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Palladium-Catalyzed Enantioselective Intramolecular Dearomative Heck Reaction

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ABSTRACT: Enantioselective intramolecular dearomative Heck reactions have been developed by Pd-catalyzed cross-coupling of aryl halides or aryl triflates with the internal C=C bond of indoles, benzofurans, pyrroles, and furans. A variety of structurally unique spiroheterocycles and benzofused heterocycles having N/O-substituted quaternary carbon stereocenters and exocyclic olefin moieties were afforded in moderate to excellent yields with good to excellent enantioselectivities, showing a broad scope of the present protocol. A series of new BINOL- and H8-BINOL-based phosphoramidite ligands were synthesized and proved to be efficient chiral ligands in the reactions of C2-tethered substrates to form spiroheterocycles. (*S*)-SEGPHOS turned out to be a good ligand for the reaction delivering benzofused indolines and pyrrolines. Synthetic applications based on transformations of the exocyclic double bonds were realized without loss of enantiopurities, including hydrogenation, hydroborylation, and stereospecific ring-expanding rearrangement.

Introduction

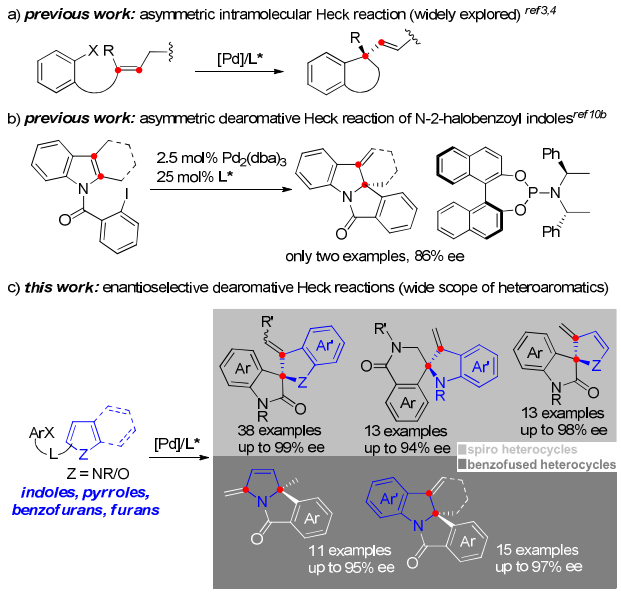
Heck reaction, the cross-coupling of organohalides and olefins to form new alkene derivatives, represents one of the most important carbon-carbon forming reactions, which has been extensively applied in organic synthesis.[1,2] The asymmetric intramolecular Heck reaction, pioneered by Shibasaki and Overman in 1989,[3] has been intensely studied in the past few decades and shows an important role in the synthesis of natural products (Scheme 1a).[4] Considerable advances have also been achieved for enantioselective intermolecular Heck reactions since Hayashi and co-workers reported the first example of arylation of cyclic olefin in 1991.[5] From then on, a range of Heck reactions of cyclic olefins have been realized based on the development of new chiral ligands.[4,6] More recently, by employing a redox-relay strategy Sigman and co-workers have developed a series of highly enantioselective intermolecular Heck reactions of acyclic olefins with aryldiazonium salts or arylboronic acids as coupling partners.[7]

Catalytic asymmetric dearomatization reaction has been extensively developed in the past few years, which constitutes a straightforward access to optically active alicyclic molecules as key moieties of bioactive natural products and pharmaceuticals.[8] Many of current enantioselective dearomatization reactions relied on the transformations of aromatic substrates containing free N-H or O-H bonds, such as anilines, indoles, pyrroles, and phenols, where dearomatization was facilitated via keto-enol tautomerism under basic condition.[8,9] Dearomative Heck reaction, the arylation of internal C=C bonds of aromatic compounds, would provide another avenue for dearomatization reaction. However, due to the challenging in achieving enantiocontrol and breaking the aromaticity, enantioselective dearomative Heck reaction has remained underdeveloped. So far, a few enantioselective dearomative Heck arylation and related domino sequences have been reported. In 2012, Yao and Wu reported a racemic dearomative Heck reaction of *N*-2-halobenzoyl 2,3-disubstituted indoles.[10a] The asymmetric variant was then established in 2016 by Kitamura, Fukuyama, and co-workers and applied as a key step in the total synthesis of (+)-hinckdentine A, but only two single substrates were tested in their report and the ee was up to 86% (Scheme 1b).[10b] In 2015, our group disclosed a reductive Heck reaction of 2-substituted *N*-2-halobenzoyl indoles, which afforded chiral indolines bearing C2-quaternary carbocenters in excellent enantioselectivities.[11a] Zhou and co-workers showed a chiral nickel catalyst was also efficient for the same reaction with zinc powder as a reducing agent.[12] Moreover, dearomative difunctionalization reactions of indoles and furans have been developed by Lautens, Yin, and our groups via domino Heck/anionic-capture sequences employing a range of nucleophiles to terminate the alkyl-Pd species.[13] Despite of the above progress, most of the examples furnished in their racemic versions and the dearomative Heck reaction to form heterocyclic alkylidene prodcuts has remained much less developed.

As part of our ongoing work on enantioselective Heck reactions, we report herein a protocol of asymmetric intramolecular dearomative Heck reaction of indoles, benzofurans, pyrroles, and furans, which serves as a straightforward synthetic approach to chiral spiroheterocyclic and benzofused heterocyclic scaffolds (Scheme 1c). Through the Pd-catalyzed Heck arylation of internal C=C

bonds of the abovementioned heteroaromatics, a range of structurally unique spiro- or benzofused heterocycles bearing N/O-substituted quaternary carbon stereocenters and exocyclic olefin moieties were afforded in moderate to good yields with excellent enantioselectivities. New BINOL- and H8-BINOL-based phosphoramidite ligands were developed and showed good asymmetric induction ability in achieving spiroheterocycles, while ligand (*S*)-SEGPHOS proved to be efficient in the formation of benzofused indolines and pyrrolines. Synthetic transformations of the products were realized based on the conversion of the exocyclic C=C bonds, including hydrogenation, hydroboration, and stereospecific ring-expanding rearrangement followed by nucleophilic additions.

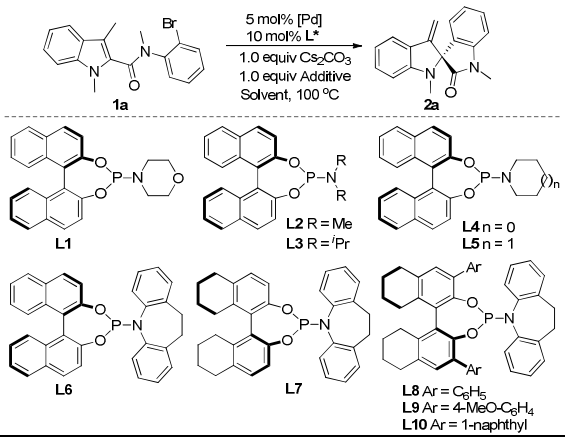
Scheme 1. Enantioselective intramolecular Heck reaction.



Results and Discussions

Reaction of Indoles and Benzofurans. At the beginning, the model reaction of 2-aminocarbonyl indole **1a** was studied (Table 1). In the presence of $Pd(OAc)_2$ (5 mol %), phosphoramidite **L1** (10 mol %), and Cs_2CO_3 (1.0 equiv), the desired product **2a** was isolated in 83% yield with 28% ee in toluene at 100 °C (entry 1). Higher enantioselectivities were observed when the reaction carried out in THF or 1,4-dioxane (entries 3 and 4), whereas the yield was poor in methyl *tert*-butyl ether (entry 2). Interestingly, adding HCO_2H to the reaction mixture improved the ee value to 52%, while no reductive Heck product was detected (entry 5). Comparable enantioselectivities were achieved in the presence of $PhCO_2H$ (50% ee) or AcOH (51% ee). The use of $Pd(dba)_2$ led to **2a** in 90% yield with 53% ee (entry 6). Various chiral phosphoramidite ligands were then examined. Ligands **L2**–**L5** bearing different substituents on the nitrogen atom did not improve the enantioselectivities (entries 7–10). Although the ee was poor for iminodibenzyl ligand **L6** (entry 11), its analogous ligand, H8-BINOL-based **L7**, gave a higher ee than did ligand **L1** (comparing entries 12 and 6). Ligands **L8**–**L10**, which are aryl-substituted derivatives of **L7**, markedly improved the enantioselectivity, to 77% for **L8**, 79% for **L9**, and 82% for **L10** (entries 13–15). We were pleased to find that the enantioselectivity could be further improved to 89% or 92% by lowering the temperature to 60 °C or 40 °C, respectively (entries 16 and 17). In the end, **2a** could be obtained in 92% yield with 93% ee by increasing the amounts of Cs_2CO_3 and HCO_2H (entry 18).

Table 1. Condition optimization of the reaction of 1a.[a]



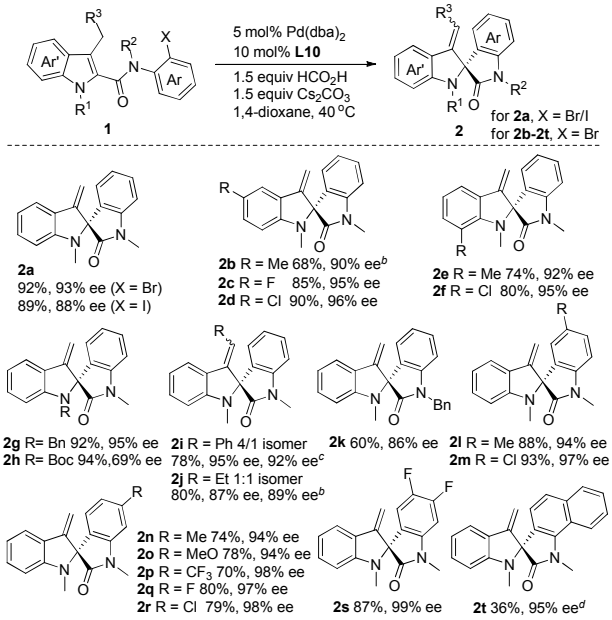
Entry	L*	Additive	Solvent	Yield (%)	ee (%)
1	**L1**	--	Toluene	83	28
2	**L1**	--	MTBE	44	24
3	**L1**	--	THF	87	32
4	**L1**	--	1,4-dioxane	85	35
5	**L1**	HCO_2H	1,4-dioxane	87	52
6	**L1**	HCO_2H	1,4-dioxane	90	53
7	**L2**	HCO_2H	1,4-dioxane	93	39
8	**L3**	HCO_2H	1,4-dioxane	89	20
9	**L4**	HCO_2H	1,4-dioxane	79	29
10	**L5**	HCO_2H	1,4-dioxane	83	42
11	**L6**	HCO_2H	1,4-dioxane	70	30
12	**L7**	HCO_2H	1,4-dioxane	76	58
13	**L8**	HCO_2H	1,4-dioxane	87	77
14	**L9**	HCO_2H	1,4-dioxane	94	79
15	**L10**	HCO_2H	1,4-dioxane	90	82
16[b]	**L10**	HCO_2H	1,4-dioxane	92	89
17[c,d]	**L10**	HCO_2H	1,4-dioxane	86	92
18[c,e]	**L10**	HCO_2H	1,4-dioxane	92	93

[a]Reaction conditions: **1a** (0.2 mmol), [Pd] (5 mol%; $Pd(OAc)_2$ for entries 1–5; $Pd(dba)_2$ for entries 6–18.), **L*** (10 mol%), Cs_2CO_3 (1 equiv), additive (1 equiv), and solvent (2 mL) at 100 °C for 24 h; MTBE = methyl *tert*-butyl ether; Isolated yield; ee was determined by chiral HPLC. [b]At 60 °C. [c]At 40 °C. [d]For 3d. [e]Cs_2CO_3 (1.5 equiv) and HCO_2H (1.5 equiv).

With the optimal conditions in hand, we investigated the scope of the reaction with various substrates **1** (Scheme 2). The yield and ee of spiro product **2a** were slightly lower for an iodinated substrate (X = I) than for the corresponding brominated substrate (X = Br). The

absolute configuration of **2a** was determined to be *R* based on X-ray crystallographic analysis of its derivative **15** (Scheme 9).[14] We also explored the effect of substituents on the indole ring. Various groups at C5 and C7, such as Me, F, and Cl, were compatible with the reaction conditions, furnishing spiro products **2b–2f** in moderate to excellent yields with 90–96% ee values. The protecting group on the indole nitrogen was also investigated. Product **2g**, which bears an *N*-benzyl group, was obtained in 92% yield with 95% ee, whereas the ee observed for **2h**, a product with an *N*-Boc group, was considerably lower (69%). The presence of an *n*-propyl group or a benzyl group at C3 led to a sluggish reaction, but the corresponding products (**2i** and **2j**) were obtained with good enantioselectivities, albeit with lower *E*/*Z* isomer ratios. Next, various substituents on the aniline ring were screened. Substrates with either an electron-donating or electron-withdrawing group were well-tolerated, furnishing desired products **2l–2s** in good yields with excellent enantioselectivities (up to 99%). Notably, we obtained a poor yield of product **2t**, which bears a naphthalene ring, even after a prolonged reaction time (5 d), although the ee was excellent (95%).

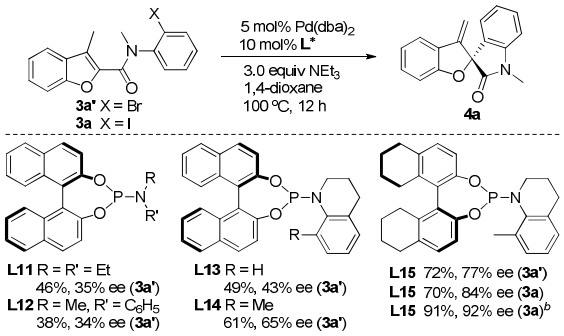
Scheme 2. Scope of indole 1.[a]



[a]Reaction conditions: **1** (0.2 mmol), $Pd(dba)_2$ (5 mol%), **L10** (10 mol%), Cs_2CO_3 (1.5 equiv), and HCO_2H (1.5 equiv) in 1,4-dioxane (2 mL) at 40 °C for 20-36 h. [b]for 60 h. [c]for 6 d. [d]for 5 d.

A dearomative intramolecular Heck reaction of 2-aminocarbonyl benzofurans **3** was also established. The effect of chiral ligands was shown in scheme 3.[15] A new H8-BINOL-based phosphoramidite ligand **L15**, bearing a 8-methyl tetrahydroquinoline moiety, led to product **4a** in 72% yields and 77% ee in the reaction of bromo-substrate **3a'** with $Pd(dba)_2$ as a catalyst and NEt_3 as a base in 1,4-dioxane at 100 °C. Other ligands **L11-L14** gave inferior results, while **L10**, the best ligand for the reaction of **1**, led to **4a** in 79% yield and 73% ee. The ee value was improved to 84% for iodo-substrate **3a** and further to 92% by lowering the temperature to 40 °C and prolonging the reaction time. The absolute configuration of **4a** was determined to be *R* by the X-ray crystallographic analysis.[14]

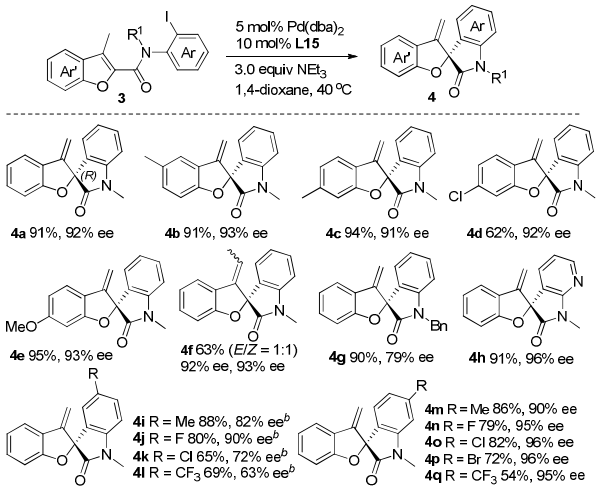
Scheme 3. Ligand effect for the reaction of 3a or 3a'.[a]



[a]Reaction conditions: **3a** or **3a'** (0.2 mmol), $Pd(dba)_2$ (5 mol%), **L*** (10 mol%), and NEt_3 (3 equiv) in 1,4-dioxane (2 mL) at 100 °C for 12 h; [b]At 40 °C for 3 d.

To investigate the scope, we tested a variety of benzofurans under the above conditions (Scheme 4). Methyl, Cl, and methoxy substituents bearing at C5 or C6 of the benzofuran ring were well tolerated. Products **4b–4e** were afforded in excellent enantioselectivities, although the yield of chlorinated product **4d** was relatively low. Reaction of a 3-ethylbenzofuran afforded product **4f** in 63% yield as a 1:1 mixture of *E* and *Z* isomers with 92% ee and 93% ee, respectively. Moreover, *N*-benzyl product **4g** was obtained in 90% yield with 79% ee. Gratifyingly, product **4h** containing a pyridine moiety was obtained in 91% yield and 96% ee. We also examined the effect of substituents on the aniline ring. The reaction was impeded by the presence of substituents (such as Me, F, Cl, and CF_3) *para* to the amide nitrogen atom; products **4i–4l** were obtained in moderate to good yields and ee values after 4 d at 60 °C. We were pleased to find that substrates bearing a substituent *para* to the iodine atom afforded products **4m–4q** in moderate to good yields with excellent enantioselectivities (90–96%). Note that the bromine atom of **4p** survived the reaction conditions.

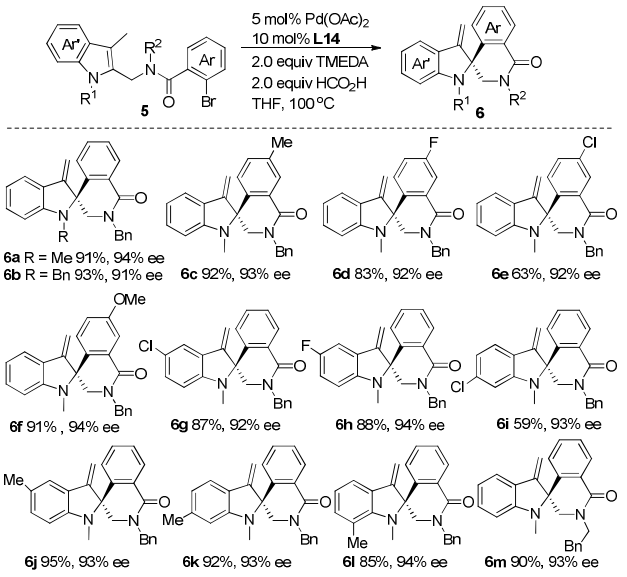
Scheme 4. Scope of benzofuran 3.[a]



[a]Reaction conditions: **3** (0.2 mmol), $Pd(dba)_2$ (5 mol%), **L15** (10 mol%), and Et_3N (3 equiv) in 1,4-dioxane (2 mL) at 40 °C for 2-3 d. [b]At 60 °C, for 4 d.

Dearomative Heck reaction of a modified indole **5** was also realized, which led to chiral spiro-[5.6]-heterocycles. BINOL-based chiral phosphoramidite **L14** was found to be the best ligand, furnishing product **6a** in 91% yield with 94% ee using TMEDA as a base and HCO_2H as an additive.[15] The absolute configuration of **6a** was determined to be *S* according to the X-ray crystallographic analysis of a single crystal of iminium salt **18**, which derived through a stereospecific rearrangement (Scheme 9). The scope of substrate **5** was then investigated (Scheme 5). *N*-Benzyl product **6b** was obtained in 93% yield with 91% ee. Substrates bearing substituents on either the indole ring or the benzene ring of the bromobenzoyl moiety were examined. Reactions of **5c**-**5f** having substituents *para* to the bromine atom furnished **6c**–**6f** with 92–94% ee values. Cl, F, and Me substituents at C5–C7 of the indole ring were well tolerated and their reactions furnished **6g**–**6l** in modest to excellent yields with excellent enantioselectivities. In addition, an *N*-phenylethyl substrate was also suitable for this reaction, furnishing **6m** in 90% yield with 93% ee.

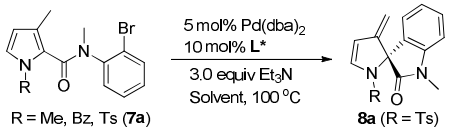
Scheme 5. Scope of indole 5.[a]



[a]Reaction conditions: **5** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), **L14** (10 mol%), TMEDA (2 equiv), and HCO_2H (2 equiv) in THF (2 mL) at 100 °C for 2-3 d.

Reaction of C2-Tethered Pyrroles and Furans. Having conducted the Heck reactions of indoles and benzofurans, we further moved our attention to more challenging heteroaromatic substrates, such as pyrroles and furans. Thus, the reaction of *N*-(2-bromophenyl)-pyrrole-2-carboxamide bearing a C3-methyl group was tested. It was found that the *N*-protecting group of pyrrole was crucial to the reactivity. Only *N*-Ts-pyrrole **7a** could give the spiro-product **8a** in a poor yield but with excellent ee with **L15** as a chiral ligand and NEt_3 as a base at 100 °C in 1,4-dioxane (Table 2, entry 3). No target products were detected for *N*-Me-pyrrole and *N*-Bz-pyrrole (entries 1 and 2). The yield of **8a** was improved when the reaction carried out in MeCN and NMP (entries 6 and 7). Product **8a** was isolated in 66% yield and 94% ee in DMF solvent (entry 8). As a comparison, a BINOL-based analogous ligand **L14** led to **8a** in inferior yield and ee (entry 9). The scope of *N*-Ts-pyrrole was subsequently examined (Scheme 6). Substituent effect on the benzene ring of aniline was investigated in the reactions of substrates bearing MeO, CF_3, F, Cl, and Me groups. Products **8a**-**8h** were isolated in moderate yields with good to excellent enantioselectivities. Substituents *para* to amide nitrogen atom resulted in slightly lower yields and ees (**8f**-**8h** *vs* **8a**-**8e**). To our delight, the reaction of C2-substituted furans could also proceed smoothly to give **8i**-**8m** in excellent enantioselectivities by lowering the temperature and adding 4Å molecular sieves to the reaction, but the yields for these products were still lower. Substrate bearing a Cl *para* to amide nitro atom failed to furnish product **8n** and no desired product **8o** was detected in the reaction of a thiophene substrate.

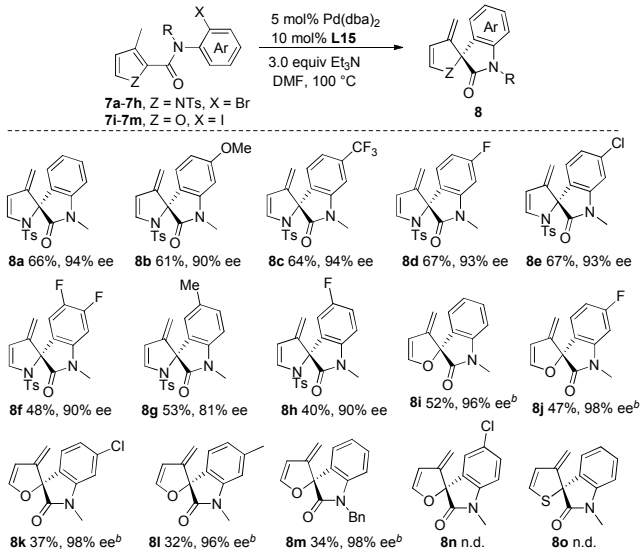
Table 2. Condition optimization of the reaction of 7a.[a]



Entry	R	L*	Solvent	Yield (%)	Ee (%)
1	Me	**L15**	1,4-dioxane	nd	--
2	Bz	**L15**	1,4-dioxane	nd	--
3	Ts	**L15**	1,4-dioxane	<10	92
4	Ts	**L15**	Toluene	nd	--
5	Ts	**L15**	THF	<10	93
6	Ts	**L15**	MeCN	34	92
7	Ts	**L15**	NMP	49	93
8	Ts	**L15**	DMF	66	94
9	Ts	**L14**	DMF	35	79

[a]Reaction conditions: **7a** (0.2 mmol), $Pd(dba)_2$ (5 mol%), **L*** (10 mol%), and NEt_3 (3 equiv) in solvent (2 mL) at 100 °C for 24 h; nd = not detected.

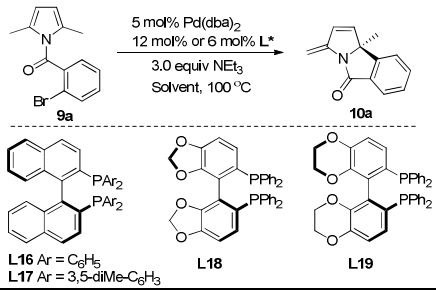
Scheme 6. Scope of C2-tethered pyrrole and furan.[a]



[a]Reaction conditions: **7** (0.2 mmol), $Pd(dba)_2$ (5 mol%), **L15** (10 mol%), NEt_3 (3 equiv) in DMF (2 mL) at 100 °C for 24-60 h. [b]100 mg 4Å molecular sieves, at 80 °C for 48 h.

Reaction of *N*-tethered Pyrroles and Indoles. Encouraged by the results achieving in the reaction of *N*-Ts-pyrroles **7**, we further tested the reaction of *N*-2-halobenzyol 2,5-dimethylpyrrole **9** to access chiral benzofused pyrrolines.[16] Pyrrole **9a** was used as a model substrate for condition optimization. As shown in Table 3, phosphoramidite ligands **L14** and **L15** resulted in the desired product **10a** in moderate yields and enantioselectivities in DMF at 100 °C for 16 h (entries 1 and 2), while better results (76% yield and 84% ee) were obtained when chiral diphosphine (*S*)-BINAP **L16** was used as a ligand (entry 3). Changing the solvent to 1,4-dioxane, toluene, and THF did not improve either yield or ee (entries 4-6), however, **10a** was isolated in an increased yield (82%) in NMP solvent (entry 7). (*S*)-Xyl-BINAP **L17** could further improve the ee to 90% but the yield was poor (entry 8). (*S*)-SEGPHOS **L18** led to **10a** in 78% yield and 93% ee (entry 9). In this case, the yield was further improved to 81% in a mixed solvent of DMF/NMP (1:1) and the excellent ee was kept (entry 11).

Table 3. Condition optimization of the reaction of 9a.[a]

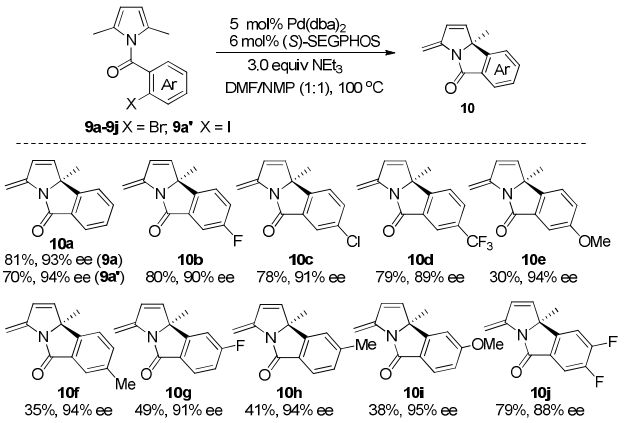


Entry	L*	Solvent	Yield (%)	Ee (%)
1	**L14**	DMF	43	65
2	**L15**	DMF	48	57
3	**L16**	DMF	76	84
4	**L16**	1,4-dioxane	53	60
5	**L16**	Toluene	30	67
6	**L16**	THF	54	60
7	**L16**	NMP	82	80
8	**L17**	DMF	20	90
9	**L18**	DMF	75	93
10	**L19**	DMF	79	90
11	**L18**	DMF/NMP[b]	81	93

[a]Reaction conditions: **9a** (0.2 mmol), $Pd(dba)_2$ (5 mol%), **L*** (12 mol% for **L14** and **L15**; 6 mol% for **L16**-**L19**), and NEt_3 (3 equiv) in solvent (2 mL) at 100 °C for 16 h. [b]V_{DMF}/V_{NMP} = 1:1.

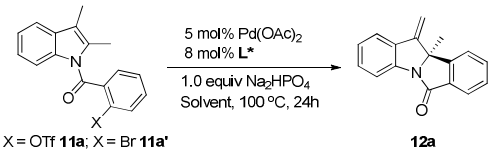
A range of *N*-substituted 2,5-dimethylpyrroles were then investigated (Scheme 7). In comparison to bromo-substrate **9a**, the reaction of iodo-substrate **9a'** gave product **10a** in a relatively lower yield (70%) but a slightly improved ee (94%). Substituents bearing on the benzene ring were tested and the reactions afforded products **10b**-**10j** in excellent enantioselectivities (88-94%). Markedly lower yields for products **10e** and **10f** were observed for the substrates having electron-donating substituents *para* to bromide atom. Substituents (F, Me, and MeO) *para* to amide tether also impeded the reactions, resulting in lower yields for products **10g**-**10i**.

Scheme 7. Scope of N-tethered pyrrole 9.[a]



[a]Reaction conditions: **9** (0.2 mmol), $Pd(dba)_2$ (5 mol%), (*S*)-SEGPHOS (6 mol%), and NEt_3 (3 equiv) in a mixed solvent of DMF/NMP (2 mL, 1:1) at 100 °C for 16-48 h.

Table 4. Condition optimization of the reaction of 11a.[a]



Entry	L*	Solvent	Yield (%)	Ee (%)
1	**L16**	MeOH	80	45
2	**L16**	MeOH	75	75
3	**L16**	EtOH	76	79
4	**L18**	EtOH	76	85
5	**L19**	EtOH	73	82
6[b]	**L18**	EtOH	72	88
7[c]	**L18**	EtOH	30	89
8[b]	**L18**	THF	76	89
9[b]	**L18**	1,4-dioxane	75	96
10[b,d]	**L18**	1,4-dioxane	95	95

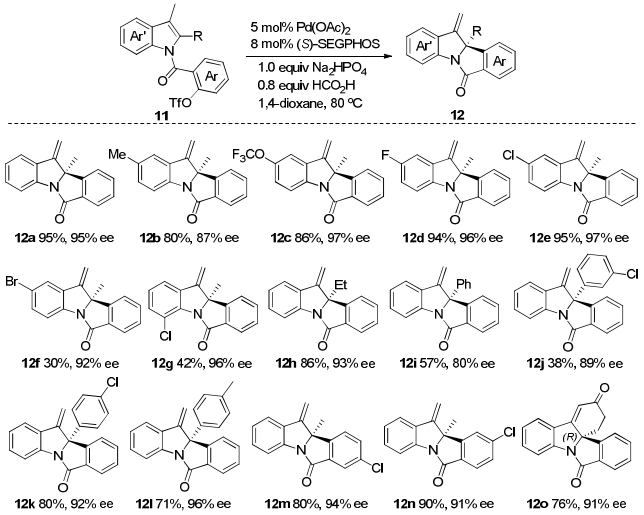
[a]Reaction conditions: **11a** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), **L*** (8 mol%), and Na_2HPO_4 (1 equiv) in solvent (2 mL) at 100 °C for 24 h; for entries 2-10, HCO_2H (0.8 equiv) was added. [b]At 80 °C. [c]At 60 °C. [d]100 mg 4Å molecular sieves was added.

The successful application of chiral diphosphine ligand in the Heck reaction of *N*-tethered pyrroles to approach benzofused products promoted us to examine the reaction of *N*-2-halobenzoyl 2,3-disubstituted indoles. Although it has been reported by Kitamura, Fukuyama, and co-workers, only two substrates were tested in their report and the highest ee was 86% by using excess amount of chiral MonoPhos-PE ligand.[10b] Herein, the reaction of a bromo substrate **11a'** was first tested with $Pd(OAc)_2$ as a catalyst and (*S*)-BINAP **L16** as a

ligand. Target product **12a** could be isolated, while the reaction was in poor reproducibility with ee ranging from 15% to 78%. A triflate substrate **11a** was then synthesized and applied as a substrate. As shown in Table 4, by using $Pd(OAc)_2$ as a catalyst and Na_2HPO_4 as a base, the reaction of **11a** in MeOH proceeded smoothly to afford **12a** in 80% yield and 45% ee (entry 1). The enantioselectivity was remarkably improved to 75% by adding HCO_2H to the reaction mixture, and further to 79% in EtOH solvent (entries 2 and 3). Ligand (*S*)-SEGPHOS (**L18**) gave a better ee (85%) (entry 4). Lowering the temperature to 80 °C further improved the ee to 88%, and further to 89% albeit with a poor yield at 60 °C (entries 6 and 7). Comparable results were observed in THF solvent (entry 8), while the enantioselectivity was sharply improved to 96% when the reaction carried out in 1,4-dioxane (entry 9). Finally, an excellent yield (95%) was obtained by adding 4Å molecular sieves to the reaction mixture and the ee was 95% ee (entry 10).

Scheme 8 disclosed the scope of the reaction **11**→**12** under the optimal conditions. All of the reactions afforded products **12a-120** in moderate to good yields and good to excellent enantioselectivities. Substituents bearing at C5 or C7 of the indole ring, including Me, CF_3O, and halides, were well tolerated to afford products **12b-12g**. C5-Br in product **12f** could survive albeit with a lower product yield. Lower yield was also observed for product **12g** having a C7-Cl group. Other than methyl group, ethyl and aryl substituents at C2 of the indole were also investigated; all these substrates reacted smoothly to give products **12h-12l** in good to excellent ees. Lower yield was observed for **12j** having a 3-chlorophenyl group, indicating a possible influence of steric hindrance on the reactivity. Moreover, substrates having chloro substituent at the benzene ring of 2-bromobenzoyl moiety were also tested, which afforded **12m** and **12n** in good yields and excellent enantioselectivities. It's worth to note that product **120**, which has been used as a key starting material for the total synthesis of (+)-hinckdentine A, was obtained in 76% yield and 91% ee, and its absolute configuration was determined to be *R* by comparison to the reported value.[10b]

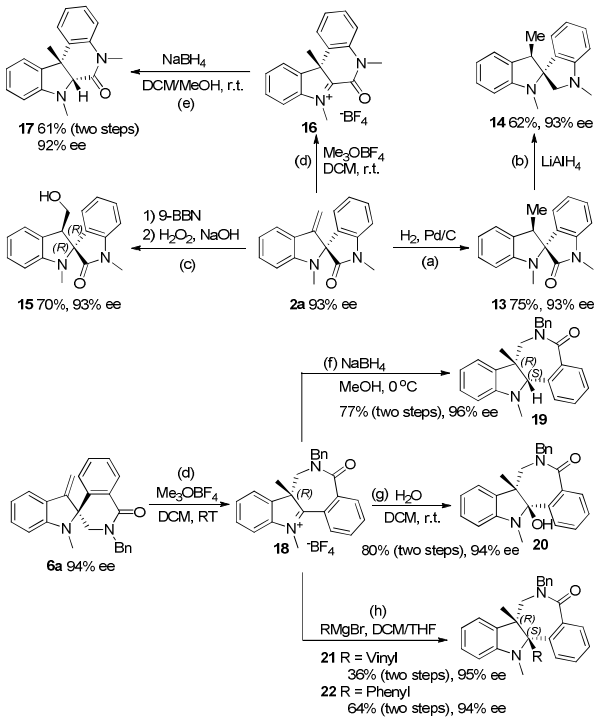
Scheme 8. Scope of the reaction with respect to 11.[a]



[a]Reaction conditions: **11** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), (*S*)-SEGPHOS (8 mol%), Na_2HPO_4 (1 equiv), HCO_2H (0.8 equiv), and 100 mg 4Å molecular sieves in 1,4-dioxane (2 mL) at 80 °C for 24-80 h.

Synthetic Transformations. We further carried out the synthetic transformations of two typical products **2a** and **6a** based on the conversion of their exocyclic C=C bonds (Scheme 9). A Pd/C-catalyzed hydrogenation of the exocyclic olefin of **2a** under H_2 (50 atm) at room temperature afforded compound **13** in 75% yield. Subsequent reduction of the carbonyl group with $LiAlH_4$ in refluxing THF converted **13** to amine **14** in 62% yield. Hydroboration of **2a** with 9-BBN followed by an oxidation with H_2O_2 furnished alcohol **15** in 70% yield. The absolute configuration of **15** was determined to be (2'*R*, 3'*R*) by its X-ray crystallographic analysis.[14] Compounds **13–15** were all isolated as single isomer and without any loss of ee. Moreover, a stereospecific ring-expanding rearrangement of **2a** promoted by Me_3OBF_4 took place to give iminium salt **16**, which was treated with $NaBH_4$ without further purification to deliver dihydroquinolinone-fused indoline **17** in 61% yield (for two steps) with 92% ee. Product **6a** was also readily converted to iminium salt **18**[14] having a seven-membered lactam moiety by treating with Me_3OBF_4. In fact, aqueous HBF_4 could also promote this rearrangement reaction of **2a** and **6a** at 80 °C albeit with a lower yield. Reduction of the unpurified **18** by $NaBH_4$ gave amine **19** in 77% yield (for two steps) and 96% ee. Hemiaminal **20** was obtained in 80% yield and 94% ee by treating **18** with H_2O. Indolines **21** and **22** having vicinal quaternary stereocenters were obtained in excellent enantioseletivities as single isomers by the addition of Grignard reagents to **18**. The relative configuration of compound **19** and **21** was determined by 2D-NOSEY spectrum.

Scheme 9. Synthetic transformations of 2a and 6a.[a]



[a]Reaction conditions: (a) Pd/C (10 mol%), H_2 (50 atm) in ethyl acetate at r.t. for 60 h; (b) $LiAlH_4$ (10 equiv) in refluxing THF for 55 h; (c) 9-BBN (2 equiv) in THF at 40 °C for 2 h, then 3 M NaOH and 30% H_2O_2 at r.t. for 15 h; (d) Me_3OBF_4 (2 equiv) in CH_2Cl_2 at r.t. for 8 h; (e) $NaBH_4$ (3 equiv) in

CH_2Cl_2/MeOH (4:1) at o °C for 30 min; (f) $NaBH_4$ (3 equiv) in MeOH at o °C for 30 min; (g) H_2O (2 equiv) in CH_2Cl_2 at r.t. for 12 h; (h) RMgBr (2 equiv) in CH_2Cl_2/THF at r.t. for 12 h.

Conclusions

We have developed a protocol for Pd-catalyzed enantioselective intramolecular dearomative Heck reactions of indoles, benzofurans, pyrroles, and furans. This protocol offers a straightforward access to a range of chiral spiro- and benzofused heterocycles bearing nitrogen-/oxygen-substituted quaternary carbon stereocenters. By the help of new BINOL- or H8-BINOL-based chiral phosphoramidite ligands and chiral diphosphine ligand, the reactions were accomplished in moderate to excellent yields with good to excellent enantioselectivities. Synthetic transformations of the typical products were conducted based on the conversion of the exocyclic C=C bonds, which led to structurally unique heterocycles in excellent enantioselectivities.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.
Full experimental and characterization data, including ^1H and ^{13}C NMR for all the new compounds, chiral HPLC spectra for the products (PDF)
Crystallographic data for **4a**, **15**, and **18** (CIF)

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Notes

The authors declare no competing financial interests.

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Palladium-Catalyzed Enantioselective Intramolecular Dearomative Heck Reaction