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Nickel-Catalyzed Regiodivergent Reductive Hydroarylation of Styrenes

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Modern Nickel-Catalyzed Reactions

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Abstract We report a ligand-controlled nickel-catalyzed reductive hydroarylation of styrenes with predictable and controllable regioselectivity. With a diamine ligand, the reaction produces selective linear hydroarylation products. Alternatively, with a chiral PyrOx ligand, branch-selective enantioenriched 1,1-diarylalkane products are obtained. Preliminary mechanistic results are consistent with a reductive Heck process.

Key words asymmetric catalysis, hydroarylation, nickel catalysis, reductive Heck, regiodivergence, styrene

Catalytic hydroarylation of readily available styrenes has recently emerged as a powerful approach for the synthesis of enantioenriched 1,1-diarylalkanes,^{1,2} which are key structural motifs in many biologically active molecules (Scheme 1a).³ Great progress has been achieved in metal hydride catalyzed⁴ asymmetric hydroarylation either in a redox-neutral fashion with aryl nucleophile as a coupling partner,^{1b,c,e,g} or in a reductive fashion with aryl halides as the coupling partner^{2d,f} (Scheme 1b). However, asymmetric reductive Heck reaction of styrenes,⁵ a complementary approach, has not been reported to date. Herein, we report this process which employs earth-abundant nickel⁶ as a catalyst and aryl triflate as a coupling partner. In addition, depending on the ligand used, either branch-selective^{1,2,7-9} or linear-selective¹⁰⁻¹² hydroarylation products were obtained in a regiodivergent¹³ fashion (Scheme 1c).

Our proposed mechanism for this regiodivergent reductive hydroarylation is shown in Scheme 2. Initially, the arylnickel(II) species II is generated through the oxidative addition of an aryl triflate with an active Ni(0) species I. Depending on the choice of the ligand, subsequent migratory insertion will generate either linear alkyl nickel(II) III or en-



antioenriched branched benzylic nickel(II) species **III'**. An alkyl-Ni(II)-H intermediate **IV** or **IV'** is then formed through an anion exchange with an appropriate base and subsequent transmetallation with a hydrosilane. Irreversible reductive elimination of the alkyl-Ni(II)-H complex that is obtained would ultimately produce either the terminal arylation product **3** or the benzylic arylation product **4** and nickel(0) species **I**, closing the catalytic cycle.

Our investigation began with the reductive coupling of styrene (1a) with 4-methoxyphenyl trifluoromethanesulfonate (2a, Table 1). Systematical evaluation of possible ligands revealed that the diamine ligand L1 provided the





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Scheme 2 Proposed pathways for regiodivergent nickel-catalyzed reductive hydroarylation of styrenes

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anti-Markovnikov hydroarylation product 3a exclusively (entry 1 vs. entries 4-6), with NiBr₂·3H₂O as the best nickel source (entry 2 vs. entry 1).¹⁴ Interestingly, the aryl iodide was found to be an unsuitable coupling partner and gave no desired hydroarylation product (entry 3). We then focused on the asymmetric branch-selective reductive hydroarylation (entries 4-14). Evaluation of ligands revealed that chiral PyrOx ligand L4 was the best ligand with highest yield and excellent enantioselectivity (entry 6 vs. entries 1, 4, and 5). Further examination of different bases and nickel sources showed that the regioselectivity (rr) could be dramatically improved by use of K_2PO_4 ·H₂O as a base (entry 7 vs. 6), and the yield could be slightly increased by using Ni-Br₂·glyme as the nickel source (entry 8 vs. 7). The solvent effect was investigated, and we found that a 3:1(v/v) mixture of ether and toluene as co-solvent provided the desired product 4a with highest yield and ee with no significant change in the rr (entry 11 vs. entries 8–10). A higher vield was obtained from the reaction at 0 °C than that at room temperature (entry 12 vs. 11), and the yield was further improved by the addition of 0.5 equiv of MeOH (entry 13 vs.

Table 1 Optimization of Regiodivergent Reductive Hydroarylation of Styrene^a



В

Entry	Ni source	L	Base	Solvent	Yield of 3a (%) ^a	Yield of 4a (%) ^a	ee (%) ^b
1	NiCl ₂	L1	CsF	THF	90	<1	ND
2	NiBr ₂ ·3H ₂ O	L1	CsF	THF	96 (85)	<1	ND
3°	NiBr ₂ ·3H ₂ O	L1	CsF	THF	<1	<1	ND
4	NiCl ₂	L2	CsF	THF	31	<5	ND
5	NiCl ₂	L3	CsF	THF	19	38	92
6	NiCl ₂	L4	CsF	THF	22	48	92
7	NiCl ₂	L4	$K_3PO_4 \cdot H_2O$	THF	<1	20	92
8	NiBr₂∙glyme	L4	$K_3PO_4 \cdot H_2O$	THF	<1	27	92
9	NiBr₂∙glyme	L4	$K_3PO_4 \cdot H_2O$	Et ₂ O	2	36	92
10	NiBr₂∙glyme	L4	$K_3PO_4 \cdot H_2O$	Tol	<1	29	94
11	NiBr₂∙glyme	L4	$K_3PO_4 \cdot H_2O$	3:1 Et ₂ O-Tol	3	48	92
12 ^d	NiBr₂∙glyme	L4	$K_3PO_4 \cdot H_2O$	3:1 Et ₂ O-Tol	4	58	95
13 ^{d,e}	NiBr₂∙glyme	L4	$K_3PO_4 \cdot H_2O$	3:1 Et ₂ O-Tol	4	61 (55)	95
14 ^c	NiBr₂∙glyme	L4	K ₃ PO ₄ ·H ₂ O	THF	<1	67	0

^a Yields were determined by GC using n-dodecane as the internal standard. The yield in parentheses was the isolated yield of the purified product and is an average of two experiments (0.20 mmol scale). ^b Enantiomeric excess (ee) determined by chiral HPLC analysis.

^c 4-lodoanisole was used instead of 2a.

d 0 °C

^e 50% MeOH was added

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Hal

Pł

P٢

Ph

NH-

3a 85% yield

3b 92% vield

3c 82% yield

Bpir

Bnir

PMP

(+)-L1

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12).¹⁵ Notably, aryl iodide, that was used in our previous NiH-catalyzed asymmetric hydroarylation system, led to a completely racemic product (entry 14),^{2d} indicating that our current process is unlikely to be initiated by NiH species. Aryl tosylate, aryl acetate, and aryl pivalate were not effective, and no desired product was obtained in these cases.

Having established the optimal conditions, we sought to demonstrate the generality of this method (Scheme 3). As shown in Scheme 3a, an array of aryl triflates bearing either electron-donating (**2a**) or electron-withdrawing (**2b-d**) groups worked well in both reaction conditions, producing the respective linear-selective products (**3a-d**) or the branch-selective products (**4a-d**) smoothly in a regiodivergent fashion. The linear-selective products were obtained with good to excellent yields as a single isomer under the anti-Markovnikov reaction conditions, and the branchselective enantioenriched products were obtained with moderate yields under the asymmetric Markovnikov reac-

a) and triflate scope

2a

2b

20

MoC

5 mol% NiBr₂·3H₂O 6 mol% L1

2.5 equiv PMHS

2.0 equiv CsF THF (0.5 M), 25 °C, 24 h

OT

OTf

OT

tion conditions. Aryl triflate with an easily reduced ketone group (**2e**) was a suitable substrate although low regioselectivity and enantioselectivity were observed in this case. The *para*-ester-substituted aryl triflate **2f** produced the linear product smoothly but afforded the branched product in low yield. A variety of substituted styrenes were also found to be competent substrates, affording linear-selective or branch-selective products (Scheme 3b). The *ortho*-functionalized styrene **1j** also performed well. Under these exceptionally mild reaction conditions, the reaction is orthogonal to aryl boronate **2d**, aryl chloride **1i**, and aryl fluoride **1j**, providing handles for further cross-coupling. It should be noted that under the current reaction conditions, **1**,3dienes are less reactive (**1k**) and aliphatic alkenes are unsuccessful substrates.

As shown in Scheme 4a, both of the linear-selective and branch-selective hydroarylation reactions proceed smoothly on 5 mmol scale with no significant change in yield or enantioselectivity, demonstrating the scalability of both

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b) styrene scope

1g

1h

1i

5 mol% NiCl₂.glyme

6 mol% L4

2.5 equiv PMHS, 50 mol% MeOH

2.0 equiv K₃PO₄·H₂O Et₂O/toluene (3:1, 0.5 M), 0 °C, 24 h

PMF

PMF

PMP

PMP

^tBı

C

3q 75% yield

3h 79% vield

3i 51% yield

Ar²-OT

2

^tB

1 (1.5 equiv)

PMF

4a 55% yield, 94:6 rr, 95% ee

4c 58% yield, 93:7 rr, 85% ee



Boir

^{′t}Bu

PMP

PMF

РМР

4q 40% yield, 94:6 rr, 97% ee

4h 65% vield, 93;7 rr. 87% ee

4i 80% yield, 94:6 rr, 96% ee

t_D

CI

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processes. To further support the proposed reductive Heck mechanism, stoichiometric amounts of $Ni(cod)_2$ and ligands were used in the absence of a hydrosilane reductant, i.e., with no poly(methylhydrosiloxane) (PHMS). The desired two reductive Heck reaction products could be obtained with similar selectivity, although lower yields were obtained in these two cases (Scheme 4b). To further support the proposed reductive Heck pathway, (Bpin)₂ was used as a quenching reagent instead of the hydrosilane. In this case, the Heck intermediates could also be captured by (Bpin)₂ as expected, producing the arylboration product **5a** as a single regioisomer in high yield (Scheme 4c).^{16,17}



Scheme 4 Large-scale experiments and preliminary mechanistic studies

In conclusion, we have developed a nickel-catalyzed reductive hydroarylation of styrenes in a regiodivergent fashion under mild reaction conditions. Both linear-selective and branch-selective hydroarylation products could be accessed by the choice of ligands. Preliminary mechanistic experiments are consistent with a reductive Heck reaction pathway. Additional mechanistic investigations are currently underway.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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- (14) 1-Methoxy-4-phenethylbenzene (3a) General Procedure A In a nitrogen-filled glove box, to an oven-dried 8 mL screw-cap vial equipped with a magnetic stir bar were added NiBr₂·3H₂O (2.73 mg, 0.010 mmol, 5 mol%), L1 (2.55 mg, 0.012 mmol, 6 mol%), CsF (60.8 mg, 0.40 mmol, 2.0 equiv), and 0.40 mL anhydrous THF. The mixture was stirred for 5 min, at which time PMHS (30 µL, 0.50 mmol, 2.5 equiv) was added, and the stirring was continued for another 5 min at r.t. Styrene (1a, 31.2 mg, 0.30 mmol, 1.5 equiv) and 4-methoxyphenyl trifluoromethanesulfonate (2a, 51.2 mg, 0.20 mmol, 1.0 equiv) were added to the resulting mixture in this order. The tube was sealed with a Teflon-lined screw cap, removed from the glove box and stirred at 25 °C for up to 24 h. The reaction was guenched upon the addition of H_2O . and the mixture was extracted with EtOAc (3 ×). The organic layer was concentrated to give the crude product. *n*-Dodecane $(20 \ \mu L)$ was added as an internal standard for GC analysis. The product was purified by chromatography on silica gel for each substrate. The crude material was purified by flash column chromatography (PE-EtOAc = 100:1) to provide the title compound as a white solid in 85% yield (36.0 mg). The analytical data are consistent with values reported in the literature.^{10e}

(15) (S)-1-Methoxy-4-(1-phenylethyl)benzene (4a) – General Procedure B

In a nitrogen-filled glove box, to an oven-dried 8 mL screw-cap vial equipped with a magnetic stir bar were added NiCl₂·glyme (2.20 mg, 0.010 mmol, 5 mol%), L4 (4.27 mg, 0.012 mmol, 6 mol%), K₃PO₄·H₂O (92.1 mg, 0.40 mmol, 2.0 equiv), methanol (3.2 mg, 0.10 mmol, 0.5 equiv), and mixed solvent (Et₂Otoluene = 3:1, 0.40 mL). The reaction mixture was stirred for 5 min, at which time PMHS (30 μL , 0.50 mmol, 2.5 equiv) was added, and the stirring was continued for another 5 min at r.t. Styrene (1a, 31.2 mg, 0.30 mmol, 1.5 equiv) and 4-methoxyphenyl trifluoromethanesulfonate (2a, 51.2 mg, 0.20 mmol, 1.0 equiv) were added to the resulting mixture in this order. The tube was sealed with a Teflon-lined screw cap, removed from the glove box and stirred at 0 °C for up to 24 h. The reaction was quenched upon the addition of H₂O, and the mixture was extracted with EtOAc (3 ×). The organic layer was concentrated to give the crude product. n-Dodecane (20 µL) was added as an internal standard for GC analysis. The crude material was purified by flash column chromatography (PE-EtOAc = 100:1) to provide the title compound as a colorless oil in 55% yield (23.3 mg), 94:6 rr. HPLC analysis (OJ-H, 5% ⁱPrOH/hexane, 1.0 mL/min, 220 nm) indicated 95% ee, t_R (major) = 16.9 min, t_R (minor) = 18.1 min. The analytical data are consistent with values reported in the literature.^{2f}

- (16) Under branch-selective reaction conditions, when $(Bpin)_2$ was used instead of PMHS, the regioreversed arylboration product was obtained in 36% yield, 94:6 rr, 94% ee.
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