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Nickel-Catalyzed Asymmetric Reductive Diarylation of Vinylarenes

David Anthony, Qiao Lin, Judith Baudet, and Tianning Diao*^[a]

Abstract: A Ni-catalyzed asymmetric diarylation reaction of vinylarenes represents a compelling method for preparing chiral α, α, β -triarylated ethane scaffolds, which exist in a number of biologically active molecules. The use of reducing conditions with aryl bromides as coupling partners avoids stoichiometric organometallic reagents and tolerates a broad range of functional groups. The application of an *N*-oxyl radical as a ligand to Ni catalysts represents a novel approach to facilitate Ni-catalyzed cross-coupling reactions.

Alkenes are versatile functional groups that enjoy some of the most successful asymmetric catalytic transformations, such as hydrogenation^[1] dihydroxylation.[2] and Hydrocarbofunctionalization^[3] and 1,2-dicarbofunctionalization of alkenes^{[4],[5]} have emerged as compelling approaches to rapidly increase molecular complexity by forming vicinal di-substitution patterns and tertiary carbon centers. Asymmetric alkene 1,2dicarbofunctionalization would enable efficient construction of new C-C bonds while simultaneously introducing stereocenters,^[6] but this strategy has been restricted to a handful of precedents, with the scope limited to intramolecular^[7] and diene substrates.^[8] Liu and others have reported intermolecular, asymmetric trifluoromethylation and cyanation of vinylarenes,^[9] but intermolecular, asymmetric diarylation has not been developed before.

The α, α, β -triarylated ethane motif is present in a number of important pharmaceutical compounds and biologically active molecules.^[10] Examples include carboxylic acid 2, a molecule tested as a bone-selective estrogen receptor ligand,^[11] indole derivative 3, an inhibitor of human $\alpha\text{-thrombin},^{[12]}$ and 4, an inhibitor of phosphodiesterase 4 (PDE 4A) (Scheme 1).^[13] While many biological studies are performed with racemic samples, access to enantioenriched compounds would facilitate the assessment of their efficacy. These molecules could be hydrogenation^[14] synthesized by asymmetric or stereospecific^[15]/stereoconvergent^[16] cross-coupling, but these methods would require preparation of the substrates in multiple steps. We report an asymmetric diarylation of vinylarenes, as an alternative to access chiral α, α, β -triarylated ethane structures from readily available vinylarenes. This method could be used to rapidly build a library of triarylated molecules for drug discovery. The use of an aryl bromide as the coupling partner under reducing conditions eschews the need for pre-generating airsensitive organometallic coupling reagents,^[17] and thus enables a broad scope with good functional group compatibility.

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Scheme 1. Strategies for Preparing Chiral α, α, β -Triarylated Ethane and Relevant Target Molecules.

Our development of this asymmetric diarylation capitalizes on the hypothesis that Ni catalysts can create new modes of stereo-control for alkene functionalization via radical addition (Scheme 2).^[18] The first irreversible enantio-differentiating step would determine the enantioselectivity.^[19] In traditional asymmetric alkene functionalization reactions, such as the Pdcatalyzed asymmetric Heck reaction, the enantio-determining step is either alkene coordination (*step i*) or migratory insertion (*step ii*).^[20] Ni catalysts can initiate radical formation from alkyl^[21] or aryl halides,^[22] and the resulting organic radicals could add to alkenes.^[23] Through this pathway, carbofunctionalization would be expected to have different enantio-determining steps, such as radical capture by Ni (*step v*) or reductive elimination (*step v*).^[24]

- Heck reaction: <u>alkene coordination</u> or <u>migratory insertion</u>

$$[Pd-Ph]^{+} + \underbrace{\bigcirc}_{[(Ph)Pd]^{+-}} \underbrace{\bigcirc}_{[(Ph)Pd]^{+-}} \underbrace{\bigcirc}_{[Pd]^{+}} \underbrace{(iii)}_{Ph} \underbrace{\overset{Ph}{}_{-} \underbrace{\bigcirc}_{[PdH]^{+}}_{(iii)}} \underbrace{\overset{Ph}{}_{-} \underbrace{\overset{O}{}_{-} \underbrace{(iii)}_{(iii)}}_{[Pd]^{+-}} \underbrace{\overset{Ph}{}_{-} \underbrace{\overset{O}{}_{-} \underbrace{(iii)}_{(iii)}}_{(iii)} \underbrace{\overset{Ph}{}_{-} \underbrace{\overset{O}{}_{-} \underbrace{(iii)}_{(iii)}}_{(iii)} \underbrace{\overset{Ph}{}_{-} \underbrace{\overset{O}{}_{-} \underbrace{(iii)}_{(iii)}}_{(iii)} \underbrace{\overset{O}{}_{-} \underbrace{(iii)}_{(iii)}}_{(iii)} \underbrace{\overset{Ph}{}_{-} \underbrace{\overset{O}{}_{-} \underbrace{(iii)}_{(iii)}}_{(iii)} \underbrace{\overset{O}{}_{-} \underbrace{(iii)}_{(iii)}}_{(iii)} \underbrace{\overset{O}{}_{-} \underbrace{(iii)}_{(iii)}}_{(iiii)} \underbrace{\overset{O}{}_{-} \underbrace{(iii)}_{(iii)}}_{(iii)} \underbrace{(iii)}_{(iii)} \underbrace{(iii)} \underbrace{(iii)}_{(iii)} \underbrace{(iii)}_{$$

- Ni-catalyzed alkene functionalization: <u>radical capture</u> or <u>reductive elimination</u>

$$\begin{array}{c} R^{1} & & \\ R^{2} & & \\ R^{2} & & \\ R^{2} & & \\ \hline (iv) & R^{1} & \\ \hline (iv) & R^{2} & \\ \hline (iv) & R^{2} & \\ \hline (v) & \\ \hline (v) & R^{2} &$$

Scheme 2. Enantio-determining Steps for Alkene Carbofunctionalization.

Our catalyst development employed para-acetoxystyrene 1 as the model substrate and PhBr as the electrophile coupling partner (Table 1). Initial optimization concluded that the use of 10 mol% Ni(DME)Br₂ as the catalyst and Zn powder as the reductant resulted in conversion of 1 to the desired diphenylation product, which upon hydrolysis gave 5, an appealing precursor 2. Replacing Zn with Mg and TDAE to (tetrakis(dimethylamino)ethylene) both gave product 5 with modest ee (Table S1). When PhZnCl was subjected to the conditions in place of PhBr, the reactions failed to afford any alkene arylation product (Scheme S1). These results rule out organo-zinc reagents as intermediates, suggesting that zinc merely serves as a reductant.

Bi-oxazoline (biOx) ligands have been extensively utilized in recent Ni-catalyzed asymmetric coupling reactions, [16, 25] and proved to be effective with ABNO as an additive, whose role will be discussed below in Table 2 (Table 1, entries 1-7). The substituents on the biOx ligand, surprisingly, have only a minor effect on the ee, except for tBu-biOx and Ph-biOx, which resulted in significantly lower yields and no enantioselectivity (entries 4-5). This observation could be attributed to the bulky substituents that prevent coordination, evident from the different reaction color. Other common N-ligands frequently used in asymmetric Ni catalysis, such as bis-oxazoline (box), pyridinebisoxazoline (pybox), and pyridine-oxazoline (pyrox) resulted in low conversion (entries 8-10). Lowering the temperature led to slightly higher ee, albeit with a lower yield (entry 11). The low yield could result from inefficient mixing, due to high viscosity of N,N'-dimethylpropyleneurea (DMPU) at low temperatures. A mixture of DMPU and THF in a 1:1 ratio ameliorated this viscosity issue, improving the yield to 90% with an ee of 91% (entry 13).

Table 1. Catalyst Optimization: Effect of ligands and solvents. [a]



Entry	Ligand	Solvent	T (°C)	Yield (%)	ee (%)
1	<i>i</i> Pr-biOx	DMPU	25	52	83
2	<i>i</i> Bu-biOx	DMPU	25	69	89
3	Cy-biOx	DMPU	25	41	87
4	<i>t</i> Bu-biOx	DMPU	25	28	0
5	Ph-biOx	DMPU	25	25	0
6	4-hept-biOx	DMPU	25	64	73
7	indane-biOx	DMPU	25	52	64
8	Ph-box	DMPU	25	0	-
9	<i>i</i> Pr-pyrox	DMPU	25	30	28

10	<i>i</i> Pr-pybox	DMPU	25	5	-
11	<i>i</i> Bu-biOx	DMPU	10	38	90
12	<i>i</i> Bu-biOx	DMPU/THF (3:1)	10	74	90
13	<i>i</i> Bu-biOx	DMPU/THF (1:1)	10	90	91
14	<i>i</i> Bu-biOx	DMPU/THF (1:3)	10	28	91



[a] Reaction conditions: [1 (0.2 mmol)] = 1 M, [PhBr] = 4 M. Yields determined by ¹H NMR spectroscopy using mesitylene as an internal standard. Ee determined by HPLC.

During catalyst optimization, we noticed that the N-oxyl additive exerts a significant effect the radical on enantioselectivity (Table 2). Examining a number of N-oxyl radical derivatives, we used multivariate analysis^[26] to deconvolute parameters that contribute to affecting the ee. Several parameters were computed to describe the electronic and steric effects of various N-oxyl radicals, including SOMO energy (E_{SOMO}), redox potential, IR stretching frequency of the corresponding $R_2N^+=O$ ($\upsilon N^+=O$), polarizability, and buried volume (%Vbur) (Table S2). In particular, %Vbur is obtained by submitting the structures of (bipyridine)Ni(N-oxyl) after geometry optimization to SambVca 2.0.[27] When we applied linear regression modeling to relate the enantioselectivity (expressed as $\Delta\Delta G^{\ddagger}$) and the computed parameters, %Vbur exhibits a dominant effect, providing a linear correlation with an R² value of 0.8 when plotted directly against $\Delta\Delta G^{\ddagger}$ (Figure S3). The most sterically unhindered N-oxyl additives, ABNO and AZADO, gave the greatest ee. A stronger correlation ($R^2 = 0.96$) was obtained when E_{SOMO} and $vN^+=O$ were included along with %Vbur as descriptors (Figure S4). Examining the stoichiometry of Ni:ABNO revealed that it is critical to apply a Ni:ABNO ratio of 1:1-1:0.8 to obtain high yield and ee, as a slight excess of ABNO led to complete inhibition of the diarylation reaction. While characterizing the precise nature of the observed N-oxyl effect needs further investigation, the required 1:1 ratio of Ni:ABNO is consistent with it serving as a ligand.^[28]

Table 2. Catalyst Optimization: Effect of an N-oxyl Additive. [a]

		Ni(DI (<i>S</i>)- <i>i</i> E	Ni(DME)Br ₂ (10 mol%) (<i>S</i>)- <i>i</i> Bu-biOx (20 mol%)			Ph		
P	AcO 1 + PhBr	Ac Zr DMP	<i>Additive</i> (8 mol%) Zn (2 equiv.), 16 h DMPU:THF = 1:1, 10 °C		но	5		
	Additive	Yield (%)	ee (%)	Additive	Yield (%)	ee (%)		
	none	78	26	tBu NO	63	60		
	TEMPO	60	21	2-Me-AZADO	71	57		
	4-oxo-TEMPO	50	29	AZADO	76	89		

4-OAc-TEMPO	64	33	ABNO	90	91
4-OH-TEMPO	82	46	NO	39	54

[a] Reaction conditions: [1 (0.2 mmol)] = 1 M, [PhBr] = 4 M. Crude reaction mixtures were treated with aqueous NaOH to saponify the acetate. Yields determined by ¹H NMR using mesitylene as an internal standard. Ee determined by HPLC.

With the optimized conditions, we explored the scope of asymmetric diarylation (Table 3). The enantioselectivity of the reactions, in general, appeared to be insensitive to the electronic nature of the electrophile component. The low ee of 10 may be attributed to an interaction of Ni with the boronic ester. The reaction conditions are compatible with a number of functional groups, including fluoride, chloride, ester, amine, and indole moieties. When bromobenzene was used as the electrophile and the vinylarene component was varied, a wide variety of electron-rich and electron-deficient vinylarenes underwent diphenylation to give α, α, β -triarylethane products (19-30). Changing the electronic nature of the vinylarene component by using various para-substituted styrenes seemed to have a modest effect on enantioselectivity. However, the observed enantiomeric ratios of products do not show a linear-free-energy relationship with the Hammett parameters for the corresponding para-substituents ($R^2 = 0.17$, Figure S6). Simple disubstituted olefins, such as α - and β -methylstyrene, gave no diarylation product under the optimized conditions. Performing the diphenylation of 1 on a 1.0 mmol scale furnished 5 in 71% isolated yield and 92% ee. When the reaction was conducted on bench using standard Schlenk techniques, 5 was formed in 66% yield and 90% ee. The catalyst, once activated, decomposes in air, thus the reaction requires an inert atmosphere.

Subsequently, we carried out preliminary studies to probe factors that control the enantioselectivity. We first sought to examine the ratio of the ligand to Ni. The ee of the product exhibits a linear correlation with the ee of the ligand (Figure S7).^[29] This observation suggests that the ligand to Ni ratio is 1:1 in the enantio-determining step, although excess ligand is required to stabilize the Ni catalyst in solution.

Table 3. Substrate Scope of Asymmetric Diarylation of Vinylarenes. [a]



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[a] Reaction conditions: [vinylarene (0.2 mmol)] = 1 M, [ArBr] = 4 M. Yields determined by ¹H NMR using mesitylene as an internal standard. Ee determined by HPLC. Absolute stereochemistry was assigned for **29** based on X-ray crystallography, while all other products were assigned by analogy. [b] [vinylarene] = 0.5 M. [c] With 20 mol% Ni(DME)Br₂, 40 mol% *i*Bu-biOX, and 16 mol% ABNO. [d] Isolated yield. The error bar is based on four duplicate experiments. [e] The product was isolated as the corresponding phenol following deacylation with aq. NaOH.

It is generally accepted that Ni-catalyzed cross-coupling reactions proceed through radical intermediates. $^{\rm [31]}$ Several

observations provide evidence for the formation of radical intermediates at the benzylic position: (1) inhibition of the reaction by excess N-oxyl, which could be attributed to its interaction with organic radicals; (2) formation of benzylic dimers, such as 32, with several substrates (eq 1);^[32] (3) selective formation of trans-diphenylation product 33 in 70% ee with indene (eq 2). A difunctionalization going through olefin migratory insertion has been reported to form *cis*-products.^[33] The trans-diastereoselectivity observed here could arise from a cis-migratory insertion, followed by reversible radical ejection that scrambles the benzylic stereocenter as the coordination favors the less-hindered face (step vi, Scheme 3). This proposal serves as an experimental support for Kozlowski and Molander's computational study.^[24] The observation of 70% ee of 33 could rule out free phenyl radical addition to indene. In Scheme 3, we present a plausible mechanism. Detailed mechanistic study is underway to fully elucidate the sequence of reagent activation and the identity of the enantio-determining step.



Scheme 3. Proposed Mechanism.

In summary, we developed a Ni-catalyzed asymmetric diarylation reaction of vinylarenes. The reaction represents a compelling method for preparing chiral α,α,β -triarylated ethane scaffolds. The use of reducing conditions with aryl bromides as the coupling partner avoids the use of stoichiometric organometallic reagents and allows for tolerance of a broad range of functional groups. During catalyst development, we discovered that the use of an auxiliary *N*-oxyl ligand, in

conjunction with a chiral Ni catalyst, enabled the formation of dicarbofunctionalized products with high enantioselectivity. We anticipate that this insight could inform catalyst development for other Ni-catalyzed cross-coupling reactions.

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Keywords: Diarylation • Alkenes • Nickel • Asymmetric catalysis • ABNO

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Entry for the Table of Contents (Please choose one layout)

Layout 1:

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A nickel catalyst with chiral bioxazoline ligands in combination of ABNO effects asymmetric 1,2diarylation of vinyl arenes to form α, α, β -triarylated ethane scaffolds.



David Anthony, Qiao Lin, Judith Baudet, and Tianning Diao*

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