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Nickel-Catalyzed Asymmetric Intramolecular Reductive Heck Reaction of Unactivated Alkenes

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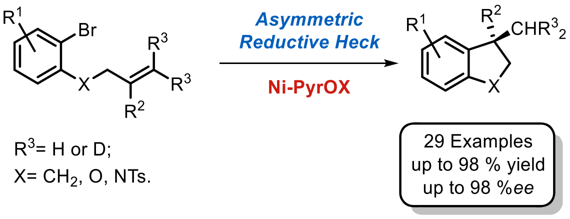
Supporting Information

ABSTRACT: An asymmetric Ni-catalyzed intramolecular reductive Heck reaction of unactivated alkenes tethered to aryl bromides has been accomplished, providing a variety of benzene-fused cyclic compounds bearing a quaternary stereogenic center in good to excellent yields and high enantioselectivities. A mechanism has been proposed, which involves the enantiodetermining migratory insertion and the following protonation with water or alcoholic solvents as the proton source.

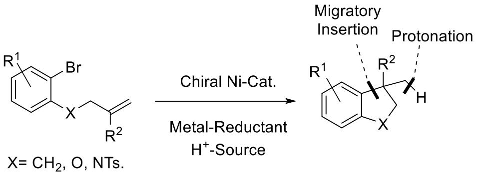


Reductive Heck reactions, in which migratory insertion of a carbometal species into a C−C double bond is followed by protonation or coupling with a hydride, enable the cross-coupling between aryl or alkenyl (pseudo)halides and alkenes, while avoiding the use of organometallics, which suffer from low functionality tolerance (Grignard reagents, organolithiums), toxicity (organotins),[1] or pyrophoricity (diorganozincs).[2] Therefore, reductive Heck reactions have emerged as a powerful tool for construction of saturated C−C bonds in the synthesis of natural products,[3] since its Pd- and Ni-catalyzed versions were discovered by Cacchi and Umani-Ronchi in the 1980s, respectively.[4] Significant advances have also been achieved in the asymmetric reductive Heck reaction using chiral Pd-catalysts.[5] Elegant work in this field include hydroarylation or hydroalkenylation of norbornene,[5a−c] *α*,*β*-unsaturated ketones[5d−f] and amides,[5g] 2-substituted indoles,[5h,i] 1,1-disubstituted and 1,1,2-trisubstituted alkenes,[5j−l] and cyclopentenes.[5m] Furthermore, numerous examples of highly enantioselective hydrocarbonation with aryl or alkyl halides as precursors proceeding in a nonreductive-Heck reaction pathway have also been reported.[6]

In comparison to the noble metal palladium, nickel is a more desirable catalyst in the viewpoint of abundance and cost. Although nickel has been reported as an efficient catalyst for Heck reaction,[7] reductive Heck reaction,[4b,7a,8] and reductive-Heck-like hydrocarbonation,[6c,d,9] the Ni-catalyzed enantioselective variant of reductive Heck reaction is very scarce. To the best of our knowledge, only Zhou and his co-workers described a Ni-catalyzed asymmetric reductive Heck reaction of aryl chlorides to the electron-rich C−C double bond of the indole ring.[10]

Recently, significant progress has been achieved in the field of asymmetric functionalizations of tethered alkenes including Heck reaction,[7j] reductive Heck reaction,[5] carbohalogenation,[11] diarylation,[12] arylalkylation,[13] and arylalkenylation,[14] in which intramolecular arylmetalation is engaged as an enantiodetermining step.[15] As a continuation of our ongoing interest in Ni-catalyzed reductive electrophilic functionalizations of olefins,[13,16] we envisage a Ni-catalyzed asymmetric intramolecular reductive Heck reaction of unactivated 1,1-disubstituted alkenes with tethered aryl bromides with the assistance of a stoichiometric amount of metal as a reductant, to afford an array of enantioenriched benzene-fused cyclic compounds bearing a quaternary stereocenter via a migratory insertion/protonation cascade (Scheme 1). Notably, asymmetric construction of quaternary stereogenic centers is highly challenging due to the steric congestion imposed by four attached carbon atoms.[17]

Scheme 1. Ni-Catalyzed Enantioselective Intramolecular Reductive Heck Reaction of Unactivated Alkenes with Tethered Aryl Bromides



For optimization of the reaction conditions, we used the aryl bromide **1a** tethering a 1,1-disubstituted olefinic unit as the standard substrate and water as the proton source (Table 1). Initially, a series of chiral ligands were examined for this reaction. When BINAP **L1**, Trost-ligand **L2**, PyBOX **L3**, and BOX **L4** were employed as the ligand, only a trace amount of the desired product **2a** was formed (entries 1−4). In contrast, in the case of BOX **L5**, PyrOX **L6** and **L7** the reductive Heck reaction occurred, albeit in low yields (entries 5−7). Importantly, moderate to excellent enantiomeric excesses

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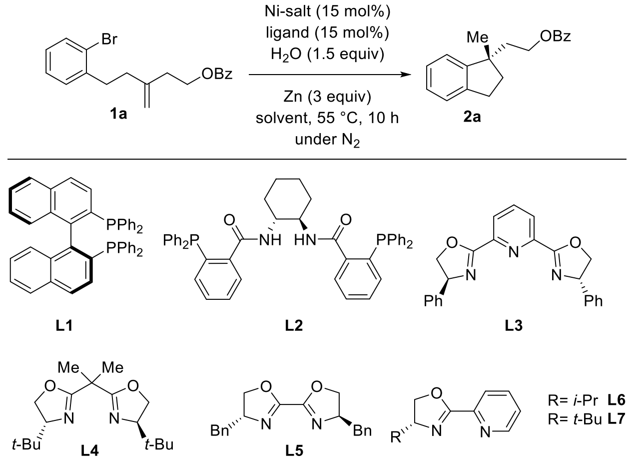
Table 1. Metals, Ligands, Solvents, and Reductants Screening for the Ni-Catalyzed Enantioselective Reductive Heck Reaction[a]



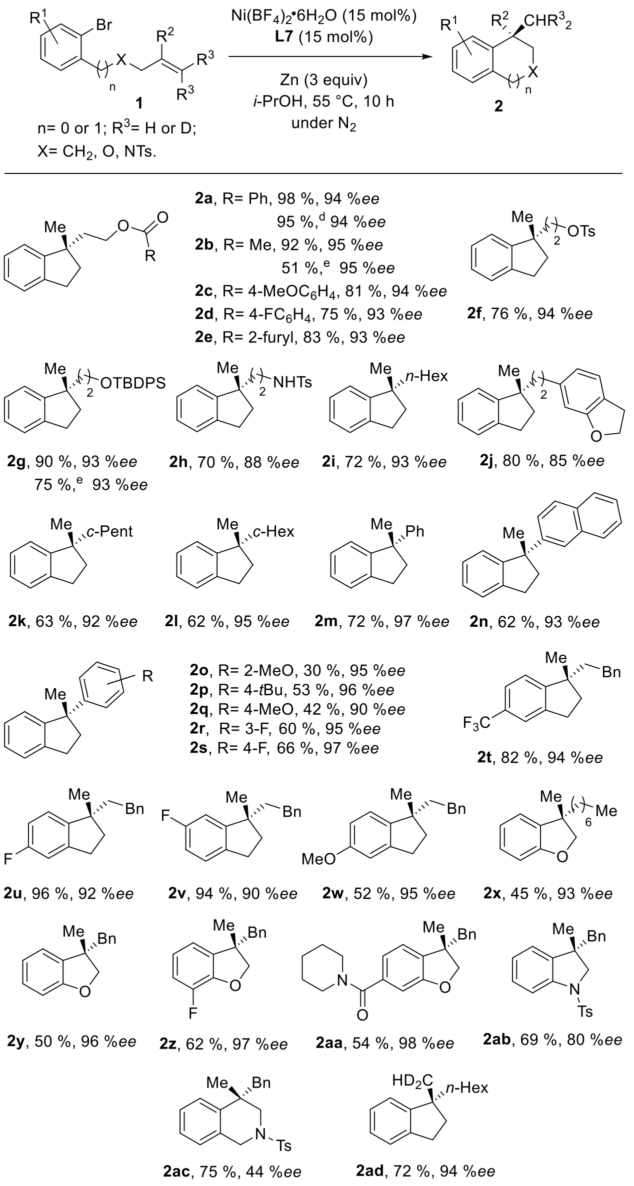
entry	metal	ligand	solvent	yield (%)[b]	*ee* (%)[c]
1	$NiBr_2$	**L1**	DMA	trace	n.d.[d]
2	$NiBr_2$	**L2**	DMA	trace	n.d.[d]
3	$NiBr_2$	**L3**	DMA	trace	n.d.[d]
4	$NiBr_2$	**L4**	DMA	trace	n.d.[d]
5	$NiBr_2$	**L5**	DMA	20	92
6	$NiBr_2$	**L6**	DMA	10	60
7	$NiBr_2$	**L7**	DMA	25	94
8	$Ni(acac)_2$	**L7**	DMA	0	–
9	$Ni(dme)Br_2$	**L7**	DMA	30	90
10	$Ni(BF_4)_2{\cdot}6H_2O$	**L7**	DMA	51	94
11	$Ni(BF_4)_2{\cdot}6H_2O$	**L7**	DMF	54	92
12	$Ni(BF_4)_2{\cdot}6H_2O$	**L7**	THF	trace	n.d.[d]
13	$Ni(BF_4)_2{\cdot}6H_2O$	**L7**	MeOH	50	94
14	$Ni(BF_4)_2{\cdot}6H_2O$	**L7**	*i*PrOH	98	94
15[e]	$Ni(BF_4)_2{\cdot}6H_2O$	**L7**	*i*PrOH	71	88
16[f]	**$Ni(BF_4)_2{\cdot}6H_2O$**	**L7**	***i*PrOH**	**98**	**94**
17[f,g]	$Ni(BF_4)_2{\cdot}6H_2O$	**L7**	*i*PrOH	90	94
18[f,h]	$Ni(BF_4)_2{\cdot}6H_2O$	**L7**	*i*PrOH	82	94

[a] Unless otherwise specified, reactions were performed on a 0.2 mmol scale of the aryl bromide **1a** using 1.5 equiv of H_2O, 15 mol % Ni-salt, 15 mol % ligand, and 3 equiv of Zn at 55 °C in 0.5 mL of solvent for 10 h under a N_2 atmosphere (Set-up in glovebox). [b] Yields of the isolated product after flash chromatography. [c] Determined by HPLC-analysis on chiral stationary phase. [d] Not determined. [e] Mn was used as reductant instead of Zn. [f] Reaction was performed without H_2O. [g] Reaction was performed with 10 mol % catalyst loading. [h] Reaction was performed with 5 mol % catalyst loading.

could be achieved in these cases. Encouraged by this result, we then surveyed various Ni-salts as catalysts (entries 8–10), and the best outcome in terms of both efficiency and selectivity was obtained in the case of $Ni(BF_4)_2{\cdot}6H_2O$ (entry 10). Next, a brief solvent screening was undertaken (entries 11–14) and it turned out that the yield of the reductive Heck reaction could be improved to an excellent level when isopropanol was used as solvent (entry 14). Replacing Zn by Mn as the reducing agent resulted in a decreased yield and enantioselectivity (entry 15). Notably, the reductive Heck reaction still proceeded smoothly in the absence of additional water, affording the product with the same efficiency and enantiocontrol (entry 16). Finally, reducing the catalyst loading to 5 or 10 mol % led to diminished yields (entries 17 and 18).

After establishing the optimal reaction conditions, we started to evaluate the substrate spectrum of this Ni-catalyzed reaction (Scheme 2). First, permutation of the geminal substituent of the terminal olefinic unit was carried out. In the case of a linear primary alkyl chain as a substituent, all the reactions proceeded smoothly, furnishing the products **2a–j** in good to excellent yields and enantiomeric excesses. Good compatibility of functional moieties including carboxylate, tosylate, silyl ether, and sulfonamide was observed. When the geminal substituent is a bulkier secondary alkyl group, the reactions still provided the desired products **2k** and **2l** in moderately good yields and

Scheme 2. Evaluation of the Substrate Scope[a–c,20]

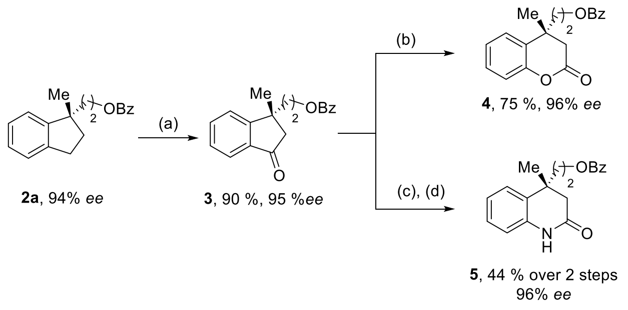


[a] Unless otherwise specified, reactions were performed on a 0.2 mmol scale of the aryl bromides **1** using 15 mol % $Ni(BF_4)_2{\cdot}6H_2O$, 15 mol % ligand **L7**, and 3 equiv of Zn at 55 °C in 0.5 mL of *i*-PrOH for 10 h under a N_2 atmosphere (Set-up in glovebox). [b] Yields of the isolated products after flash chromatography. [c] All enantiomeric excesses were determined by HPLC-analysis on chiral stationary phase. [d] Reaction performed on a scale of 5 mmol. [e] The iodo analogue of **1b** or **1g** was used instead.

excellent enantioselectivities. Moreover, the aryl-substituted alkenes turned out to be successful substrates for this reductive Heck reaction, affording the corresponding products **2m–s** with high enantiocontrol. Subsequently, we investigated the substrate scope further by varying the substitution of the tethered aryl bromides. In this case, both electron-donating and electron-withdrawing groups were well tolerated and the corresponding products **2t–w** were obtained in excellent enantioselectivities. Furthermore, this method was also applicable for the synthesis of the dihydrobenzofurans **2x–aa** and the indoline **2ab**. Although the yields were relatively low, the level of asymmetric induction remained high. Of note is that compound **2aa** is a selective CB2 receptor antagonist.[18] Unfortunately, the reaction yielding tetrahydroisoquinoline **2ac** as the product resulted in low enantioselectivity. To our gratification, the alkene **1ad** containing a deuterated methylene moiety was also successfully employed as a precursor, furnishing the product **2ad** with a CD_2H group in good yield and excellent enantioselectivity. In addition, a 5-mmol-scale reaction using **1a** as substrate was conducted, affording the product **2a** in a similar yield. Tethered aryl iodides were also employed as the substrates, and the corresponding reactions proceeded in lower yields in comparison to these using the bromides (**2b** and **2g**). In these cases a significant amount of deiodination product was observed. Remarkably, most of the products mentioned above are inaccessible (**2j–w** and **2y–ac**) or difficult to prepare (**2a–h**) through our previously reported Ni-catalyzed reductive arylalkylation,[13] enabling this reductive Heck reaction to be a complementary method for synthesis of benzene-fused cyclic compounds. Unsuccessful substrates for this Ni-catalyzed reaction include 1,2-disubstituted and 1,1,2-trisubstituted alkenes, α-thienyl-substituted terminal olefin, 1-bromo-2-(2-methyleneheptyl)-benzene, and the ones with a substituent ortho to bromide.[19]

Some derivatizations based on the conversion of the indane scaffold were carried out in order to achieve some other benzene-fused cyclic compounds (Scheme 3). First, Ru-catalyzed benzylic oxidation of the indane **2a** provided an indanone **3** in an excellent yield.[21] Subsequently, a dihydrocoumarin **4** was synthesized with good efficiency starting from the indanone **3** by means of *m*CPBA-mediated Baeyer–Villiger oxidation. Furthermore, upon treatment with a hydroxyl amine the indanone **3** was readily transferred into an oxime, from which a dihydroquinolinone **5** was obtained through a PCl_5-mediated Beckmann rearrangement.

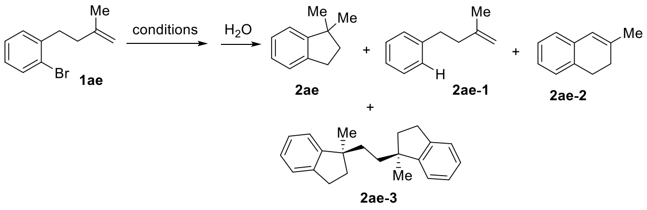
Scheme 3. Derivatizations of the Reductive Heck Reaction Product 2a[a]



[a](a) $RuCl_3$ (0.16 mol%), PhI (5 mol%), oxone, $MeCN/H_2O$ (1:1), rt, 10 h; (b) *m*CPBA, *p*TsOH·H_2O, DCE, 60 °C, 5 h; (c) NH_2OH·HCl, NaOAc·$3H_2O$, MeOH, reflux,1 h; (d) PCl_5, THF, reflux, 1.5 h.

To gain some insight into the migratory insertion step, a number of stoichiometric reactions using the olefin **1ae** as the substrate were conducted (Table 2). In our previously reported Ni-catalyzed reductive arylalkylation reaction,[13] we disclosed that Ni(II) species, generated through oxidative addition of aryl bromides to Ni(0), undergoes preferentially 6-endo cyclization (entry 1). In contrast, under the conditions of this reductive Heck reaction, the stoichiometric reaction using $Ni(COD)_2$ provided the 5-exo ring closure product **2ae** as the major product, while the formation of **2ae-2** was not observed (entry 2). A similar product profile was obtained when performing the stoichiometric reaction in the presence of Zn (entry 3). The generation of **2ae-2** and the dimer **2ae-3** was obviously benefited in the case of the chiral BOX **L5** as ligand, which was the one used in the previous arylalkylation reaction (entry 4). These results indicate that both ligand and solvent could have significant influence on the migratory insertion step. In addition, the stoichiometric reaction involving the Ni(II)-salt in the presence of Zn afforded **2ae** in an excellent yield with a slight amount of debromination product **2ae-1** (entry 5). In conclusion, the results aforementioned support a Ni(II)-mediated cyclization process with Zn as the terminal reductant.

Table 2. Stoichiometric Reactions[a,b]



Condition A: $Ni(COD)_2$ (1 equiv), **L5** (1 equiv), DMA, 40 °C, 1 h;
Condition B: $Ni(COD)_2$ (1 equiv), **L7** (1 equiv), *i*-PrOH, 55 °C, 8 h;
Condition C: $Ni(COD)_2$ (1 equiv), **L7** (1 equiv), *i*-PrOH, Zn (4 equiv), 55 °C, 8 h;
Condition D: $Ni(COD)_2$ (1 equiv), **L5** (1 equiv), *i*-PrOH, 55 °C, 8 h;
Condition E: $Ni(BF_4)_2$• $6H_2O$ (1 equiv), **L7** (1 equiv), *i*-PrOH, Zn (4 equiv), 55 °C, 8 h.

entry	condition	1ae (%)	2ae (%)	2ae-1 (%)	2ae-2 (%)	2ae-3 (%)
1	A	20	5	1	56	17
2	B	9	60	21	0	10
3	C	0	68	20	0	12
4	D	0	48	0	16	35
5	E	0	94	6	0	0

[a]Unless otherwise specified, reactions were performed on a 0.2 mmol scale of the aryl bromide **1ae** using 1 equiv of Ni-salt and 1 equiv of ligand under a N_2 atmosphere (Set-up in glovebox). [b]GC-yields using *n*-dodecane as an internal standard.

Regarding the source of the upcoming hydrogen we hypothesized two reaction pathways: (A) protonation of the Ni(II) species **6**; (B) radical H-abstraction of the intermediate **7** from the solvent molecules, which is generated through homolyptic Ni–C bond cleavage of **6** (Scheme 4). A series of deuterium labeling experiments were carried out to shed light on the origin of the introduced hydrogen in the reductive Heck product (Table 3). First, the reactions conducted in d_8-isopropanol or d_4-methanol with $Ni(BF_4)_2$·$6H_2O$ as catalyst provided the cyclization product with a significant amount of incorporated deuterium (entries 1 and 2). In contrast, when CD_3OH was used as solvent, no trace of deuterium was detected in the reductive Heck product (entry 3). These results rule out the radical hydrogen abstraction from the C–D

Scheme 4. Possible Pathways for the Installation of Hydrogen

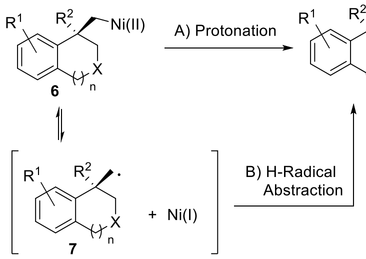
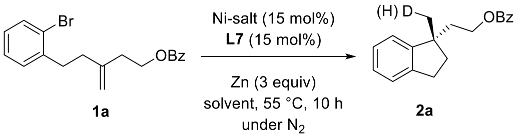


Table 3. Deuterium-Labeling Experiments[a,b]



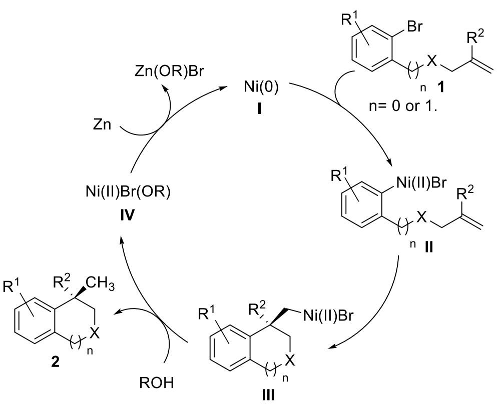
entry	Ni-salt	solvent	yield (%)[b]	% D
1	$Ni(BF_4)_2{\cdot}6H_2O$	d_8-isopropanol	98	78
2	$Ni(BF_4)_2{\cdot}6H_2O$	CD_3OD	70	87
3	$Ni(BF_4)_2{\cdot}6H_2O$	CD_3OH	50	0
4[c]	$Ni(dme)Br_2$	DMA	29	86
5[c]	$Ni(BF_4)_2{\cdot}6H_2O$	isopropanol	90	0

[a] Unless otherwise specified, reactions were performed on a 0.2 mmol scale of the aryl bromide **1a** using 15 mol % Ni-salt, 15 mol % ligand **L7**, and 3 equiv of Zn at 55 °C in 0.5 mL of solvent for 10 h. [b] Yields of the isolated products after flash chromatography. [c] Reaction performed with 5 equiv of D_2O.

bond of the solvent and indicate that the proton in the reaction mixture serves as the source of the upcoming hydrogen atom in the product. To exclude the influence of the water contained in $Ni(BF_4)_2{\cdot}6H_2O$, we performed the reaction using $Ni(dme)Br_2$ as catalyst in DMA with 5 equiv of D_2O (entry 4). In this case the product was formed with 86% deuterium incorporation. In contrast, the reaction facilitated in isopropanol with $Ni(BF_4)_2{\cdot}6H_2O$ as catalyst and 5 equiv of D_2O did not yield a trace of deuterated product (entry 5). These results suggest that both water and alcoholic solvents might act as the proton source for this reductive Heck reaction.

On the basis of the control experiments, we proposed the following reaction mechanism (Scheme 5). Initially, Ni(0) species **I** is generated under the reaction conditions, which subsequently undergoes the oxidative addition with the aryl bromides **1**, affording Ni(II) complex **II**. In the next step, the enantiodetermining intramolecular migratory insertion leads to the formation of a cyclic Ni(II) intermediate **III**. Alternatively, the absolute configuration might be controlled by the energies of the oxidative addition transition states.[7j] The subsequent protonation provides the reductive Heck product **2** and the Ni(II) species **IV**. Finally, the Ni(0) species **I** was regenerated through Zn-mediated reduction for the next catalytic cycle.

Scheme 5. Proposed Reaction Mechanism



In summary, we developed an asymmetric Ni-catalyzed intramolecular reductive Heck reaction of unactivated alkenes, offering an efficient entry to a variety of benzene-fused cyclic compounds bearing a quaternary stereogenic center in a highly enantioselective manner. Preliminary mechanistic studies suggest a mechanism involving the enantiodetermining migratory insertion and the following protonation with water or alcoholic solvents as the proton source.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02577.

Representative experimental procedures and necessary characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Kimbrough, R. D. Toxicity and Health Effects of Selected Organotin Compounds: a Review. *Environ. Health Perspect.* **1976**, *14*, 51−56. (b) Graceli, J. B.; Sena, G. C.; Lopes, P. F.; Zamprogno, G. C.; da Costa, M. B.; Godoi, A. F.; Dos Santos, D. M.; de Marchi, M. R.; Dos Santos Fernandez, M. A. Organotins: a Review of Their Reproductive Toxicity, Biochemistry, and Environmental Fate. *Reprod. Toxicol.* **2013**, *36*, 40−52.

(2) (a) *Organozinc Reagents in Organic Synthesis*; Erdik, E., Ed.; CRC Press: Boca Raton, FL, 1996. (b) *Organozinc Reagents—A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford University Press: Oxford, U.K., 1999.

(3) (a) Schmidt, B.; Hoffmann, H. M. R. On the Way to Aflatoxins and Related Structure Types. Regio-Controlled Annulations by Application of Homogenous Palladium Catalysis, Urethane Tether and ortho, ortho'-Diiodine Effect. *Tetrahedron* **1991**, *47*, 9357−9368. (b) Clayton, S. C.; Regan, A. C. A Total Synthesis of (±)-Epibatidin. *Tetrahedron Lett.* **1993**, *34*, 7493−7496. (c) Trost, B. M.; Toste, F. D. Palladium-Catalyzed Kinetic and Dynamic Kinetic Asymmetric

Transformation of 5-Acyloxy-2-(5H)-furanone. Enantioselective Synthesis of (−)-Aflatoxin B Lactone. *J. Am. Chem. Soc.* **1999**, *121*, 3543−3544. (d) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. Total Synthesis of (−)-Strychnine via the Wieland−Gumlich Aldehyde. *Angew. Chem., Int. Ed.* **1999**, *38*, 395−397. (e) Lee, K.; Cha, J. K. Formal Synthesis of (+)-Phorbol. *J. Am. Chem. Soc.* **2001**, *123*, 5590−5591. (f) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. DYKAT of Baylis−Hillman Adducts: Concise Total Synthesis of Furaquinocin E. *J. Am. Chem. Soc.* **2002**, *124*, 11616−11617. (g) Ichikawa, M.; Takahashi, M.; Aoyagi, S.; Kibayashi, C. Total Synthesis of (−)-Incarvilline, (+)-Incarvine C, and (−)-Incarvillateine. *J. Am. Chem. Soc.* **2004**, *126*, 16553−16558. (h) Li, Z.; Watkins, B.; Liu, H.; Chittiboyina, A. G.; Carvalho, P. B.; Avery, M. A. 1,3-Diaxially Substituted *trans*-Decalins: Potential Nonsteroidal Human Progesterone Receptor Inhibitors. *J. Org. Chem.* **2008**, *73*, 7764−7767. (i) Peng, R.; VanNieuwenhze, M. S. A Model Study for Constructing the DEF-Benzoxocin Ring System of Menogaril and Nogalamycin via a Reductive Heck Cyclization. *Org. Lett.* **2012**, *14*, 1962−1965. (j) Chen, J.-Q.; Xie, J.-H.; Bao, D.-H.; Liu, S.; Zhou, Q.-L. Total Synthesis of (−)-Galanthamine and (−)-Lycoramine via Catalytic Asymmetric Hydrogenation and Intramolecular Reductive Heck Cyclization. *Org. Lett.* **2012**, *14*, 2714−2717. (k) Gao, P.; Cook, S. P. A Reductive-Heck Approach to the Hydroazulene Ring System: A Formal Synthesis of the Englerins. *Org. Lett.* **2012**, *14*, 3340−3343. (l) Diethelm, S.; Carreira, E. M. Total Synthesis of (±)-Gelsemoxonine. *J. Am. Chem. Soc.* **2013**, *135*, 8500−8503. (m) Blair, L. M.; Sperry, J. Total Syntheses of (±)-Spiroindimicins B and C Enabled by a Late-Stage Schöllkopf−Magnus−Barton−Zard (SMBZ) Reaction. *Chem. Commun.* **2016**, *52*, 800−802.

(4) (a) Cacchi, S.; Arcadi, A. Palladium-Catalyzed Conjugate Addition Reaction of Aryl Iodides with.alpha.,.beta.-Unsaturated Ketones. *J. Org. Chem.* **1983**, *48*, 4236−4240. (b) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Ronchi, A. U. Nickel-Catalyzed Coupling of Activated Alkenes with Organic Halides. *J. Organomet. Chem.* **1986**, *301*, C62−C64.

(5) (a) Namyslo, J. C.; Kaufmann, D. E. Palladium-Catalyzed Reactions, 1 Palladium-Catalyzed Enantioselective Hydro-phenylation and Hydrohetarylation of Bicyclo[2.2.1]Hept-2-ene: Influence of the Chiral Ligand, the Leaving Group, and the Solvent. *Chem. Ber.* **1997**, *130*, 1327−1331. (b) Wu, X.-Y.; Xu, H.-D.; Zhou, Q.-L.; Chan, A. S. C. Enantioselective Heck-Type Hydroarylation of Norbornene with Phenyl Iodide Catalyzed by Palladium/quinolinyl-Oxazolines. *Tetrahedron: Asymmetry* **2000**, *11*, 1255−1257. (c) Liu, S.; Zhou, J. S. Desymmetrization of Cyclic Olefins *via* Asymmetric Heck Reaction and Hydroarylation. *Chem. Commun.* **2013**, *49*, 11758−11760. (d) Minatti, A.; Zheng, X.; Buchwald, S. L. Synthesis of Chiral 3-Substituted Indanones via an Enantioselective Reductive-Heck Reaction. *J. Org. Chem.* **2007**, *72*, 9253−9258. (e) Yue, G.; Lei, K.; Hirao, H.; Zhou, J. S. Palladium-Catalyzed Asymmetric Reductive Heck Reaction of Aryl Halides. *Angew. Chem., Int. Ed.* **2015**, *54*, 6531−6535. (f) Mannathan, S.; Raoufmoghaddam, S.; Reek, J. N. H.; de Vries, J. G.; Minnaard, A. J. Enantioselective Intramolecular Reductive Heck Reaction with a Palladium/Monodentate Phosphoramidite Catalyst. *ChemCatChem* **2017**, *9*, 551−554. (g) Kong, W.; Wang, Q.; Zhu, J. Water as a Hydride Source in Palladium-Catalyzed Enantioselective Reductive Heck Reactions. *Angew. Chem., Int. Ed.* **2017**, *56*, 3987−3991. (h) Shen, C.; Liu, R.-R.; Fan, R.-J.; Li, Y.-L.; Xu, T.-F.; Gao, J.-R.; Jia, Y.-X. Enantioselective Arylative Dearomatization of Indoles via Pd-Catalyzed Intramolecular Reductive Heck Reactions. *J. Am. Chem. Soc.* **2015**, *137*, 4936−4939. (i) Liang, R.-X.; Yang, R.-Z.; Liu, R.-R.; Jia, Y.-X. Palladium-Catalyzed Asymmetric Dearomative Alkenylation of Indoles through a Reductive-Heck Reaction. *Org. Chem. Front.* **2018**, *5*, 1840−1843. (j) Diaz, P.; Gendre, F.; Stella, L.; Charpentier, B. New Synthetic Retinoids Obtained by Palladium-Catalyzed Tandem Cyclisation-Hydride Capture Process. *Tetrahedron* **1998**, *54*, 4579−4590. (k) Hou, L.; Yuan, Y.; Tong, X. Pd(0)-Catalysed Asymmetric Reductive Heck-Type Cyclization of (*Z*)-1-Iodo-1,6-dienes and Enantioselective Synthesis of Quaternary Tetrahydropyridines. *Org. Biomol. Chem.* **2017**, *15*, 4803−4806. (l) Zhang, Z.-M.; Xu, B.; Qian, Y.; Wu, L.; Wu, Y.; Zhou, L.; Liu, Y.; Zhang, J. Palladium-Catalyzed Enantioselective Reductive Heck Reactions: Convenient Access to 3,3-Disubstituted 2,3-Dihydrobenzofuran. *Angew. Chem., Int. Ed.* **2018**, *57*, 10373−10377. (m) Yuan, Z.; Feng, Z.; Zeng, Y.; Zhao, X.; Lin, A.; Yao, H. Palladium-Catalyzed Asymmetric Intramolecular Reductive Heck Desymmetrization of Cyclopentenes: Access to Chiral Bicyclo[3.2.1]octanes. *Angew. Chem., Int. Ed.* **2019**, *58*, 2884−2888.

(6) (a) Friis, S. D.; Pirnot, M. T.; Buchwald, S. L. Asymmetric Hydroarylation of Vinylarenes Using a Synergistic Combination of CuH and Pd Catalysis. *J. Am. Chem. Soc.* **2016**, *138*, 8372−8375. (b) Jang, Y. J.; Larin, E. M.; Lautens, M. Rhodium-Catalyzed Enantioselective Reductive Arylation: Convenient Access to 3,3-Disubstituted Oxindoles. *Angew. Chem., Int. Ed.* **2017**, *56*, 11927−11930. (c) Wang, Z.; Yin, H.; Fu, G. C. Catalytic Enantioconvergent Coupling of secondary and tertiary Electrophiles with Olefins. *Nature* **2018**, *563*, 379−383. (d) Zhou, F.; Zhang, Y.; Xu, X.; Zhu, S. NiH-Catalyzed Remote Asymmetric Hydroalkylation of Alkenes with Racemic *α*-Bromo Amides. *Angew. Chem., Int. Ed.* **2019**, *58*, 1754−1758.

(7) (a) Lebedev, S. A.; Lopatina, V. S.; Petrov, E. S.; Beletskaya, I. P. Condensation of Organic Bromides with Vinyl Compounds Catalysed by Nickel Complexes in the Presence of Zinc. *J. Organomet. Chem.* **1988**, *344*, 253−259. (b) Matsubara, R.; Jamison, T. F. Nickel-Catalyzed Allylic Substitution of Simple Alkenes. *J. Am. Chem. Soc.* **2010**, *132*, 6880−6881. (c) Matsubara, R.; Gutierrez, A. C.; Jamison, T. F. Nickel-Catalyzed Heck-Type Reactions of Benzyl Chlorides and Simple Olefins. *J. Am. Chem. Soc.* **2011**, *133*, 19020−19023. (d) Gøgsig, T. M.; Kleimark, J.; Lill, S. O. N.; Korsager, S.; Lindhardt, A. T.; Norrby, P.-O.; Skrydstrup, T. Mild and Efficient Nickel-Catalyzed Heck Reactions with Electron-Rich Olefins. *J. Am. Chem. Soc.* **2012**, *134*, 443−452. (e) Ehle, A. R.; Zhou, Q.; Watson, M. P. Nickel(0)-Catalyzed Heck Cross-Coupling via Activation of Aryl C−OPiv Bonds. *Org. Lett.* **2012**, *14*, 1202−1205. (f) Standley, E. A.; Jamison, T. F. Simplifying Nickel(0) Catalysis: An Air-Stable Nickel Precatalyst for the Internally Selective Benzylation of Terminal Alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 1585−1592. (g) Tasker, S. Z.; Gutierrez, A. C.; Jamison, T. F. Nickel-Catalyzed Mizoroki-Heck Reaction of Aryl Sulfonates and Chlorides with Electronically Unbiased Terminal Olefins: High Selectivity for Branched Products. *Angew. Chem., Int. Ed.* **2014**, *53*, 1858−1861. (h) Harris, M. R.; Konev, M. O.; Jarvo, E. R. Enantiospecific Intramolecular Heck Reactions of Secondary Benzylic Ethers. *J. Am. Chem. Soc.* **2014**, *136*, 7825−7828. (i) Desrosiers, J.-N.; Hie, L.; Biswas, S.; Zatolochnaya, O. V.; Rodriguez, S.; Lee, H.; Grinberg, N.; Haddad, N.; Yee, N. K.; Garg, N. K.; Senanayake, C. H. Construction of Quaternary Stereocenters by Nickel-Catalyzed Heck Cyclization Reactions. *Angew. Chem., Int. Ed.* **2016**, *55*, 11921−11924. (j) Desrosiers, J.-N.; Wen, J.; Tcyrulnikov, S.; Biswas, S.; Qu, B.; Hie, L.; Kurouski, D.; Wu, L.; Grinberg, N.; Haddad, N.; Busacca, C. A.; Yee, N. K.; Song, J. J.; Garg, N. K.; Zhang, X.; Kozlowski, M. C.; Senanayake, C. H. Enantioselective Nickel-Catalyzed Mizoroki−Heck Cyclizations To Generate Quaternary Stereocenters. *Org. Lett.* **2017**, *19*, 3338−3341.

(8) (a) Sustmann, R.; Hopp, P.; Holl, P. Reactions of Organic Halides with Olefins under Ni°-Catalysis. Formal Addition of Hydrocarbons to CC-Double Bonds. *Tetrahedron Lett.* **1989**, *30*, 689−692. (b) Kim, H.; Lee, C. Nickel-Catalyzed Reductive Cyclization of Organohalides. *Org. Lett.* **2011**, *13*, 2050−2053. (c) Márquez, I. R.; Miguel, D.; Millán, A.; Marcos, M. L.; De Cienfuegos, L. A.; Campaña, A. G.; Cuerva, J. M. Ti/Ni-Mediated Inter- and Intramolecular Conjugate Addition of Aryl and Alkenyl Halides and Triflates. *J. Org. Chem.* **2014**, *79*, 1529−1541. (d) Shukla, P.; Sharma, A.; Pallavi, B.; Cheng, C. H. Nickel-Catalyzed Reductive Heck Type Coupling of Saturated Alkyl Halides with Acrylates and Oxabenzonorbornadiene. *Tetrahedron* **2015**, *71*, 2260−2266.

(9) (a) Green, S. A.; Matos, J. L. M.; Yagi, A.; Shenvi, R. A. Branch-Selective Hydroarylation: Iodoarene−Olefin Cross-Coupling. *J. Am. Chem. Soc.* **2016**, *138*, 12779−12782. (b) Lu, X.; Xiao, B.; Zhang, Z.; Gong, T.; Su, W.; Yi, J.; Fu, Y.; Liu, L. Practical Carbon−Carbon

Bond Formation from Olefins through Nickel-Catalyzed Reductive Olefin Hydrocarbonation. *Nat. Commun.* **2016**, *7*, 11129−11136. (c) He, Y.; Cai, Y.; Zhu, S. Mild and Regioselective Benzylic C−H Functionalization: Ni-Catalyzed Reductive Arylation of Remote and Proximal Olefins. *J. Am. Chem. Soc.* **2017**, *139*, 1061−1064. (d) Shevick, S. L.; Obradors, C.; Shenvi, R. A. Mechanistic Interrogation of Co/Ni-Dual Catalyzed Hydroarylation. *J. Am. Chem. Soc.* **2018**, *140*, 12056−12068. (e) Zhou, F.; Zhu, J.; Zhang, Y.; Zhu, S. NiH-Catalyzed Reductive Relay Hydroalkylation: A Strategy for the Remote C(sp^3)-H Alkylation of Alkenes. *Angew. Chem., Int. Ed.* **2018**, *57*, 4058−4062. (f) Nguyen, J.; Chong, A.; Lalic, G. Nickel-catalyzed anti-Markovnikov hydroarylation of alkenes. *Chem. Sci.* **2019**, *10*, 3231−3236. (g) Green, S. A.; Huffman, T. R.; McCourt, R. O.; van der Puyl, V.; Shenvi, R. A. Hydroalkylation of Olefins To Form Quaternary Carbons. *J. Am. Chem. Soc.* **2019**, *141*, 7709−7714.

(10) Qin, X.; Lee, M. W. Y.; Zhou, J. S. Nickel-Catalyzed Asymmetric Reductive Heck Cyclization of Aryl Halides to Afford Indolines. *Angew. Chem., Int. Ed.* **2017**, *56*, 12723−12726.

(11) (a) Newman, S. G.; Howell, J. K.; Nicolaus, N.; Lautens, M. Palladium-Catalyzed Carbohalogenation: Bromide to Iodide Exchange and Domino Processes. *J. Am. Chem. Soc.* **2011**, *133*, 14916−14919. (b) Yoon, H.; Marchese, A. D.; Lautens, M. Carboiodination Catalyzed by Nickel. *J. Am. Chem. Soc.* **2018**, *140*, 10950−10954. (c) Zhang, Z. M.; Xu, B.; Wu, L.; Zhou, L.; Ji, D.; Liu, Y.; Li, Z.; Zhang, J. Palladium/XuPhos-Catalyzed Enantioselective Carboiodination of Olefin-Tethered Aryl Iodides. *J. Am. Chem. Soc.* **2019**, *141*, 8110−8115.

(12) Wang, K.; Ding, Z.; Zhou, Z.; Kong, W. Ni-Catalyzed Enantioselective Reductive Diarylation of Activated Alkenes by Domino Cyclization/Cross-Coupling. *J. Am. Chem. Soc.* **2018**, *140*, 12364−12368.

(13) Jin, Y.; Wang, C. Nickel-Catalyzed Asymmetric Reductive Arylalkylation of Unactivated Alkenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 6722−6726.

(14) Tian, Z.-X.; Qiao, J.-B.; Xu, G.-L.; Pang, X.; Qi, L.; Ma, W.-Y.; Zhao, Z.-Z.; Duan, J.; Du, Y.-F.; Su, P.; Liu, X.-Y.; Shu, X.-Z. Highly Enantioselective Cross-Electrophile Aryl-Alkenylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 7637−7643.

(15) For a review on asymmetric functionalizations of tethered alkenes involving Heck-type migratory insertion as an enantiodetermining step, see: Ping, P.; Li, Y.; Zhu, J.; Kong, W. Construction of Quaternary Stereocenters by Palladium-Catalyzed Carbopalladation-Initiated Cascade Reactions. *Angew. Chem., Int. Ed.* **2019**, *58*, 1562−1573.

(16) (a) Lan, Y.; Yang, F.; Wang, C. Synthesis of *gem*-Difluoroalkenes via Nickel-Catalyzed Allylic Defluorinative Reductive Cross-Coupling. *ACS Catal.* **2018**, *8*, 9245−9251. (b) Wang, L.; Wang, C. Ni-Catalyzed 1,2-Iminoacylation of Alkenes *via* a Reductive Strategy. *Org. Chem. Front.* **2018**, *5*, 3476−3482. (c) Jin, Y.; Wang, C. Ni-Catalysed Reductive Arylalkylation of Unactivated Alkenes. *Chem. Sci.* **2019**, *10*, 1780−1785. (d) Lin, Z.; Lan, Y.; Wang, C. Synthesis of *gem*-Difluoroalkenes via Nickel-Catalyzed Reductive C−F and C−O Bond Cleavage. *ACS Catal.* **2019**, *9*, 775−780. (e) Ding, D.; Lan, Y.; Lin, Z.; Wang, C. Synthesis of *gem*-Difluoroalkenes by Merging Ni-Catalyzed C−F and C−C Bond Activation in Cross-Electrophile Coupling. *Org. Lett.* **2019**, *21*, 2723−2730.

(17) For reviews on enantioselective construction of quaternary stereocenters, see: (a) Christoffers, J.; Baro, A. Stereoselective Construction of Quaternary Stereocenters. *Adv. Synth. Catal.* **2005**, *347*, 1473. (b) Trost, B. M.; Jiang, C. Catalytic Enantioselective Construction of All-Carbon Quaternary Stereocenters. *Synthesis* **2006**, 369. (c) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. Enantioselective Catalytic Formation of Quaternary Stereogenic Centers. *Eur. J. Org. Chem.* **2007**, *2007*, 5969. (d) Quasdorf, K. W.; Overman, L. E. Catalytic Enantioselective Synthesis of Quaternary Carbon Stereocentres. *Nature* **2014**, *516*, 181. (e) Marek, I.; Minko, Y.; Pasco, M.; Mejuch, T.; Gilboa, N.; Chechik, H.; Das, J. P. All-Carbon Quaternary Stereogenic Centers in Acyclic Systems through the Creation of Several C−C Bonds per Chemical Step. *J. Am. Chem. Soc.* **2014**, *136*, 2682. (f) Zeng, X.; Cao, Z.; Wang, Y.; Zhou, Y.; Zhou, J. Catalytic Enantioselective Desymmetrization Reactions to All-Carbon Quaternary Stereocenters. *Chem. Rev.* **2016**, *116*, 7330.

(18) (a) Luo, Z.; Naguib, M. A. Synthetic Approach for (*S*)-(3-Benzyl-3-methyl-2,3-dihydro-benzofuran-6-yl)-piperidin-1-yl-methanone, a Selective CB2 Receptor Agonist. *Tetrahedron Lett.* **2012**, *53*, 3316−3318. (b) Diaz, P.; Phatak, S. S.; Xu, J.; Fronczek, F. R.; Astruc-Diaz, F.; Thompson, C. M.; Cavasotto, C. N.; Naguib, M. 2,3-Dihydro-1-benzofuran Derivatives as a Series of Potent Selective Cannabinoid Receptor 2 Agonists: Design, Synthesis, and Binding Mode Prediction through Ligand-steered Modeling. *ChemMedChem* **2009**, *4*, 1615−1629.

(19) For substrates failing to deliver the reductive Heck reaction products, see: SI, Page S23.

(20) The absolute configuration of compound **2y** was determined as *S* by comparison of the retention time (HPLC analysis) with the same compound with known absolute configuration in the literature (ref 5l.). For details, see: SI, p S211. The stereochemistry of the other products were assigned by assuming a common reaction pathway.

(21) Yusubov, M. S.; Nemykin, V. N.; Zhdankin, V. V. Transition Metal-Mediated Oxidations Utilizing Monomeric Iodosyl- and Iodylarene Species. *Tetrahedron* **2010**, *66*, 5745−5752.