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Enantioselective Nickel-Catalyzed Mizoroki-Heck Cyclizations to Generate Quaternary Stereocenters

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Abstract

The development of enantioselective carbon-carbon bond couplings catalyzed by non-precious metals is highly desirable in terms of cost-efficiency and sustainability. The first nickel-catalyzed enantioselective Mizoroki-Heck coupling is reported. This transformation is accomplished via mild reaction conditions, leveraging on QuinoxP* as a chiral ligand to afford oxindoles containing quaternary stereocenters. Good reactivity and selectivity are observed in the presence of various functional groups. Computational studies suggest that the oxidative addition assembles an atropisomeric intermediate responsible for the facial selectivity of the insertion step.

Graphical Abstract

The development of enantioselective processes with non-precious metals has recently received significant attention.¹ Natural abundance, affordability and chemical sustainability

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Complete experimental details, DFT calculations

X-Ray crystallographic data

are amongst numerous advantages found when coupling transformations are performed with non-precious metals, such as nickel catalysts.² The combination of nickel- and asymmetric-catalysis procures reaction conditions that are cost-efficient and provides step-economy as no chiral auxiliary or resolution is required, which consequently results in reduction of waste.

The enantioselective nickel-catalyzed variant of some of the classic carbon-carbon couplings have been developed (Scheme 1). The nickel-catalyzed Kumada coupling was first reported in 1973 by Consiglio,³ and then by Kumada⁴ himself in 1976 with significant improvement of enantioinduction. The research group of Fu then developed the asymmetric Negishi⁵ and Suzuki-Miyaura⁶ couplings using nickel catalysts. Despite those precedents, the enantioselective nickel-catalyzed Mizoroki-Heck coupling has not been reported to date.^{7, 8, 9} The absence of any such examples can be attributed, in part, to the challenge of developing reaction conditions that: 1) provide high reactivity and selectivity 2) overcome the high energy barrier of the β -hydride elimination, and 3) address the regeneration of Ni(0) from the Ni(II) byproduct.^{10, 11}

In the context of the Non-Precious Metal Consortium,¹² to explore sustainable syntheses of biologically active molecules, and our previous efforts in asymmetric Mizoroki-Heck cyclizations,¹³ we focused on the development of an unprecedented enantioselective nickel-catalyzed Mizoroki-Heck coupling. To accomplish this goal, we initiated our studies from our recently published work that allows the construction of quaternary carbon centers, albeit without control of absolute stereochemistry.¹⁴ We had discovered that the combination of an unhindered electron-rich phosphine with manganese¹⁵ gave rise to Mizoroki-Heck cyclization to form oxindoles with high functional group tolerance. From control experiments, we propose a Ni(0)/Ni(II) catalytic cycle instead of a radical-induced cyclization. The selection of this strategy was also reinforced by the previous successes of the palladium-catalyzed parent system that was first reported by Overman.^{13,16}

After extensive screening of ligands, encouraging hits were obtained with phosphine ligands such as CatASium Ktb¹⁴ and Duanphos¹⁷ (Table 1, entry 2). However, use of the *P*-chiral bisphosphine QuinoxP*¹⁸ led to the highest enantioselectivity with ee values up to 96% (entry 1). The NiCl₂(QuinoxP*) complex was prepared by mixing both NiCl₂ and QuinoxP* in ethanol under reflux, followed by a crystallization (See Supporting Information). The resulting pre-catalyst is a dark red crystalline solid that is air-stable for several months without noticeable decrease in reactivity. X-Ray analysis of this complex revealed a slightly distorted square planar configuration (Figure 1).

After selecting NiCl₂(QuinoxP*) as the optimal pre-catalyst, several reaction parameters were optimized (Table 1). The alkene geometry was crucial to give high conversion as well very high enantioselectivity. While substrate **1** containing a *Z* alkene derived from angelic acid provided **2** in up to 96% ee (entry 1), the corresponding *E* alkene synthesized from tiglic acid gave rise to the same enantiomer of **2** product in only 56% ee (entry 3). When the reaction was conducted at a temperature 15 °C below the standard conditions, 99% ee could be reached, but at the expense of a much reduced yield (entry 4). Aryl chlorides also underwent the cyclization, but with a dramatically inferior yield (entry 5). The use of aryl

triflates or Ag_2CO_3 as a base to scavenge halides did not provide improvement (entries 6 and 7). With the objective to favor the neutral Mizoroki-Heck catalytic cycle and to suppress the hypothetically less selective cationic pathway, exogenous halide sources were tested (entries 8–11).¹⁹ LiI as an additive improved the enantioselectivity at 60 °C while maintaining good yields. TBAI was equally effective as LiI (entry 10), but purification of the product was more challenging due to the TBA cation carrying over in the crude mixture. The use of chloride or bromide salts led to a somewhat diminished effect compare to iodide (entries 8 and 9). In the absence of catalyst (entry 12), poor yields were obtained which demonstrates the rate acceleration induced by nickel.

With the optimal reaction conditions established, a survey of substrates containing various functional groups was conducted (Scheme 2). The mild reaction conditions provided a high tolerance to functional groups such as ketal (**3**), tolyl (**4**), ethers (**5** and **6**), nitrile (**7**), trifluoromethyl (**8**) and ester (**9**). In general, the presence of an electron-donating group at 4 or 5-position provided the corresponding oxindoles with high enantioselectivities (90–96% ee). Having an electron-withdrawing group at those positions instead leads to lower selectivities ranging from 77–84% ee. The MOM-protected aniline, which can be readily deprotected under acidic conditions led to **10** with 61% yield and 89% ee. Oxindole **11** containing an elongated side-chain chain was produced as the *E*-alkene with 82% yield and 92% ee. Finally, spirooxindole **12** was synthesized from the corresponding *E*-alkene derived from indene carboxylic acid with 66% yield and 55% ee.

To understand the origin of the observed high enantioselectivity, we initiated DFT studies of the mechanism of this transformation by taking into account our preliminary studies.¹⁴ We initially focused our attention on the migratory insertion step of the *Z*-alkene. Detailed analysis of the energetics of the transformation revealed that the insertion step proceeds with only low selectivity (Scheme 3, selectivity of insertion, theory=15% ee). This small energy difference does not correlate with our experimental results (96% ee).

Closer examination of the corresponding transition states identified interactions between the terminal methyl of the alkene moiety with the ^tBu groups of the ligand as the selectivity controlling elements (Scheme 3, **13** and **14**). This interaction results in a change in selectivity depending on the geometry of the double bond and the disposition of this methyl group with respect to the chiral ligand. As a result, opposite selectivities were computed for the cyclizations of the *E* and *Z* isomers (see Supp. Info. for calculations on *E* alkene), which conflicts with the experimental outcome. This discrepancy suggests that the facial preference for the insertion originates earlier in the reaction. This idea is supported by experimental findings in earlier work by Stephenson and by Curran²⁰ on related Pd system. This study proposes a selective oxidative addition step that provides stereocontrol by governing the configuration of the amide in the pre-insertion intermediate.

To test this hypothesis, we analyzed the energetics of the oxidative addition transition states and found that they do indeed match experimental outcomes (scheme 4, oxidative addition: theory=88% ee vs expt.=96% ee). In the oxidative addition transition states, there is an agostic interaction present that steers the *N*-methyl fragment toward the bisphosphine ligand (scheme 4, **15** and **16**, blue arrow). This interaction, combined with π -stacking (**16**, CH-

π),²¹ provides the basis for the facial discrimination of the catalyst approach. With this control element dominating, the methyl substituent of the alkene is oriented away from the chiral ligand (Figure 2), which results in the alkene geometry (*E* or *Z*) having little impact on the selectivity. In line with this observation, the computed selectivities of the oxidative addition of both *E* and *Z* isomers are very similar.

The experimentally observed lower selectivity with the *E*-alkene (56% ee) may be the result of a partial re-equilibration of the pre-insertion intermediates. For the *E*-alkene, the equilibration after oxidative addition favors the pro-*Re* intermediate (see Supp. Info.) leading to the minor (*S*)-enantiomer and lowering the resulting enantiomeric excess (Scheme 4, “mismatched case”). For the case of the *Z*-alkene, both the oxidative addition and migratory insertion are lowest in energy for the pro-*Si* pathway leading to the major (*R*)-enantiomer. This “matched case” accounts for the higher selectivity with the *Z*-alkene.

In conclusion, we have developed the first enantioselective nickel-catalyzed Mizoroki-Heck coupling. This method allows for the formation of enantioenriched pharmaceutically relevant 3,3'-disubstituted oxindoles containing quaternary stereocenters with good yields and selectivities. Various functional groups were tolerated under the mild reaction conditions. Computational studies suggest that the absolute stereochemistry is governed by the energies of the nickel oxidative addition transition states. The geometry of the starting alkene was found to be crucial in order to obtain a “matched case” with the catalyst and therefore, generate high selectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. ORTEP diagram of $\text{NiCl}_2(\text{R,R-QuinoxP}^*)$ using 50% probability ellipsoids (CCDC 1536324), hydrogen atoms omitted.

Figure 2.
Geometry of the oxidative addition transition state from *Z*-alkene.

Enantioselective Nickel-Catalyzed Kumada Coupling (Kumada, ref 4): **Enantioselective Nickel-Catalyzed Negishi Coupling** (Fu, ref 5): **Enantioselective Nickel-Catalyzed Suzuki-Miyaura Coupling** (Fu, ref 6): **Enantioselective Nickel-Catalyzed Mizoroki-Heck Coupling** (This work): **Scheme 1.**

Seminal Examples of Nickel-Catalyzed Enantioselective Classic Carbon-Carbon Coupling Reactions

Scheme 2. Scope of the Nickel-Catalyzed Mizoroki-Heck Cyclization.^a^aAbsolute configurations determined by analogy to **2** and **11**.

Scheme 3.

Energetic Profiles for Oxidative Addition and Insertion Steps of Mizoroki-Heck Cyclization.^a

^aBlue and red pathways correspond to Re and Si-attacks respectively. Re attack leads to the formation of *S*-isomer, Si attack leads to the formation of *R*-isomer. In inset boxes, blue and red arrows indicate stabilizing and destabilizing interactions, respectively. Free energies were computed using M06/6-311+G(d,p)-SMD-DMF//B3LYP/6-31G(d); values are in kcal/mol.

Scheme 4. Proposed Stereoselection Mechanism for the *E*- and *Z*-Alkenes.

Table 1

Optimization of Reaction Conditions.

entry	modification from std conditions	yield (%) ^a	ee (%) ^b
1	none (standard conditions)	81 (75) ^c	96
2	Duanphos ^d as a ligand	90	16
3	<i>E</i> alkene, instead of <i>Z</i> - 1	70	56
4	Reaction performed at 45 °C	20	99
5	Aryl-Cl substrate, instead of Br- 1	26	86
6	Aryl-OTf substrate, instead of Br- 1	17	33
7	Ag ₂ CO ₃ , instead of Na ₂ CO ₃ , no LiI	41	57
8	TBAC as an additive, instead of LiI	54	89
9	TBAB as an additive, instead of LiI	69	97
10	TBAI as an additive, instead of LiI	84	96
11	no LiI	60	92
12	no NiCl ₂ (<i>R,R</i> -QuinoxP*) catalyst	2	--

^aDetermined by ¹H NMR assay yield using dimethylfumarate as an internal standard^bDetermined by chiral stationary phase HPLC.^cIsolated yield in parenthesis determined after flash chromatography^dDuanphos = 2,2'-Di-tert-butyl-2,3,2',3'-tetrahydro-1H,1'H-(1,1')biisophosphindolyl