	TDAE instead of Mn	17	<5
6	bpy (12 mol %)	35	62
7	QuinOx (12 mol %)	40	59
8	PyBox (12 mol %)	<5	14
9	BiOx (12 mol %)	42	76
10	no ligand	<5	13
11	no Ni	0	0
12	no reductant	0	0

[a]Determined by GC using dodecane as an internal standard.

selectivity for the desired product **2** over biaryl **3** arising from homocoupling of the aryl iodide. In previous work from the Doyle laboratory on Ni-catalyzed coupling of acetals and aryl iodides, we identified the tridentate 2,6-bis(*N*-pyrazolyl)-pyridine (bpp) ligand as effective in increasing selectivity for product over biaryl formation.[22] A similar benefit was observed here; bipyridine, QuinOx, PyBOX, and BiOx ligands gave poor to moderate yields of **2** (entries 6−9) whereas the bpp ligand delivered **2** in 80% yield (entry 1). Reducing the catalyst loading or lowering the equivalents of aryl iodide led to the diminished yield of **2** (entries 2−3). However, with other aryl iodides such as *p*-Ac-Ph-I, use of 1.1 equiv of the reaction partner gave the corresponding product in 81% yield (see Supporting Information (SI)). Tetrakis(dimethylamino)-ethylene (TDAE) also works as a reductant,[23] albeit in poorer reaction efficiency (entry 5). In the absence of ligand, only trace product was detected (entry 10), and control reactions without Ni or reductant did not yield product (entries 11−12). In all cases, C−C bond formation takes place at the benzylic carbon of **1a**.

Under the optimal reaction conditions, the aziridine ring-opening reaction proved amenable to a wide array of aryl and heteroaryl iodides (Table 2). Electron-rich (**2**), electron-neutral

Table 2. Reaction Scope[a]



[a]Yield of isolated product (2 equiv of iodide, 14−24 h).

(**4**, **5**), and electron-poor (**6**−**8**) aryl iodides undergo reaction in high yield. Cross-coupling occurs with aryl iodides bearing chloro- and pinacol boronate groups, generating products **9** and **12** with functional group handles for subsequent metal-catalyzed cross-coupling. Furthermore, nitrogen-containing heteroaromatics (**14**, **15**) as well as oxygen-containing heterocycles (**16**, **17**) are well tolerated, making this an attractive method for preparing potential bioactive agents. While *meta*-substitution is well tolerated (**10**−**12**), *ortho*-substitution does curtail reactivity (see SI).

Broad functional group compatibility is also displayed for the styrenyl aziridine coupling partner.[24] Electron-rich and -poor *para*- and *meta*-substituted aziridines function well (**18**−**25**). Cross-coupling takes place with an aziridine bearing *ortho*-substitution, highlighting a complementarity to the aryl iodide scope (**25**). Overall, the transformation has advantages over our previously described Negishi coupling, since it avoids the need for pregeneration of relatively harsh organozinc reagents. Additionally, the arylations reported here are especially productive in comparison to the previous system where 3 equiv of the PhZnBr nucleophile were needed to achieve only a moderate yield.[6]

We next proceeded to examine the feasibility of pursuing a stereoconvergent coupling. Subjecting enantiopure aziridine (+)-**1a** to the coupling conditions produced **7** as a racemate, while recovered (+)-**1a** remained enantiopure (Scheme S3). Among a collection of chiral amine- and phosphine-based

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ligands examined for the enantioselective coupling with *rac*-**1a**, the BiOx ligand framework proved most promising. As expected from the optimization studies of the racemic reaction, yields initially suffered without the bpp ligand. However, we found that inclusion of NaI and catalytic TMSCl as additives improved the cross selectivity (see SI).[25] Notably, ee's ranging from 10−78% were observed with seemingly minor perturbations to the BiOx substituent. Use of the unique 4-heptyl BiOx ligand **L7** afforded **7** in 78% ee under these conditions, and in 90% ee under optimized conditions (Figure 2).

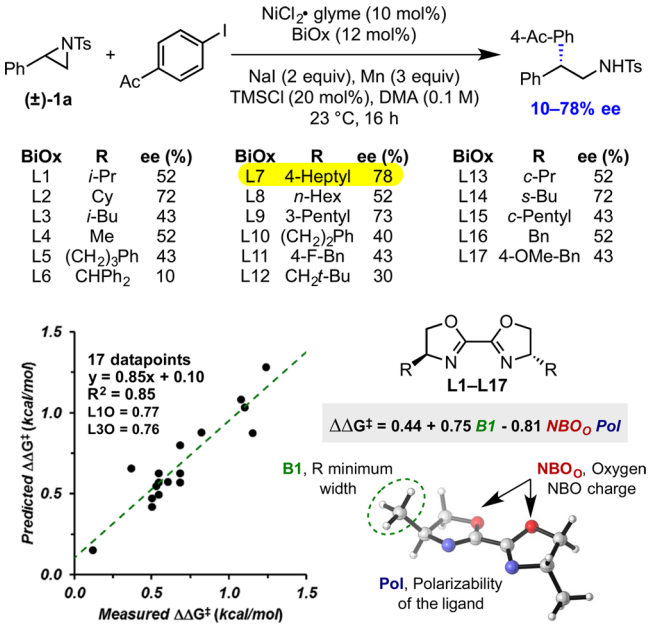
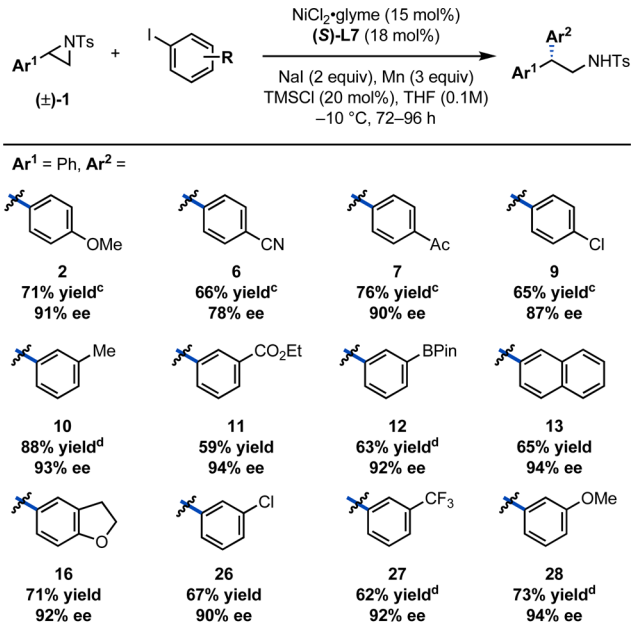


Figure 2. Impact of BiOx ligand substituent on asymmetric cross-coupling.

Since the enantioselectivity presented a nonobvious dependence on the ligands' structural features and the BiOx ligand class has seen extensive recent application in the development of both asymmetric reductive cross-couplings[20a,d] as well as Ni/photoredox catalysis,[26] we sought to apply the multivariate analysis tools[27] developed by the Sigman lab to understand the origins of enantioselectivity. Molecular vibrations,[28] Sterimol descriptors,[29] and molecular charges[30] were computed for a total of 17 BiOx ligands[31] as parameters to describe electronic, steric, and electrostatic effects. Additionally, polarizability was calculated to probe if noncovalent interactions (NCIs) were potentially involved.[32] Linear regression modeling was applied to relate the enantioselectivity (expressed as $\Delta\Delta G^{\ddagger}$) and the collected parameters. Only three parameters, condensed in two terms, were required to obtain the correlation depicted in Figure 2 (R^2 = 0.85): ***B1*** (minimum width of the ligand substituent R) accounting for steric effects, ***NBO$_O$*** (NBO charge of the oxazoline oxygen atoms) mainly representing the electronic character of the catalyst, and ***Pol*** (polarizability of the ligand), which suggests the presence of NCIs. The single-parameter correlations reported in Figure S2 support the model, highlighting the importance of each one of these parameters with qualitative trends (see SI). Through interpretation of the model's equation, a long, branched, alkyl chain is suggested as the preferred substituent on the ligand. Such a substituent would display enhanced steric effects while providing a nonpolar surface for possible NCIs, such as dispersion forces or CH−π interactions.[33] Additionally, ligands containing longer alkyl chains present higher ***NBO$_O$*** (see SI for more details), which may affect catalysis by modifying the electron density at the metal center. We anticipate that the correlations discovered here, particularly regarding NCIs, will be informative for the development of additional transformations as the field progresses.

The reaction with **L7** as ligand is highly enantioselective, producing various phenethylamine products in up to 94% ee at −10 °C in THF (Table 3). Both electron-rich and -deficient

Table 3. Scope of Stereoconvergent Reaction[a,b]



	Ar^1	Ar^2	yield	ee
19	*p*-OAc-Ph	*p*-Ac-Ph	78%	90%
20	*m*-OMe-Ph	*p*-Ac-Ph	61%	78%
29	*p*-CO_2Me-Ph	*p*-OMe-Ph	47%	88%
30	*p*-CO_2Me-Ph	2-naphthyl	70%	78%
31	*p*-CF_3-Ph	*p*-OMe-Ph	67%	85%
32	*p*-CF_3-Ph	2-naphthyl	70%	75%
33	*p*-F-Ph	*m*-CO_2Et-Ph	45%	91%
34	*p*-F-Ph	2-naphthyl	86%	83%
35	*p*-F-Ph	*p*-Cl-Ph	79%	82%

[a]Yield of isolated product (3 equiv of iodide). [b]Determined by chiral HPLC. [c]10 mol % Ni, 12 mol % **L7**. [d]No TMSCl added.

aryl iodides are tolerated, with meta-substituted aryl iodides delivering the highest levels of enantioinduction. Furthermore, substituted styrenyl aziridines undergo C−C bond formation in moderate yield and ee (**19**, **20**, **29**−**35**). As evidence of the stereoconvergent nature of the reaction, racemic aziridine **1a** was subjected to two reactions of identical conditions, except for the enantiomer of ligand involved. As expected, the coupling with ligands (*S*)-**L7** and (*R*)-**L7** generated enantioenriched product **7** of equal and opposite sign, both in high yield (Scheme S5). In light of the stereospecific aziridine cross-coupling reactions already reported,[9−12] we expect that this enantioselective variant will offer a valuable complement where

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either enantiomer of product can be accessed from racemic starting material.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b03448.

Experimental procedures, additional reaction optimization, and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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