Enantioselective Synthesis of Aminals via Nickel-Catalyzed Hydroamination of 2-Azadienes with Indoles and *N*-Heterocycles

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ABSTRACT: New methods for the enantioselective synthesis of *N*-alkylated indoles and their derivatives are of great interest, because indoles are pivotal structural elements in biologically active molecules and natural products. They are also versatile intermediates in organic synthesis. Among well-established asymmetric hydroamination methods, the asymmetric hydroamination with indole-based substrates is a formidable challenge. This observation is likely due to the reduced nucleophilicity of the indole nitrogen. Herein, a unique nickel-catalyzed enantio- and branched-selective hydroamination of 2-azadienes with indoles and structurally related *N*-heterocycles is reported for the generation of enantioenriched *N*,*N*-aminals. Salient features of this reaction include good yields, mild reaction conditions, high enantioselectivities and broad substrate scope (60 examples, up to 96% yield and 99% ee). The significance of this approach with indoles and other *N*-heterocycles is demonstrated through structural modification of natural products and drug molecules and the preparation of enantioenriched *N*-alkylated indole core structures. Mechanistic studies reveal that olefin insertion into a Ni–H in the hydroamination is enantiodetermining step and oxidative addition of the N–H bond may be the rate-limiting.

1. INTRODUCTION

Indole derivatives are ubiquitous in natural products and biologically active compounds.[1-5] In fact, the indole core is one of the most common heterocycles in FDA-approved drugs.[6] A lesser studied subset of indoles are *N*-alkylindole aminals,[7] which contain the indole core as part of an aminal.[8-10] These structurally interesting functional groups have emerged as motifs in pharmaceuticals, biologically active molecules, and natural alkaloids. For example, indole aminals are found in antibiotics[11,12] and Vernavosine[13] (Figure 1). *N*-Indole aminals share a structure possessing a carbon bearing two nitrogen atoms prone to undergo ionization, increasing opportunities for variation of their 3-diminsional structures.[14] Enantioenriched *N*-alkylindole aminals, however, are often difficult to synthesize with high enantioselectivity, partly due to the sensitivity of aminals to acids and Lewis acidic catalysts, reagents, and purification media.[15]

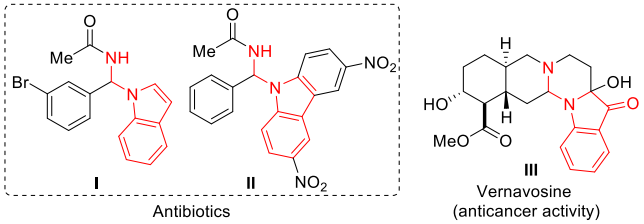


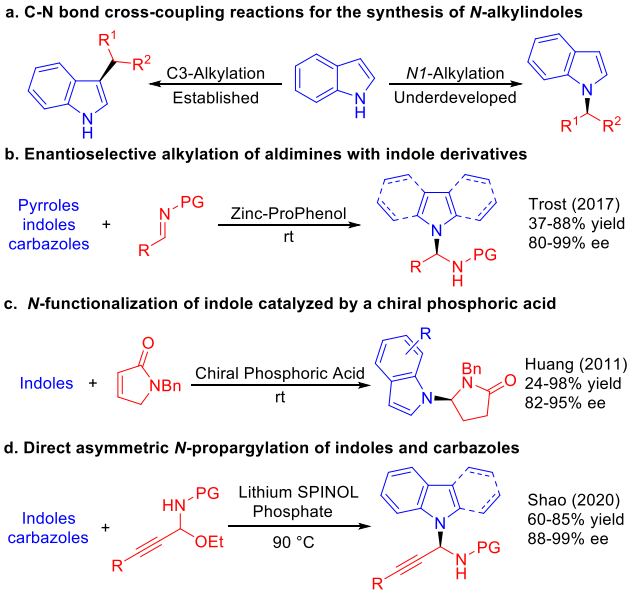
Figure 1. Selected biologically active *N*-alkylated indole aminals.

Given the potential value of *N*-alkylindole aminals[16-18] the development of efficient and practical strategies to access *N*-alkylindole aminals has attracted significant attention from the synthetic community. The catalytic *N*-selective alkylation of 1*H*-indoles is one of the most synthetically efficient strategies for their synthesis. The functionalization of 1*H*-indoles, however, typically leads to reaction at the indole C3-position,[19] which is the most nucleophilic site on such substrates (Scheme 1). As a result, the regioselective *N*-alkylation of indoles remains underdeveloped (Scheme 1a).[20-23]

A few strategies for the intermolecular N–H functionalization of indoles in a chemo- and enantioselective manner have been reported. An early pioneering work was reported by Trost and co-workers who developed a catalytic zinc-Prophenol mediated *N*-alkylation of indole and its derivatives with aldimine electrophiles for the construction of enantioenriched aminals of indoles (Scheme 1b).[24]

During the last two decades, chiral phosphoric acids (CPAs) have been advanced by Terada,[25-27] You,[28-31] Sun[32-34] and others[35-40] for numerous asymmetric transformations, including the *N*-alkylation of 1*H*-indoles with imines and their precursors.[41-43] In 2011, Huang and co-workers provided the first example of a CPA-catalyzed intermolecular enantioselective N–H alkylation of 1*H*-indoles with -unsaturated -lactam precursors to prepare indole aminals with high enantioselectivities (Scheme 1c).[44] Another approach employing catalytic CPA is by Shao and co-workers, who recently reported the enantioselective *N*-propargylation of indoles and carbazoles, providing *N*,*N*-aminals in good yields with excellent enantiocontrol. In this work, substituents were placed at the more nucleophilic C3 and the C2-positions of the indole substrates to prevent reactions at those sites (Scheme 1d).[45] Although these methods represent significant advances, strategies to access new classes of acyclic *N*-indole-based aminals with high enantioselectivities remain in demand.

Scheme 1. Approaches to the synthesis of *N,N*-aminals of indoles

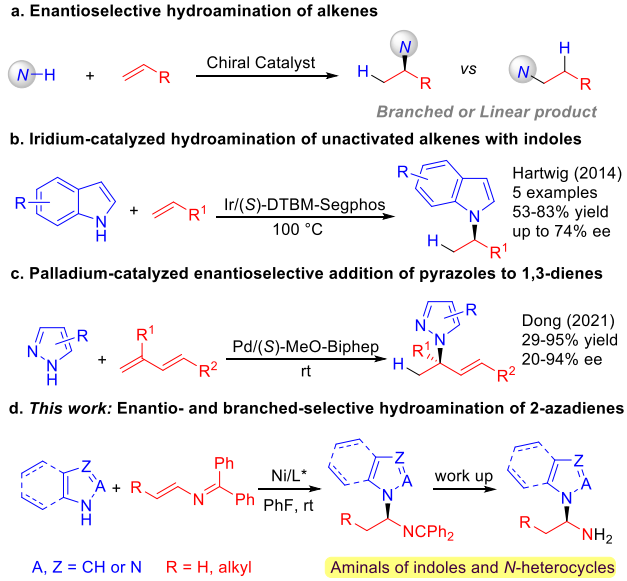


Catalytic asymmetric hydroamination of alkenes constitutes the most direct and atom-economical approach toward chiral amines.[46,47] Despite tremendous advances in this challenging arena, significant obstacles remain, including control of regio- and enantioselectivity (Scheme 2a).[48-52] Nonetheless, the hydroamination of olefins with indoles, has been reported to occur selectively at the N–H bond, which represents an efficient method for the synthesis of enantioenriched *N*-alkylindoles.[53] In 2014, Hartwig's group reported a pioneering intermolecular hydroamination of unactivated olefins with indoles as the N–H donor in the presence of an Ir-precatalyst and (*S*)-SEGPHOS derivative (Scheme 2b).[54] Unfortunately, the enantioselective version of the reaction was complicated by the formation of an achiral enamine intermediate, which underwent hydrogenation by the catalyst to give the opposite enantiomer of the product compared to the direct hydroamination. Dong and Yang recently reported a palladium catalyzed enantioselective hydroamination of 1,3-dienes to access *N*-allylic pyrazoles (Scheme 2c).[55] These works inspired us to consider a hydroamination strategy to prepare *N*-indole aminals from 2-azadienes. To the best of our knowledge, *the hydroamination of C=C bonds with the goal to access N-indole aminals has not been advanced*.

As part of our interest in the synthesis of multifunctional amines via deprotonation of ketimines or aldimines to form 2-azaallyl anions, our laboratory[56-59] and other teams,[60] have achieved concise syntheses of arylmethylamines,[61] diarylmethylamines,[62] allylic amines,[63] and homoallylic amines[64] through umpolung reactions.[65,66] By using Cu–H catalysis, Malcolmson and co-workers demonstrated beautiful reductive couplings of 2-azadienes with ketones or imines to give optically active amino alcohols and diamines, respectively.[67,68] Inspired by Malcolmson's excellent studies on the hydrofunctionalisation of 2-azadienes, we reported an enantioselective hydrophosphinylation to access enantioenriched α-aminophosphine oxides via nickel catalysis.[69] Based on these works, we envisioned a regio- and enantioselective addition of indole derivatives to 2-azadienes with the goal of furnishing enantioenriched *N*-indole aminal derivatives.

Herein, we disclose the development of highly chemo- and regioselective catalytic asymmetric functionalizations of 1*H*-indoles and structurally related *N*-heterocycles through a hydroamination strategy (Scheme 2d). Employing a Ni/(*R*)-SEGPHOS catalyst system, *N*-alkylated indole aminals, which are difficult to access by other methods, can be efficiently synthesized with excellent enantioselectivities (up to 99%) and good yields (up to 96%). Our hydroamination of 2-azadienes features broad substrate scope and complete *N*-selectivity, regardless of the electronic properties and substitution patterns of the aromatic heterocycles.

Scheme 2. Enantioselective hydroamination of C=C double bond compounds



2. RESULTS AND DISCUSSION

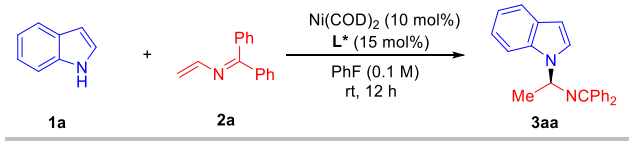
Reaction development and optimization. We commenced our studies by examining the reaction using indole (**1a**) and 1,1-diphenyl-*N*-vinylmethanimine (**2a**) as the model substrates in the presence of 10 mol% $Ni(COD)_2$ in PhF at room temperature for 12 h (Table 1). After initial evaluation of an extensive set of commercially available enantioenriched ligands (see Supporting Information for full details), we identified the most promising ones (**L1**–**L8**, 15 mol%, Table 1). This set included enantioenriched phosphinooxazoline ligands (**L1** and **L2**), a BOX ligand (**L3**) and C_2-symmetric bisphosphine ligands (**L4**–**L8**).

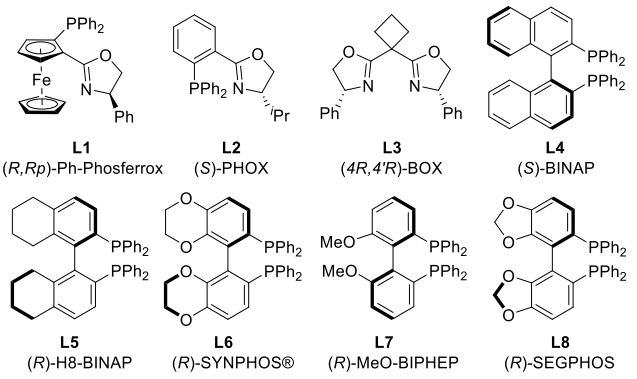
Starting with the nitrogen containing ligands **L1–L3**, (*R*,*Rp*)-PhPhosferrox **L1** outperformed the ferrocenyl-based ligands (*S*)-PHOX **L2** and (*4R*,*4'R*)-BOX **L3**, exhibiting both better reactivity and enantioselectivity for the desired product **3aa** with 85% assay yield (AY, determined by ^{1}H NMR integration against an internal standard) and 84% enantiomeric excess (ee) (entry 1 *vs.* entries 2 and 3, Table 1). Evaluation of commercially available axial chiral bisphosphine ligands (**L4**–**L8**) indicated that (*R*)-SEGPHOS (**L8**) stood out in terms of both reactivity and enantioselectivity (99% AY and 95% ee) (entry 8 *vs.* entries 4–7, Table 1).

With the most promising ligand **L8** identified, we next investigated the impact of solvent. Most aprotic solvents, including $PhCF_3$, PhMe, MeCN, DMSO, THF and DME, were effective, providing **3aa** in moderate to good yields with good to excellent enantioselectivities (entries 9–14, Table 1). Notably, DMSO was found to be comparable to PhF, exhibiting excellent enantioselectivity and superior dissolution properties, although slightly inferior yield (92 *vs.* 99%, entry 12 *vs.* entry 8, Table 1). We next examined the impact of reduced catalyst loading. The loading of $Ni(COD)_2$ was reduced from 7.5 mol% to 5 mol%, affording **3aa** with 99% AY, 95% isolated yield and 95% ee (entry 15 and 16, Table 1). However, re-

ducing the loading to 3 mol% decreased the yield and enantioselectivity of **3aa** to 75% and 89%, respectively (entry 17, Table 1). Under otherwise identical conditions, replacing $Ni(COD)_2$ with $NiBr_2$, $Cu(OAc)_2$ and CoI_2, did not generate the desired aminal products (entry 18, Table 1; see Supporting Information for full details).

Table 1. Optimization of the hydroamination of 2-azadiene 2a[a]



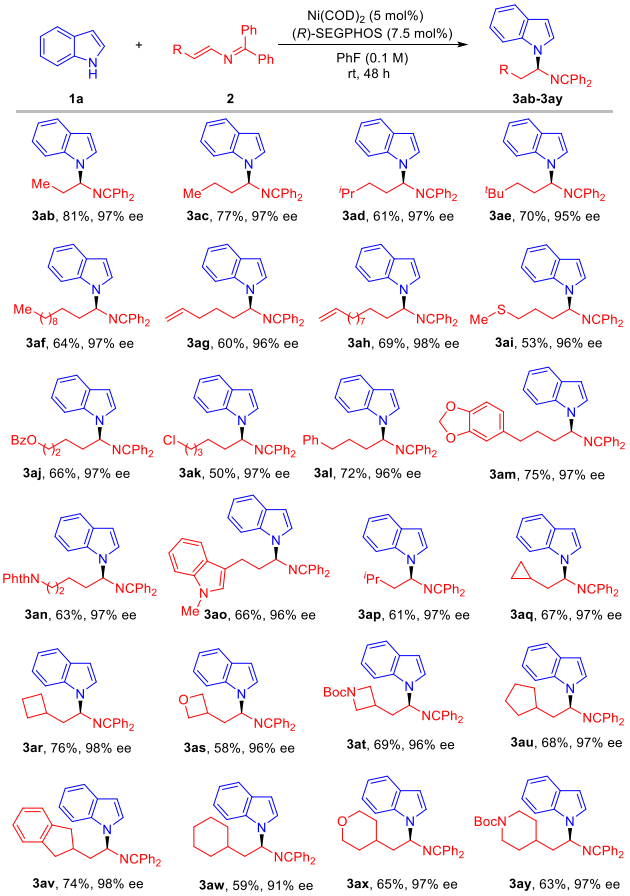


Entry	L	Ni/L (mol%)	Solvent	**3aa** (%)[b]	ee (%)[c]
1	**L1**	10/15	PhF	85	84
2	**L2**	10/15	PhF	70	67
3	**L3**	10/15	PhF	30	68
4	**L4**	10/15	PhF	45	82
5	**L5**	10/15	PhF	38	82
6	**L6**	10/15	PhF	80	90
7	**L7**	10/15	PhF	75	89
8	**L8**	10/15	PhF	99	95
9	**L8**	10/15	$PhCF_3$	65	94
10	**L8**	10/15	PhMe	51	85
11	**L8**	10/15	MeCN	78	89
12	**L8**	10/15	DMSO	92	95
13	**L8**	10/15	THF	63	87
14	**L8**	10/15	DME	71	86
15	**L8**	7.5/12	PhF	99	95
16	**L8**	5/7.5	PhF	99(95)[d]	95
17	**L8**	3/4	PhF	75	89
18[e]	**L8**	5/7.5	PhF	0	-

[a]Reactions conducted on a 0.1 mmol scale using 1.5 equiv. of **1a**, 1.0 equiv. of **2a**. [b]Assay yields (AY) were determined by ^1H NMR spectroscopy with CH_2Br_2 as internal standard. [c]Enantiomeric excess (ee) of **3aa** was determined by chiral-phase HPLC. [d]Isolated yield (IY) of **3aa** after chromatographic purification. [e]$NiBr_2$, $Cu(OAc)_2$ and CoI_2 instead of $Ni(COD)_2$.

Scope of the 2-azadiene coupling partners. With the optimized conditions in hand (entry 16, Table 1), we explored the hydroamination of 2-azadienes bearing different substituents with indole **1a**. Increased steric hindrance about the double bond of the substrates slowed the hydroamination and required prolonged reaction periods (48 h, Table 2). Despite the longer reaction times, we observed that the substituent on the 2-azadiene had a negligible impact on the reaction yield (58–81%) or enantioselectivity (91–98% ee). Employing 2-azadiene coupling partners with simple primary aliphatic groups furnished the desired products (**3ab–3ah**) in moderate to good yields (60–81%) with excellent enantioselectivities (95–98%). This protocol also tolerated substrates with thioether (**2i**), ester (**2j**), alkyl chloride (**2k**) and pendent aryl groups (**2l** and **2m**), delivering the corresponding products (**3ai–3am**) in 50–75% yields with high enantioselectivities. It is gratifying that substrates with imide and heteroarene functionalities (**2n** and **2o**) were smoothly converted to the corresponding products **3an** and **3ao** in moderate yield with 97% and 96% ee, respectively. In addition, 2-azadienes containing secondary aliphatic groups like *i*-Pr, cyclic and heterocyclic groups (**2p–2y**) were also compatible coupling partners, generating products (**3ap–3ay**) with 58–76% yields and high enantioselectivities (91–98% ee).

Table 2. Scope of the *N*-alkylation of 2-azadienes with indole 1a[a]

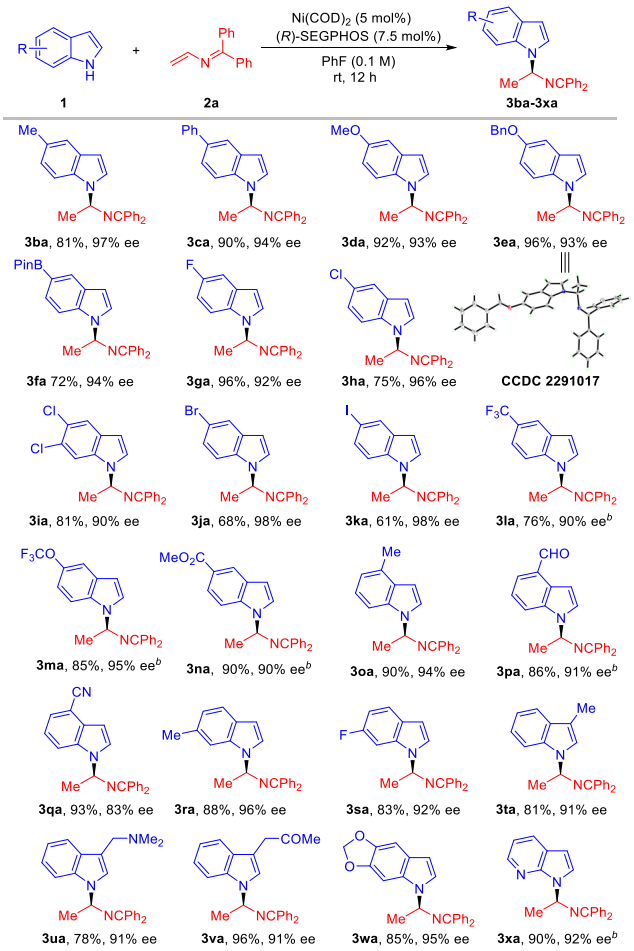


[a]Reactions conducted on a 0.4 mmol scale using 1.5 equiv. **1a**, 1.0 equiv. **2** at 0.1 M. Isolated yields after chromatographic purification. Ee determined by HPLC analysis. PhthN = Phthaloyl.

Scope of the indole coupling partners. Next, we examined the scope of indole N–H donors to 2-azadiene **2a** (Table 3). Indoles bearing electron-donating or electron-withdrawing groups at the 4-position provided aminals (**3ba**–**3la**) in 61–96% yields and 90–98% ee. The absolute configuration of product **3ea** was determined to be (*S*) by X-ray crystallography (Table 3, CCDC 2291017; see Supporting Information for full details). On the basis of this structure, the configuration of the remaining products were assigned as *S* by analogy. The 5-trifluoromethoxy-substituted indole was also suitable under our reaction conditions, furnishing the desired product **3ma** with 85% yield and 95% ee. Despite electronic deactivation of an indole bearing an ester group at the 5-position, this substrate performed well, giving 80% yield and 90% ee. We also investigated the impact of substituents at other positions on the indole backbone. Employing indoles with 4-methyl, 4-formyl

or 4-cyano groups resulted in the generation of the products (**3oa**–**3qa**) in 86–93% yields with 83–94% ee. Similarly, 6-methyl and 6-F containing indoles exhibited good reactivities, affording the corresponding products (**3ra** and **3sa**) in 88 and 83% yields with 96% and 92% ee, respectively. Use of a 3-methyl or alkyl groups containing *N,N*-dimethyl and ester substituents at the 3-position proceeded in 78–96% yields with all products furnished with 91% ee (**3ta**–**3va**). Indole derivatives bearing dioxole (**1w**) or heteroatoms in the indole backbone (1*H*-pyrrolo[2,3-*b*]pyridine, **1x**) proved viable and coupled with 2-azadiene **2a** to afford the desired products in 85–90% yield with ee values of 92–95%.

Table 3. Scope for the *N*-alkylation of indoles with 2-azadiene 2a[a]

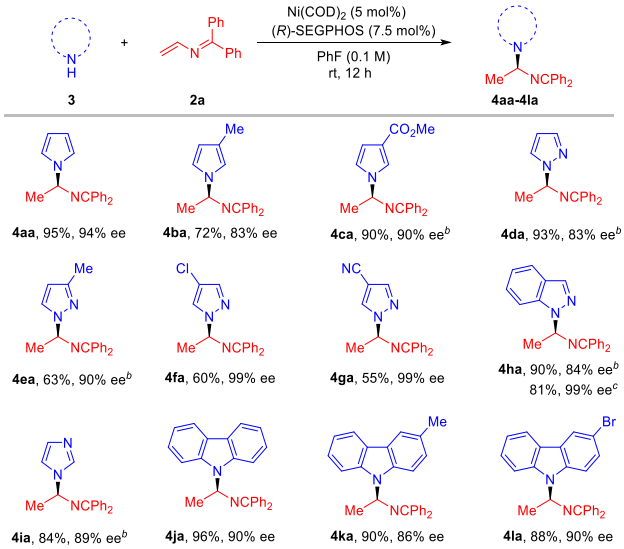


[a]Reactions conducted on a 0.4 mmol scale using 1.5 equiv. **1**, 1.0 equiv. **2a** at 0.1 M. Isolated yields after chromatographic purification. Ee determined by HPLC analysis. [b]DMSO was used as the solvent.

Scope of the N-heterocyclic coupling partners. We next turned our attention to other *N*-heterocycles, including pyrrole, pyrazole, indazole, imidazole and carbazole derivatives. Overall, these *N*-heterocycles exhibited moderate to good reactivities (55–96% yields) and furnished the corresponding products (**4aa**–**4la**) with high enantioselectivities (83–99% ee, Table 4).

Pyrrole was an excellent coupling partner, providing the desired product **4aa** in 95% yield with 94% ee. Pyrroles substituted with 3-methyl and 3-ester groups (**3b** and **3c**) also coupled with 2-azadiene **2a** in 72% and 90% yields and with enantioselectivities of 83% and 90%, respectively. Pyrazole and derivatives with 3-methyl, 4-Cl and 4-cyano were viable substrates and gave the hydroamination products **4da**–**4ga** in 55–93% yields and 83–99% enantioselectivity. This method was also compatible with indazole and imidazole, furnishing the products **4ha** and **4ia** in 84–90 % yields with 84% and 89% ee, respectively. The indazole product could be recrystallized to upgrade the ee to 99%. The parent carbazole, or derivatives bearing 3-Methyl or 3-bromo effectively participated in the hydroamination giving the products **4ja**–**4la** in 88–96% yields with high enantioselectivities (86–90%).

Table 4. Scope for the *N*-alkylation of *N*-heterocycles with 2-azadiene 2a[a]



[a]Reactions conducted on a 0.4 mmol scale using 1.5 equiv. **3**, 1.0 equiv. **2a** at 0.1 M. Isolated yields after chromatographic purification. Ee determined by HPLC analysis. [b]DMSO was used as the solvent. [c]After recrystallization.

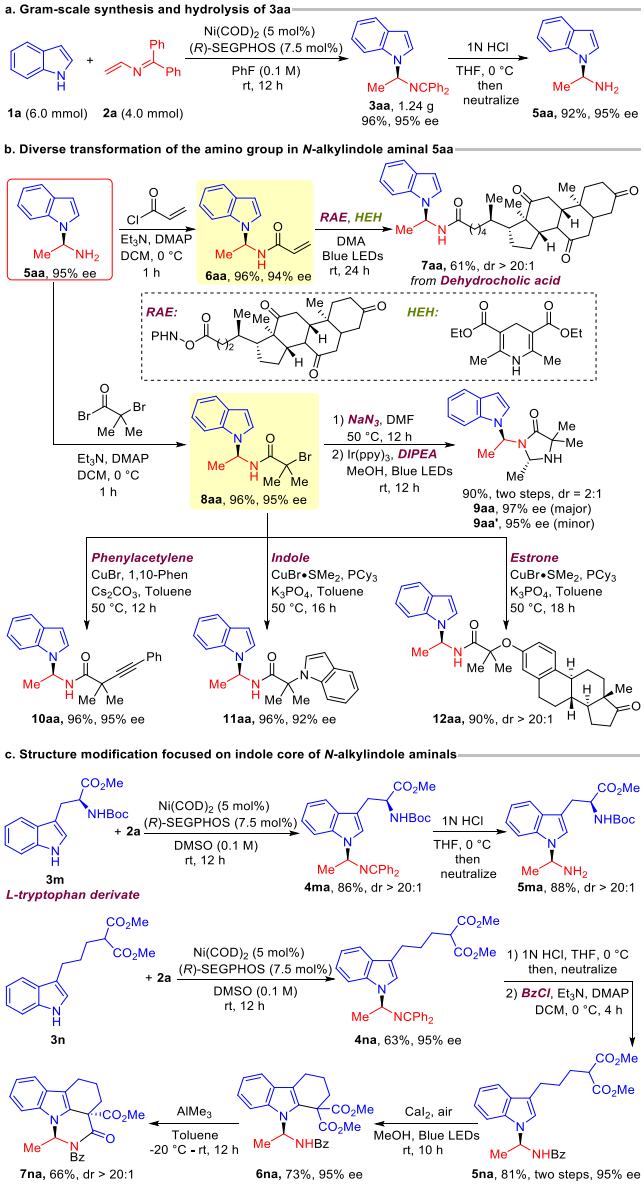
Gram scale synthesis and product derivatization. To highlight the scalability of the hydroamination protocol, a gram scale reaction and further modifications were conducted (Scheme 3). Combination of the parent indole (**1a**, 6.0 mmol) with 2-azadiene **2a** (4.0 mmol) resulted in formation of 1.24 g of the product **3aa** (96% yield) after 12 h without any drop in the enantioselectivity (95% ee). Hydrolysis of the imine of **3aa** with 1N HCl and subsequent neutralization with 1N NaOH afforded the *N*-alkylindole aminal **5aa** in 92% isolated yield with 95% ee (Scheme 3a). With the hydrolyzed product **5aa** in hand, diverse derivatizations focusing on the amino group were explored (Scheme 3b). Aminal **5aa** reacted with acryloyl chloride or 2-bromo-2-methylpropanoyl bromide to furnish the amides **6aa** and **8aa** ≥95% yields with 94% and 95% ee, respectively. Compound **6aa** was subjected to decarboxylative conjugate addition with a dehydrocholic acid-derived redox-active ester (RAE) under visible-light photoredox catalysis (see Supporting Information for full details). The reaction successfully delivered compound **7aa** in 61% yield (dr >20:1).[70] The α-bromo amide **8aa** serves as a useful handle for further diversification. For instance, treatment with sodium azide at 50 °C led to azidogenation of **8aa**, followed by the visible-light-promoted radical cyclization of α-azido amide,[71] providing the imidazolinone derivative in 90% combined yield as a separable pair of diastereomers **9aa** and **9aa'** with 97% and 95% ee (2:1 dr). Furthermore, the C–C coupling reaction of **8aa** with phenyl acetylene generated α-alkynylamide **10aa** in 96% yield with 95% ee. Meanwhile, the hindered amine **11aa**

could be readily provided in 96% yield and 92% ee by the Cu-catalyzed C–N bond formation. Similarly, the etherification of α-bromo amide **8aa** with estrone occurred smoothly to offer the hindered ether **12aa** in 90% yield (dr > 20:1).

To further demonstrate the value of the hydroamination protocol in synthetic chemistry, we turned our attention to the modification of the indole core of our products (Scheme 3c). Gratifyingly, our catalytic system was effective in the modification of commercially available *L*-tryptophan derivative **3m**. The desired product **4ma** was afforded in 86% yield (dr > 20:1) under the standard conditions. Compound **4ma** was subjected to hydrolysis to afford **5ma** in 88% yield (dr > 20:1).

To construct valuable chiral heterocycles, we used the indole derivative **3n** as a coupling partner, delivering the corresponding product **4na** in 63% yield with 95% ee. Imine hydrolysis and reaction with benzoyl chloride easily produced **5na** in 81% yield with 96% ee. According to Itoh's protocol,[72] an intramolecular dehydrogenative cyclization reaction of **5na** proceeded well and gave a C–C coupling product **6na** in 73% yield without any loss of ee. A second intramolecular cyclization onto the pendant ester of **6na** with $AlMe_3$ generated the 6-membered ring lactam **7na** at room temperature in 66% yield (dr > 20:1). This sequence illustrates the potential value of our hydroamination protocol for the construction of complex chiral heterocycles. Overall, the reactions in Scheme 3 illustrate the tolerance of the aminal motif to withstand a variety of catalysts, reagents and transformations.

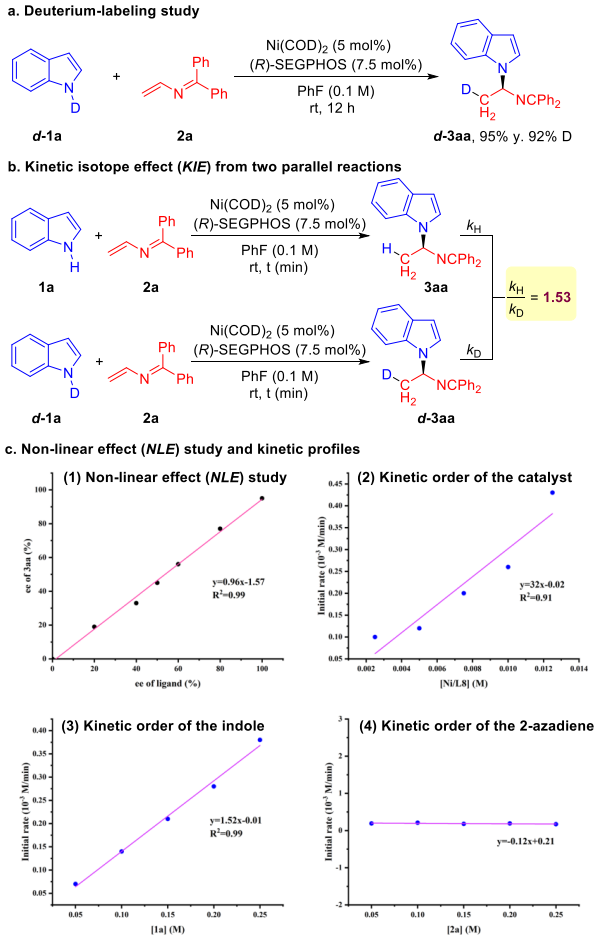
Scheme 3. Gram-scale synthesis and transformation of products



Mechanistic studies*.** To gain insights into the hydroamination process, several experiments were performed. When *N*-deuterated indole was subjected to the standard reaction conditions, 92% deuterium was found to be incorporated into the terminal position of product ***d*-3aa** with 95% yield (Scheme 4a). Only a single deuterium was found in the product by MS (see Supporting Information for full details), suggesting that the insertion step of the hydroamination process is likely irreversible.[73] A kinetic isotope effect (KIE) determination was also performed. Comparing the initial rate constants of 1*H*-indole (**1a**) and deuterated indole (d*-1a**) in parallel, we observed a KIE (k_H/k_D = 1.53, Scheme 4b) (see Supporting Information for full details). This KIE could be consistent with oxidative addition of the N–H/D bond, although interpretation of KIE's for oxidative addition of R–H bonds is notoriously difficult due to pre-coordination of the substrate to the metal complex often proceeding oxidative addition.[74] A similar coordination of the indole N to the nickel can be envisioned. To probe the catalyst speciation, non-linear effect (NLE) studies were conducted by variation of the enantiomeric excess of the SEGPHOS ligand. The ee of product **3aa** was linearly related to the ee of the catalyst employed (Scheme 4c(1)). The linear relationship implies that the active catalyst bears only one SEGPHOS ligand and dimers are not

involved.[75,76] In addition, we performed kinetic studies with respect to each reaction component (Scheme 4c(2-4); see Supporting Information for full details). Here, the model reaction was found to exhibit first-order-dependency on the catalyst and the indole but exhibited a zero-order dependence on 2-azadiene. Thus, the kinetic order suggested that the Ni catalyst and indole are involved in the turnover-limiting step,[77,78] further supporting the notion that oxidative addition of N–H bond is likely turnover-limiting.

Scheme 4. Mechanistic studies



On the basis of our observations[69] and literature precedents,[74, 79-81] we envision the following mechanistic pathway for the nickel catalyzed hydroamination of 2-azadienes (Figure 2). To begin, the Ni(0) precatalyst binds to the bisphosphine ligand, providing the enantioenriched L*Ni(0) complex **I**. This complex is likely chelated to a COD, which will become a monodentate ligand and eventually completely dissociate enroute to the oxidative addition TS and product (not shown). We proposed that the L*Ni^0 complex undergoes oxidative addition of the N–H bond of indole **1a** to form a nickel–amido hydride complex **II**. The oxidative addition of N–H bonds has been known for some years,[82-84] but has not been studied to the same extent as oxidative addition of C–H bonds. The oxidative addition adduct L*Ni(II) intermediate **II** is proposed to bind the 2-azadiene **2a** and affords complex **III**. Ni–H insertion into the 2-azadiene gives the Ni-(2-azaallyl anion) **IV**. Although it is drawn as an ^{3}-azaallyl, it may be ^{1}. It is known that, unlike Pd(II), which is usually d^8, square planar, 16 electrons, Ni(II) is common as d^8, 18 electrons. Finally, N–C reductive elimination yields hydroamination product **3aa** and closes the catalytic cycle.

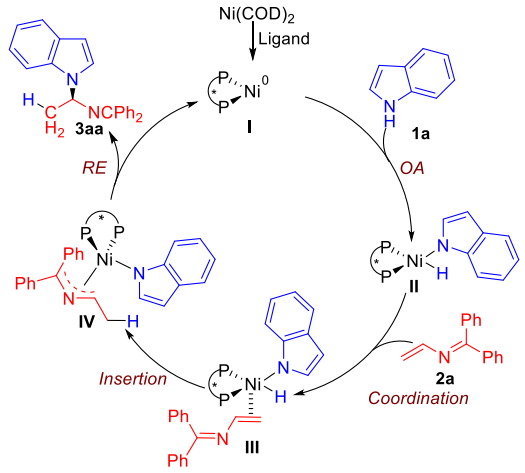


Figure 2. Key steps in the proposed mechanism.

3. CONCLUSIONS

In conclusion, the asymmetric hydroamination reaction of 2-azadienes with indole derivatives has been achieved by using a Ni(SEGPHOS)-based catalyst, providing enantioenriched indolyl aminals in good yields with excellent enantioselectivities (up to 99% ee). A variety of indoles, bearing both electron-donating and electron-withdrawing substituents, participated in this transformation and no competitive functionalization was observed at the C2 or C3 positions. This protocol constitutes a straightforward and highly efficient approach for furnishing indole-containing aminals with α-chiral centers, which are core structures in many indole alkaloids and can serve as a precursor for molecules with significant biological activity. A telescoped gram-scale synthesis confirmed the scalability, while imine hydrolysis and diverse transformations of primary amino and indole core structures showcased aminals utility in synthetic chemistry. The proposed reaction mechanism involves a Ni–H insertion into the olefin to give a Ni-bound 2-azaallyl anion, followed by C–N reductive elimination. Overall, the strategy developed in this study may be useful for coupling other nucleophilic X–H bonds with 2-azaallyl anions to generate α-chiral amine derivatives containing heteroatoms.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b0xxxx.
Experimental procedures and characterization data for all compounds (PDF)
Crystallographic information for compound **3ea** (CIF).

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Notes
The authors declare no competing financial interest.
Metrical parameters for the structures are available free of charge from the Cambridge Crystallographic Data Centre under reference number CCDC 2291017 (**3ea**).

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