

Ni-Catalyzed Enantioselective Reductive Diarylation of Activated Alkenes by Domino Cyclization/Cross-Coupling

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S Supporting Information

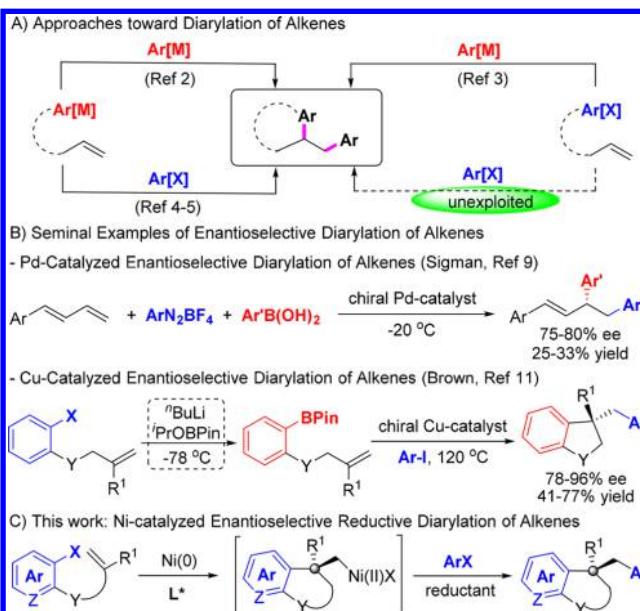
ABSTRACT: A Ni-catalyzed enantioselective reductive diarylation of activated alkenes by domino cyclizative/cross-coupling of two aryl bromides is developed. This reaction proceeds under very mild conditions and shows broad substrate scope, without requiring the use of preformed organometallic reagents. Moreover, this approach provides direct access to various bis-heterocycles bearing all-carbon quaternary centers in synthetically useful yields (up to 81%) with excellent enantioselectivity (>30 examples, 90–99% ee).

Transition metal catalyzed alkene diarylation reactions involving simultaneous incorporation of two aryl groups across the double bond in a single operation have received substantial attention, allowing for the effective construction of complex and useful compounds with stereocenters from easily accessible starting materials.¹ Oxidative diarylation of alkenes by installing two identical aryl groups using a sole organometallic reagent (ArM) as the aryl source is known.² Alternatively, diarylation by the introduction of an aryl nucleophile (ArM) and an aryl electrophile (ArX) across alkenes has also been well studied.^{3–5} However, reductive diarylation of alkenes by addition of two aryl electrophiles (ArX) without requiring the use of prepared organometallic reagents remains unexploited (Scheme 1A).^{6–8}

On the other hand, catalytical asymmetric alkene diarylation reactions are rather limited. Sigman's group demonstrated the first Pd-catalyzed asymmetric diarylation of 1,3-dienes using aryldiazonium tetrafluoroborates and arylboronic acids in good enantioselectivity, albeit with moderate yield (Scheme 1B, top).^{9,10} Brown's group developed a Cu-catalyzed enantioselective alkene diarylation by cyclizative coupling of alkene-tethered aryl-BPin, derived from the corresponding aryl halides with aryl iodides (Scheme 1B, bottom).¹¹ Another related example was reported by Fu et al., who demonstrated a Ni-catalyzed enantioselective cyclization/coupling of aryl-9-BBN with alkyl halides.¹²

Our efforts in transition metal catalyzed asymmetric dicarbofunctionalization of alkenes,¹³ have recently led to the disclosure of a Ni-catalyzed alkene diarylation by domino Heck cyclization/Suzuki coupling.¹⁴ However, attempts to render this domino reaction asymmetric by us and other groups¹⁵ were not successful. Inspired by the recent developments on Ni-catalyzed asymmetric Heck cyclization,¹⁶ we decided to target an alternative enantioselective Heck cyclization/trapping of in situ generated σ -alkyl-Ni(II) species with aryl electro-

Scheme 1. Transition Metal Catalyzed Enantioselective Diarylation of Alkenes



philes by taking advantage of the ability of Ni catalysts for facile oxidative addition and ready access to multiple oxidation states.^{7,8} Herein, we present our investigations of the first example of Ni-catalyzed enantioselective reductive diarylation of alkenes for providing access to a range of bis-heterocycles bearing all-carbon quaternary centers, which remains a challenging issue in synthetic chemistry (Scheme 1C).¹⁷

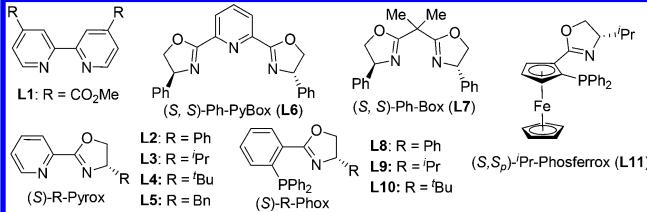
Our study commenced with the reaction of *N*-(2-bromophenyl)-*N*-methylmethacrylamide **1a** and phenyl bromide **2a** (for a systematic study of reaction conditions see Tables S1–S5 in the Supporting Information). Gratefully, the desired oxindole **3aa** could be selectively obtained in 83% yield using $\text{Ni}(\text{COD})_2$ (10 mol %), **L1** (20 mol %), B_2Pin_2 (2 equiv), Zn^0 (2 equiv), K_3PO_4 (2 equiv) as base and DMA as solvent (Table 1, entry 1).¹⁸ Replacing **L1** by a commercially available (*S*)-phenyl-PyBOX (**L2**), afforded **3aa** in 52% yield and 44% ee, along with the reductive Heck side product **4aa** in 20% yield (entry 3). Reducing the reaction temperature to 40 °C resulted in a noteworthy improvement of the enantioselectivity (62% ee, entry 6). Encouraged by this promising result, a comprehensive survey of the chiral ligands **L2–L11**

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Table 1. Optimization of the Reaction Conditions^a

entry	T (°C)	ligand	additive (equiv)	yield of 4aa (%) ^b	yield of 3aa (%) ^b	ee of 3aa (%) ^c
1 ^d	100	L1	—	<2	83	—
2	25	L1	—	50	0	—
3	100	L2	—	20	52	44
4	80	L2	—	13	62	45
5	60	L2	—	24	46	52
6	40	L2	—	38	36	62
7	40	L3	—	16	57	16
8	40	L4	—	36	20	41
9	40	L5	—	19	51	28
10	40	L6	—	28	12	0
11	40	L7	—	27	8	6
12	40	L8	—	18	5	n.d.
13	40	L9	—	40	26	77
14	40	L10	—	26	38	90
15	40	L11	—	<2	47	91
16	40	L11	KI (0.5)	<2	63	91
17 ^e	40	L11	KI (0.5)	<2	68	97
18 ^f	40	L11	KI (0.5)	0	0	—
19 ^g	40	L11	KI (0.5)	0	0	—
20	—	KI (0.5)	—	0	0	—
21 ^h	40	L11	KI (0.5)	<2	28	97



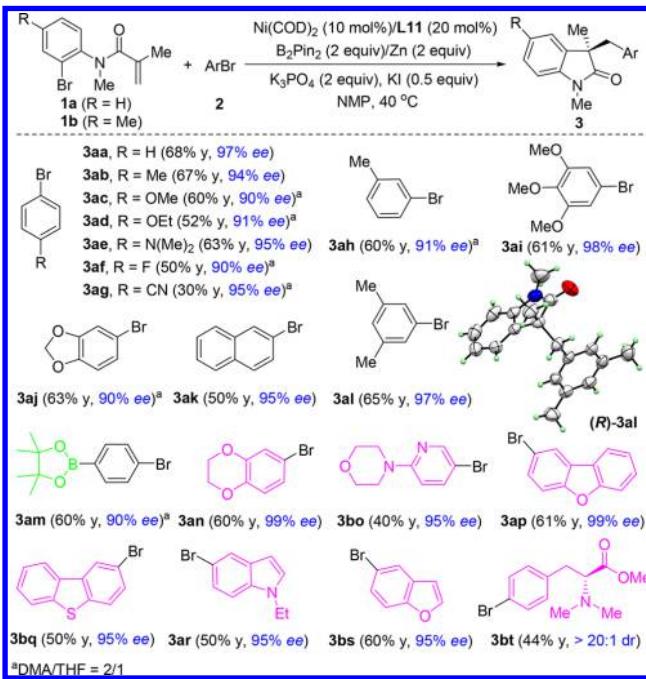
^aReactions were carried out with 1 (0.1 mmol), 2a (0.4 mmol), Ni(COD)₂ (10 mol %), ligand (20 mol %), Zn dust (0.2 mmol), Pin₂B₂ (0.2 mmol), K₃PO₄ (0.2 mmol) in 2 mL solvent for 96 h, unless noted otherwise. ^bIsolated yields. ^cDetermined by HPLC analysis with a chiral column. ^dIn DMA, 12 h. ^eIn NMP. ^fNo Ni(COD)₂. ^gNo Zn⁰. ^hNo B₂Pi_n. B₂Pi_n = bis(pinacolato)diboron.

was performed (entries 7–15), revealing that PHOX-type ligand L11 was the most effective in terms of stereoselectivity (91% ee, entry 15). Remarkably, the ferrocene skeleton of L11 proved to be critical to the selectivity of this reaction, as the formation of 4aa was completely suppressed (compare entry 15 with entries 13–14). Iodide sources have been shown to enhance the reactivity in cross-electrophiles couplings,¹⁹ and indeed, the addition of KI improved the yield of 3aa to 63% without sacrificing the enantioselectivity (entry 16). The best result was achieved using NMP as a solvent, providing 3aa in 68% yield and 97% ee (entry 17). Finally, a series of control experiments confirmed that product was not formed in the absence of Ni⁰ catalyst, Zn⁰ or ligand (entries 18–20). A reduced yield (28%) was also observed in the absence of B₂Pi_n, but the enantioselectivity was preserved (compare entry 21 with entry 17).

With optimized conditions in hand (Table 1, entry 17), we sought to investigate the scope of aryl bromides 2. We were pleased to find that a variety of aryl bromides undergo

cyclative cross coupling to furnish the target products in good yields with excellent enantioselectivities (Scheme 2). Func-

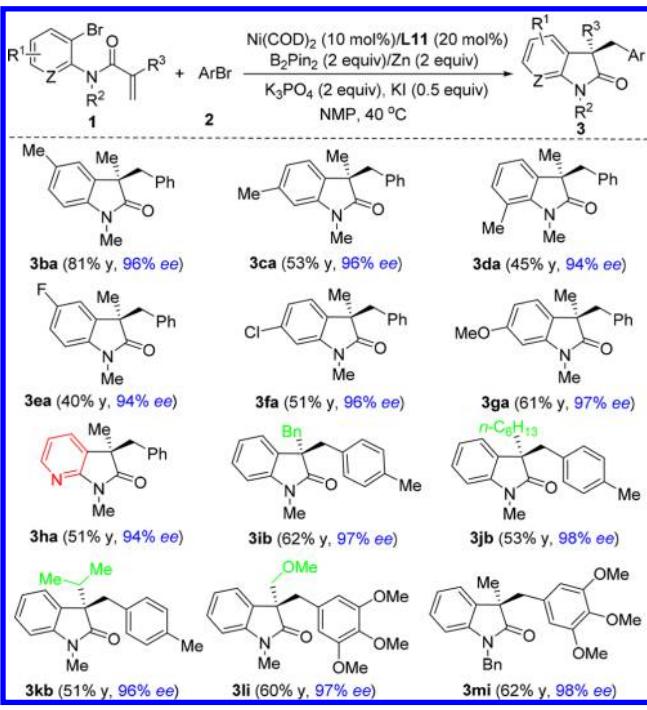
Scheme 2. Substrate Scope of Aryl Bromides 2



tional groups such as alkoxy, amino, fluoro and ketal are generally well-tolerated (3ab–3aj). It should be noted that cyano group, which was problematic in our previous method,^{14,20} was also found to be compatible with this transformation, albeit in poor yield (3ag). The absolute configuration of 3al was determined to be 3R by X-ray crystallographic analysis and that of all other products were assigned accordingly.²¹ Remarkably, the boronate-functionalized aryl bromide proceeded smoothly to afford 3am in 60% yield and 90% ee, providing an opportunity to further functionalize this obtained product. To further demonstrate the robustness and generality of synthetic utility of our method, we then explored the reductive cross-coupling reaction with a wide range of heterocycles. Benzodioxan (3an), pyridine (3bo), dibenzofuran (3ap), dibenzothiophene (3bq), indole (3ar) and benzofuran (3bs) were efficiently transformed into the corresponding products in satisfactory yields with very high enantioinduction. These results demonstrate the potential utility of this methodology for the synthesis of medicinally relevant compounds are feasible.²² Moreover, the cross coupling of phenyl alanine derivative provided the desired product (3bt) without epimerization of the stereocenter. There is no significant difference in ee values when different substituted aryl bromides 2 are used, indicating that the enantioselective-determining step of the reaction is the migratory insertion.

The substrate scope with respect to alkene-tethered aryl bromides 1 was investigated next (Scheme 3). First, we studied the substitution pattern on the benzene ring of the aniline moiety. *p*-, *m*-, and *o*-methyl and *p*-fluoro anilide substrates were efficiently transformed into the corresponding products 3ba–3ea in high enantioselectivities. Notably, functional groups (Cl, OMe) were found to be compatible with this transformation, thus enabling latter availability for additional

Scheme 3. Substrate Scope of Alkenes 1

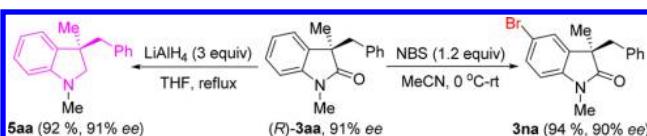


transformations (3fa–3ga). More importantly, the reaction was successfully applied to the synthesis of azaoxindole 3ha in 50% yield and 94% ee, which is of particular interest due to their prominence in natural products and drug discovery program.^{15b} The influence of the C α substituents (R^3) of the acrylamide double bond on the reaction outcome was also examined. Benzyl, *n*-hexyl, isopropyl and methoxymethyl substituents are all well tolerated leading to the corresponding oxindoles 3ib–3kb and 3li in good yields with excellent enantioselectivities. The cyclizative cross coupling reaction of *N*-benzyl acetanilide 1m proceeded efficiently to provide 3 mi in 62% yield and 98% ee. As the *N*-benzyl is easily removed, it constitutes a route to *N*-unsubstituted oxindole.

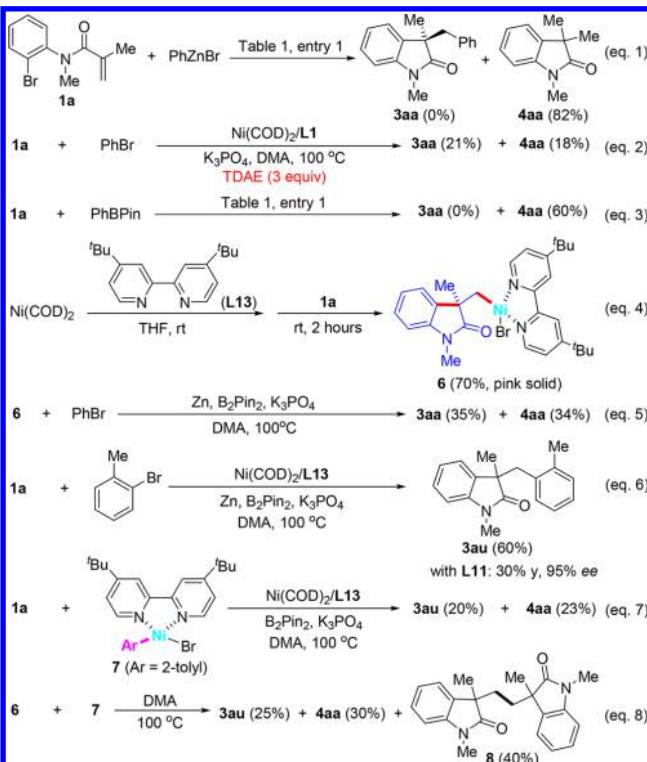
Although the enantioenriched indoline 5aa could not be synthesized directly by the cyclizative cross coupling of 2-bromo-*N*-methyl-*N*-(2-methylallyl)aniline with 2a, reduction of (R)-3aa with LiAlH₄ enabled efficient access to the enantioenriched indoline 5aa in excellent yield and with retention of enantiopurity (Scheme 4). Regioselective bromination of (R)-3aa provided 3na in 94% yield and 90% ee, thus enabling further functionalization of the oxindole ring (Scheme 4).

A series of experiments were designed to provide insight about the reaction mechanism (Scheme 5, for details see Part 4 in the Supporting Information). To assess the possibility of arylzinc intermediate, PhZnBr was subjected to our optimized reaction conditions. However, 3aa was not produced (eq 1). A reaction run without nickel (Table 1, entry 18) did not

Scheme 4. Synthetic Conversion of Enantioenriched Oxindoles



Scheme 5. Mechanistic Study



consume starting material, suggesting that direct insertion of zinc into aryl bromide is not likely. The use of an organic reducing agent TDAE (tetrakis (dimethylamino)ethylene), in place of Zn⁰ produced 3aa in an appreciable yield (eq 2). By combining these results together, we ruled out the participation of arylzinc as a key intermediate in this transformation.^{6,23} As mentioned above, in the absence of B₂Pin₂, 3aa was indeed observed albeit in a low yield (28%, Table 1, entry 21). This result clearly demonstrated the catalytic pathway could proceed in the absence of any B-based intermediates. To further understand the role of the possible arylboronate in the catalytic cycle, PhBPin was added in this cross-coupling reaction (eq 3). However, 3aa was not detected. This result argues against the intermediacy of arylboronic reagent in this transformation, which may indicate B₂Pin₂ acts as a coreducing agent.²⁴

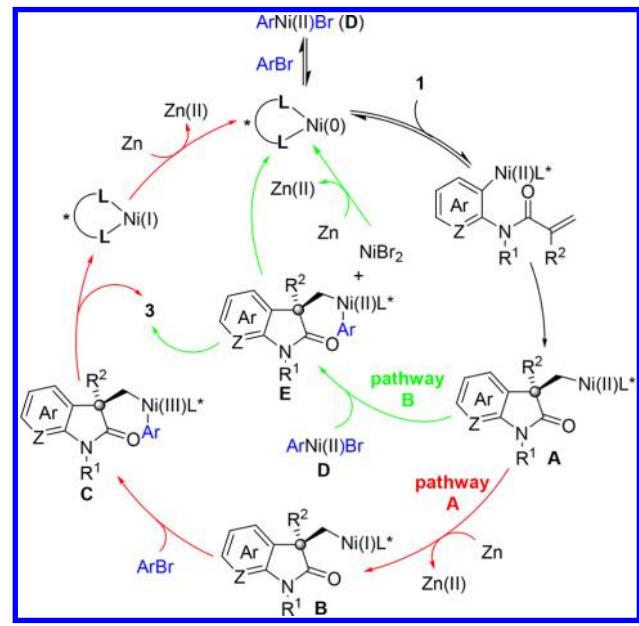
We serendipitously found that the σ-alkyl-Ni(II) complex 6 could be formed at room temperature from the oxidative addition of 1a and subsequent migratory insertion (eq 4).²⁵ Meanwhile, the catalytical reaction at room temperature delivered 4aa in 50% yield with 3aa not being detected in the reaction media (Table 1, entry 2). These results suggest that the cyclization process is not the turnover-limiting step. When complex 6 was used in a stoichiometric fashion, in the absence of Ni⁰ catalyst, the desired product 3aa was isolated in 35% yield, along with 4aa in 34% yield (eq 5), thus supporting the ideal of a mechanism which σ-alkyl-Ni(II) 6 serves as the key intermediate in the catalytic cycle. Because oxidative addition of Ni(0) with aryl halide has proven to be reversible,²⁶ we postulate that the migratory insertion process (enantioselective-determining step) should be irreversible.

Finally, 2-tolyl-Ni(II) complex 7 was synthesized^{18b,27} and subjected to our reaction condition (without Zn⁰), 3au was obtained in 20% yield (eq 7). The reaction performed

Ni(II) complex **6** with **7** formed **3au** in 25% (eq 8). These results indicate that the mechanism of transmetalation can not be ruled out.

On the basis of the above results and previous studies on the cross-electrophiles couplings,²⁶ a proposed mechanism is outlined in **Scheme 6**, in which two reaction pathways are

Scheme 6. Proposed Reaction Mechanism



considered. Oxidative addition of aryl bromide **1** to Ni(0) species followed by an intramolecular carbonickelation produces σ -alkyl-Ni(II)X species **A**, which is reduced by stoichiometric Zn/Pin₂B₂. A second oxidative addition of the resulting σ -alkyl-Ni(I) intermediate **B** with aryl bromide **2** will form σ -alkyl-Ni(III)ArX species **C**, which undergoes subsequent reductive elimination to furnish the desired product **3** while regenerating Ni(0) catalyst upon Zn/Pin₂B₂ reduction (**Scheme 6**, pathway A). Another plausible Ni(0)/Ni(II) catalytical cycle involving transmetalation between both Ni(II) centers **A** and **D** to form σ -alkyl-Ni(II)ArX species **E**, which generates product **3** following reductive elimination (**Scheme 6**, pathway B).

In conclusion, we have developed a mechanistically distinct approach to enantioselective diarylation of activated alkenes, in which two structurally distinguishable aryl bromides react together through a domino Heck cyclization/reductive cross-coupling process. The reaction occurs under mild conditions and is tolerant of a variety of functional groups, providing various bis-heterocycles bearing all-carbon quaternary centers in good yields with excellent enantioselectivities. The further development of enantioselective Heck cyclization and trapping the *in situ* generated σ -alkyl-Ni(II) species with other electrophiles, as well as mechanistic investigations, is underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/jacs.8b08190](https://doi.org/10.1021/jacs.8b08190).

Data for C₇₆H₈₄N₄O₄ (CIF)

Experimental details (PDF)

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Notes

The authors declare no competing financial interest.

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