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Nickel-Catalyzed Asymmetric Reductive Heck Cyclization of Aryl Halides to Access Indolines

Xurong Qin, Marcus Wen Yao Lee, and Jianrong Steve Zhou*

Abstract: A nickel-catalyzed asymmetric reductive Heck reaction of aryl chlorides affords substituted indolines in high enantioselectivity. Manganese powder was used as the terminal reductant and water as proton source.

Asymmetric Heck reaction of organic electrophiles has been extensively studied since late 1980s and it has been successfully employed in the synthesis of complex bioactive natural products.[1-3] In comparison, the development of asymmetric reductive Heck reaction, which produces a C-H bond at the end in the presence of hydride donors, has only met with limited success until recently,[4] ever since initial discovery of the nonstereoselective process in the 1980s.[5] For examples, Jia *et al.* recently reported palladium-catalyzed enantioselective reductive cyclization of tethered aryl bromides onto indoles, in the presence of sodium formate.[6] Zhu group[7] and our lab[8] have also disclosed palladium-catalyzed cyclization processes that afforded substituted oxindoles and indanones in good ee, respectively.

Palladium was listed as one of the strategically important elements facing supply risk by the Committee of Science and Technology of British House of Commons in 2011. Nickel, in comparison, is produced in millions of tons annually and it is over thousands-fold cheaper than palladium, rhodium and other noble metals.[9] Compared to palladium, nickel catalysts can easily insert into unactivated aryl chlorides and allow them to participate in coupling reactions. Furthermore, alkylnickel species are known to undergo much slower β-hydride elimination than the palladium counterparts, which can be advantageous to avoid such a step in catalytic reactions.[10]

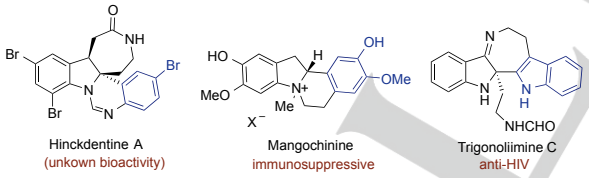
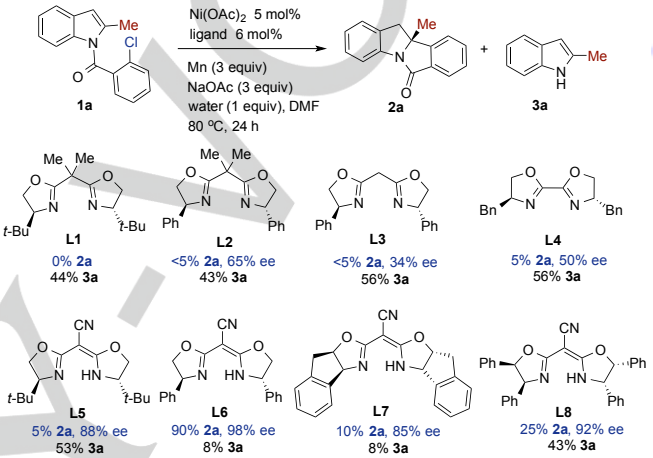


Figure 1. Examples of bioactive fused indolines carrying 2-aryl rings.

Previously, nickel catalysts were reported to facilitate Heck-type arylation,[11] allylation[12] and benzylation[13] of olefins. In a recent preliminary study, a nickel-catalyzed enantioselective Heck cyclization generated oxindoles with quaternary centers.[14] Although Ronchi and Lebedev *et al.* reported the first nickel-catalyzed reductive Heck-type reactions of aryl halides and reactive acrylates in the 1980s,[15] an asymmetric version has remained elusive until today. Herein, we describe the first example of nickel-catalyzed asymmetric reductive Heck cyclization of aryl chlorides that provides substituted indolines. Many indoline derivatives have interesting bioactivities.[16] Related to the cyclization in this study, some bioactive natural products carry aryl rings at C2 positions of indolines, such as mangochinine,[17] trigonoliimine C[18] and hinckdentine A[19] (Figure 1).



Scheme 1. The effect of chiral oxazolines in reductive Heck cyclization of an aryl chloride.

Initially, in the model study we chose to study cyclization of *N*-(*o*-chlorobenzoyl)-2-methylindole **1a** and tested some common ligands. Chiral diphosphines typically led to very low yields of **2a** and <20% ee (see the Supporting Information). Initially, we found that the use of several chelating oxazolines[20] **L1-4** led to incomplete conversion of **1a** and <5% yield of **2a**, along with significant amounts of byproduct **3a** to our disappointment. The formation of **3a** was assisted by the nickel catalysts based on our control experiments, rather than by the base NaOAc alone. Fortunately, the use of Pfaltz's semicorrin[21] **L6** gave good yield of the desired product **2a** in 90% yield and 98% ee, and also significantly minimized the formation of **3a** (Scheme 1**)**. In addition, nickel catalysts ligated with two related semicorrins **L7** and **L8** have much lower catalytic activity. Putting all the information here together, we suspect that the active nickel catalyst is ligated with an anionic form of **L6**.

When $Ni(COD)_2$ was used in a combination with **L6**, only 30% of **2a** was generated in the almost identical ee, while more byproduct of **3a** was produced. In the absence of Mn(0), **2a** was not generated. Therefore, We suspected that (COD)Ni(0), in a mixture with the active nickel catalyst of **L6**, contributed to cleavage of the amide bond in **1a**. If either $Ni(PPh_3)_4$ or $Ni(PPh_3)_2Cl_2$ was used with **L6**, catalytic activity was dimished (only 10% or 19% of **2a**). Probably, the phosphine binds to nickel centers and resulted in inactive species toward insertion of indole. The use of $NiCl_2$(DME) in the model reaction afforded good yield of **2a** (83%). Therefore, the manganese powder is needed to reduce $Ni(OAc)_2$ or $NiCl_2$(DME) to produce the active nickel catalyst of **L6** initially, but we are not sure whether

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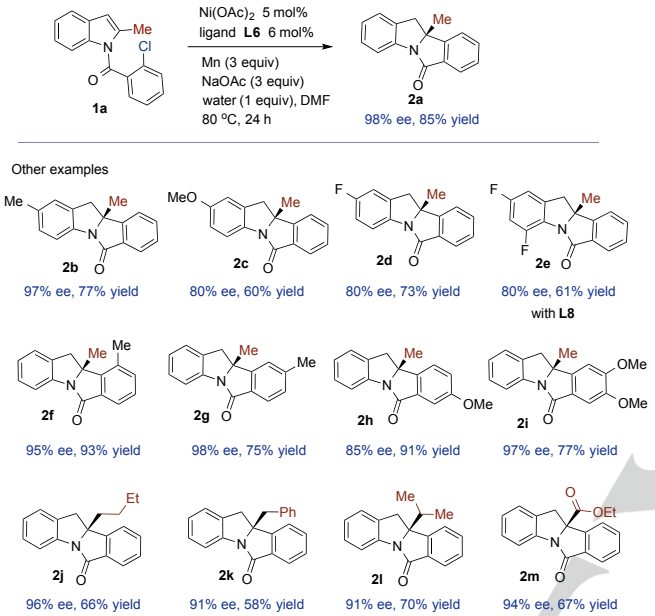
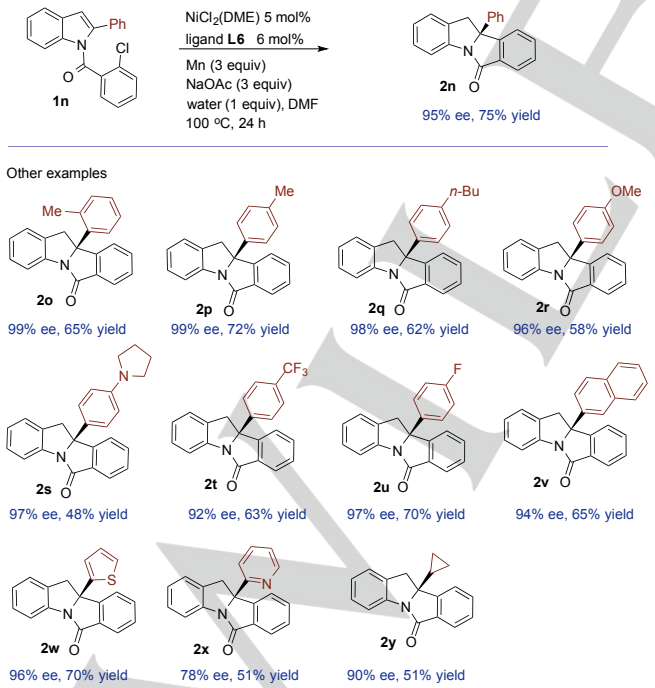
reduction of arylnickel(II) species to nickel(I) is involved in the catalytic cycle.[22]

Furthermore, 1 equiv of water was necessary in the productive pathway. Thus, the nickel-promoted insertion process is mechanistically distinct from the Pd(0)/(II) cycle in the reductive Heck process reported by Jia *et al*.[6a] Replacement of NaOAc by other bases led to much lower yields of **2a**, for example, with KOAc or Na_2CO_3 the reaction afforded <20% yield of **2a**. We also tested the cyclization of a bromo analogue of **1a**, but it only afforded **2a** in 45% yield and 57% ee.



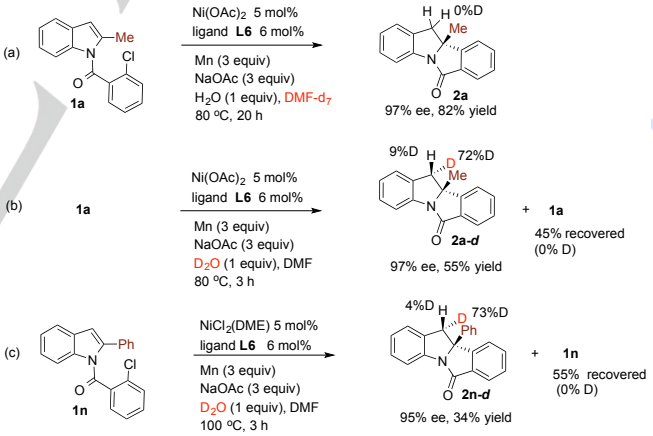
Scheme 2. Asymmetric Heck cyclization of 2-alkylindole derivatives.



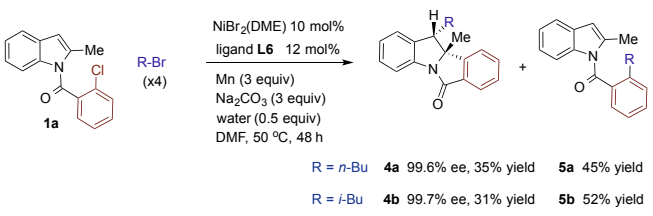
Scheme 3. Asymmetric Heck cyclization of 2-aryl- and 2-cyclopropylindole derivatives.

The nickel catalyst of **L6** was successfully applied to cyclization of other 2-alkylindole derivatives (Scheme 2), including those carrying electron-donating OMe group (**2c**) and fluorine atoms (**2d** and **2e**). When the carbocyclic ring of indole derivatives contained electron-withdrawing groups such as a trifluoromethyl, nitrile or ester group, the reductive Heck process proceeded to deliver products, but only with <20% ee values, probably due to an earlier transition state of insertion. On the benzamide fragment, steric factor (**2f**) and electron-donating groups (**2h** and **2i**) were also tolerated. When the benzamide fragment had a substitution of fluorine or trifluoromethyl group para to the C-Cl bond, the cyclization proceeded to give good yields, but the selectivity was only <30% ee. We also established that different alkyl groups can be present on C2 position of indoles, such as benzyl (**2k**), isopropyl (**2l**) and an ester group (**2m**). A single crystal of **2h** was obtained and X-ray diffraction helped to determine its absolute configuration to be (*R*).[23] When the indole ring was not substituted at C2 position, the cyclized product was formed in <5% ee, unfortunately. A derivative of 2,3-dimethylindole failed to cyclize.

The optimized nickel catalyst was also used in cyclization of 2-arylindole derivatives (Scheme 3). On the C2-aryl rings, both electron-donating (e.g., methoxy and pyrrolidinyl in **2r-s**) and electron-withdrawing groups (e.g., CF_3 and F in **2t-u**) were tolerated. To our gratification, both thiophene and pyridine (**2w-x** can also be present at C2 position, as well as a cyclopropyl ring (**2y**). In examples that gave moderate yields, cleavage of the *N*-indolyl amide bonds was the main side reaction.



Scheme 4. Deuterium labeling experiments.



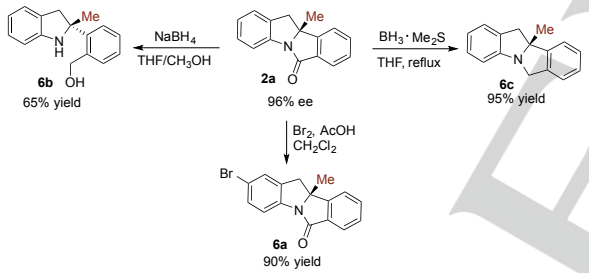
Scheme 5. Asymmetric coupling of two organic halides and a pedant indole.

In order to determine the source of the incoming hydrogen in the cyclization products, we conducted labelling experiments using either DMF-d_7 or D_2O (Scheme 4). When cyclization of **1a** was conducted in deuteriated DMF, no trace of deuterium was detected in product **2a**, which excluded the possibility of DMF as

the hydrogen source.[24] In comparison, in reactions of **1a** and **1n** containing 1 equiv of D_2O, significant amounts of deuterium was incorporated in products **2a** and **2n**, while no deuterium was detected in the recovered starting material after partial conversions. Interestingly, careful nOe analysis of **2n** revealed that the deuterium was predominantly added syn to the inserting aryl ring on the indoline. This indicates that after the insertion, the resulting carbon–nickel bond was mainly protonated at the front side of the carbon center.

Furthermore, when cyclization of **1a** was conducted together with *n*-butyl bromides under slightly modified conditions, the benzylnickel species in the catalytic cycle was trapped by *C3*-alkylation to give **4a** in moderate yield and 99.6% ee, along with an uncyclized coupling product **5a** (Scheme 5). In nOe analysis of **4a**, magnetization transfer was detected between the benzylic hydrogen and methyl group on the indoline. Therefore, the butyl group and inserting aryl ring are situated syn to each other. A similar result was obtained in the reaction of isobutyl bromide. These are the first examples of asymmetric coupling between two organic halides and an unsaturated bond (indole in this case) that give a high level of enantioselectivity.[25]

The indole ring of **2a** can be easily brominated by treatment of Br_2. Furthermore the amide linkage in **2a** was cleaved by $NaBH_4$ to give alcohol **6b** and deoxygenated by borane to afford **6c**.[6a; 26] In all cases, no *ee* erosion was detected (Scheme 6).



Scheme 6. Product derivatization without *ee* loss

In summary, we report the first example of nickel-catalyzed asymmetric reductive Heck cyclization that provides fused indolines in good ee values. Mechanistically, it is distinct from the palladium-catalyzed process as reported by Jia *et al.* in how the nickel-carbon bond is converted to a C-H bond to release the product, protonation of the carbon-nickel bond versus hydride donation followed by C-H reductive elimination on Pd.

Acknowledgements

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Keywords: nickel catalysis • reductive Heck reaction • asymmetric catalysis • indoline • cyclization

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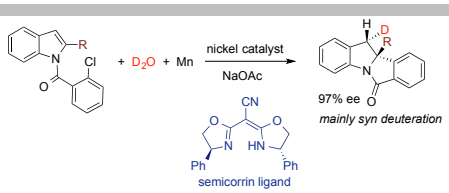
Nickel-catalyzed aryl insertion of indoles is followed by stereospecific protonation



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