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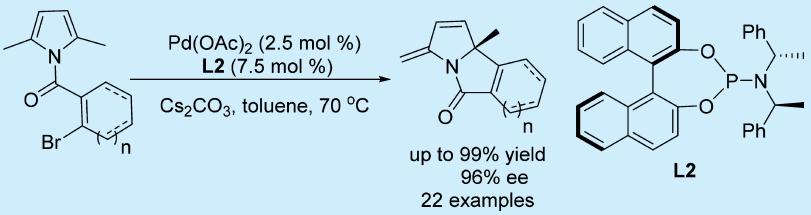
Palladium-Catalyzed Asymmetric Intramolecular Dearomative Heck Reaction of Pyrrole Derivatives

Ping Yang and Shu-Li You*

State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

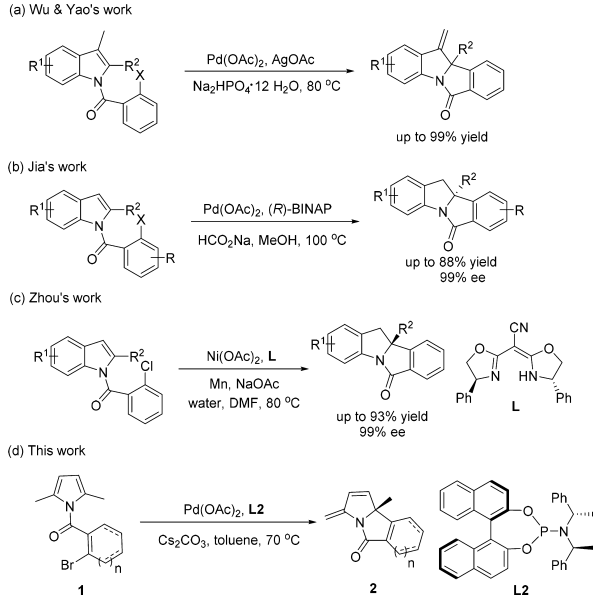
Supporting Information



ABSTRACT: The Pd-catalyzed asymmetric intramolecular dearomatization of pyrroles via the Heck reaction in the presence of commercially available $Pd(OAc)_2$ and the Feringa ligand is described. Diverse pyrroline derivatives were obtained in excellent yields (up to 99%) with high enantioselectivity (up to 96% ee). The reaction features a wide substrate scope, relatively mild conditions, and useful transformations of the products.

Catalytic asymmetric dearomatization (CADA) reactions offer an efficient strategy for the functionalization of aromatic compounds and have witnessed rapid development recently.[1] The Pd-catalyzed Heck reaction[2] is one of the methods that can be employed for the dearomatization of arenes. In this regard, several elegant dearomative Heck reactions of indoles have been documented recently.[3,4] In 2012, Yao, Wu, and their co-workers reported a dearomatization process of indoles via a Pd-catalyzed Heck reaction to construct fused indolines (Scheme 1a).[4a] In 2015, Jia and co-workers accomplished the first enantioselective arylative dearomatization of indoles via a Pd-catalyzed reductive Heck reaction in the presence of sodium formate (Scheme 1b).[3a] Recently, the Zhou group reported an elegant Ni-catalyzed asymmetric reductive Heck reaction of indoles using water as a proton source (Scheme 1c).[3d] Notably, Kitamura, Fukuyama, and their co-workers documented an enantioselective total synthesis of (+)-hinckdentine A in which a Pd-catalyzed asymmetric dearomative Heck reaction was used as a key step.[3b] However, despite these pioneering studies, all of these dearomative Heck reactions are limited to indoles. On the other hand, pyrrolidines and pyrrolines serve as vital structural cores of numerous natural products and pharmaceuticals.[5] We envisioned that asymmetric dearomatization of pyrrole derivatives would provide an efficient and straightforward approach to diverse, highly functionalized pyrrolidines and pyrrolines.[6,7] It is particularly worth noting that in 2006, the Knochel group reported a Pd-catalyzed C−H functionalization of pyrroles, and the authors later found that a dearomatization process occurred when *N*-acyl-2,5-dimethylpyrrole derivatives were utilized.[8] Inspired by this work, we recently realized a Pd-catalyzed asymmetric intramolecular dearomative Heck reaction of pyrroles employing chiral phosphine ligands. Herein we report the results of this study.[9]

Scheme 1. Pd-Catalyzed Dearomative Heck Reactions of Indole and Pyrrole Derivatives



Initially, we began our investigation by choosing *N*-(2-bromobenzoyl)-2,5-dimethylpyrrole (**1aa**) as a model substrate (Table 1). With $Pd(OAc)_2$ (5 mol %) as the palladium precursor and Cs_2CO_3 (1.2 equiv) as the base, the effects of

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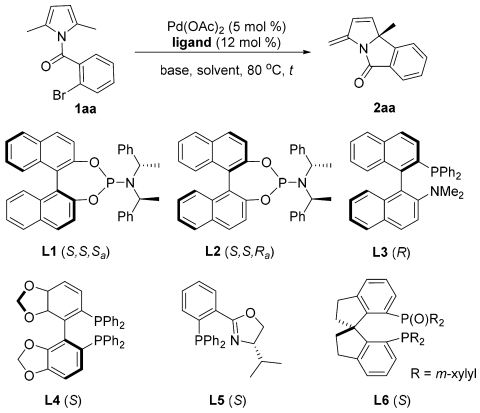
Table 1. Optimization of the Reaction Conditions[a]



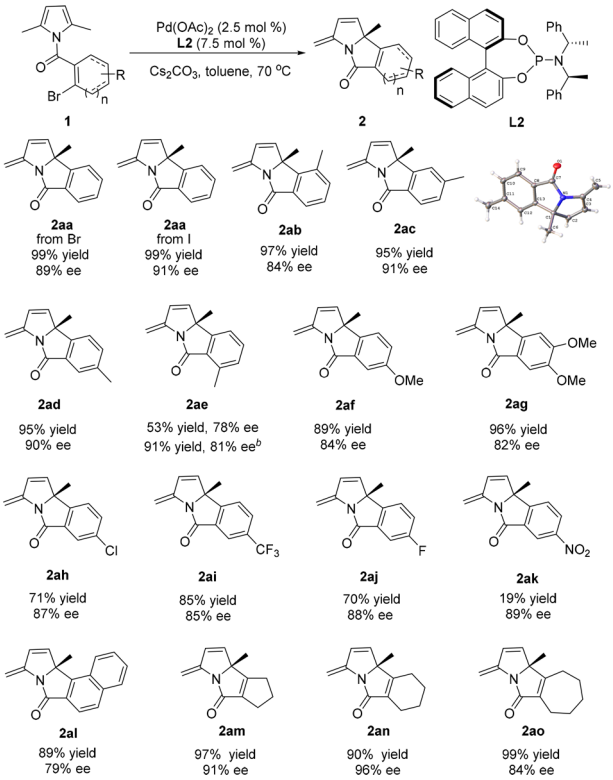
entry	ligand	base	solvent	t (h)	yields (%)[b] 2aa	yields (%)[b] 1aa	ee (%)[d]
1	**L1**	Cs_2CO_3	toluene	2	quant	trace	−76
2	**L2**	Cs_2CO_3	toluene	1	quant	trace	87
3	**L3**	Cs_2CO_3	toluene	4	96	trace	−1
4	**L4**	Cs_2CO_3	toluene	8	5	95	−15
5	**L5**	Cs_2CO_3	toluene	8	14	85	−4
6	**L6**	Cs_2CO_3	toluene	8	31	67	1
7	**L2**	K_3PO_4	toluene	1	88	7	89
8	**L2**	^{t}BuOK	toluene	1	trace	7	–
9	**L2**	K_2CO_3	toluene	1	quant	trace	85
10	**L2**	DIPEA	toluene	1	72	31	80
11	**L2**	Cs_2CO_3	DCE	1	quant	trace	61
12	**L2**	Cs_2CO_3	dioxane	1	quant	trace	85
13	**L2**	Cs_2CO_3	^{t}BuOH	1	96	trace	83
14	**L2**	Cs_2CO_3	*o*-xylene	1	quant	trace	86
15[e]	**L2**	Cs_2CO_3	toluene	1	31	70	83
16[f]	**L2**	Cs_2CO_3	toluene	1	quant	trace	88
17[f,g]	**L2**	Cs_2CO_3	toluene	1	99[c]	trace	89
18[g,h]	**L2**	Cs_2CO_3	toluene	4	46[c]	N.D.[i]	86

[a]Reaction conditions: **1aa** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), ligand (0.024 mmol), and base (0.24 mmol) in toluene (1.0 mL) at 80 °C. [b]Determined by ^{1}H NMR analysis using CH_2Br_2 (0.2 mmol) as an internal standard. [c]Isolated yield. [d]Determined by HPLC. [e]**L2** (0.01 mmol). [f]$Pd(OAc)_2$ (0.005 mmol), **L2** (0.015 mmol). [g]At 70 °C. [h]$Pd(OAc)_2$ (0.002 mmol), **L2** (0.005 mmol). [i]N.D. = not detected.

different ligands were first examined in toluene at 80 °C. The utilization of either diastereoisomer of the Feringa ligand (**L1** or **L2**) led to the desired product **2aa** in quantitative yield but with opposite absolute configurations, and **L2** gave better enantiocontrol (87% ee) (entries 1 and 2). When (*R*)-MAP (**L3**) was utilized, **2aa** could be obtained in 96% yield, albeit in nearly racemic form (entry 3). Notably, the reactions with (*S*)-Segphos (**L4**), (*S*)-PHOX (**L5**), and (*R*)-Xyl-SDP(O) (**L6**) as ligands provided **2aa** in low yields with poor enantioselectivity, while the substrates could be recovered with good mass balance (entries 4−6). Subsequently, various bases were tested with **L2** as the ligand (entries 7−10). It was found that the reaction using K_2CO_3 gave results similar to those with Cs_2CO_3, whereas a relatively lower yield was obtained with K_3PO_4. It is worth noting that the desired reaction was completely shut down when ^{t}BuOK was used. No better results in terms of enantioselectivity were obtained by using different solvents such as dioxane, ^{t}BuOH, and *o*-xylene (entries 11−14). When the **L2**/$Pd(OAc)_2$ ratio was lowered to 1:1, the NMR yield of **2aa** decreased to 31% (entry 15). It seemed that excess ligand was necessary because of oxidation of the ligand. Fortunately, the enantioselectivity improved slightly without a reduction in the efficiency when a lower catalyst loading (2.5 mol %) was employed (entry 16). Lowering the temperature to 70 °C afforded **2aa** in 99% yield with 89% ee. However, a further decrease in the loading of $Pd(OAc)_2$ to 1 mol % resulted in a significant decrease in the yield of **2aa** (46%) even with an extended reaction time (entry 18). Consequently, the optimized conditions were as follows: $Pd(OAc)_2$ (2.5 mol %), (S,S,R_a)-Feringa ligand (7.5 mol %), and Cs_2CO_3 (1.2 equiv) in toluene at 70 °C (entry 17).

With the optimized conditions in hand, we then studied the substrate scope of the reaction (Scheme 2). First, comparable

Scheme 2. Substrate Scope: Variation on the Aryl and Alkenyl Bromides[a]



[a]Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (0.005 mmol), **L2** (0.015 mmol), and Cs_2CO_3 (0.24 mmol) in toluene (1.0 mL) at 70 °C. [b]$Pd(OAc)_2$ (0.01 mmol), **L2** (0.03 mmol).

results (99% yield, 91% ee) were obtained using the corresponding iodide substrate. After that, a series of pyrrole substrates possessing electronically and sterically diverse *o*-bromobenzoyl groups were tested. Substrates decorated with a methyl group at each position on the benzoyl group were converted to their desired products with good results (91−97% yield, 81−91% ee) (**2ab**−**ae**). Sterically hindered substrate **1ab** was found to be tolerated well in this reaction (**2ab**, 97% yield, 84% ee). Dearomatized product **2ae** was obtained in 91% yield with 81% ee by improving the catalyst loading. Substrates with one or two electron-donating groups furnished the products in excellent yields and enantioselectivity (**2af**, 89% yield, 84% ee; **2ag**, 96% yield, 82% ee). A chloro substituent was also

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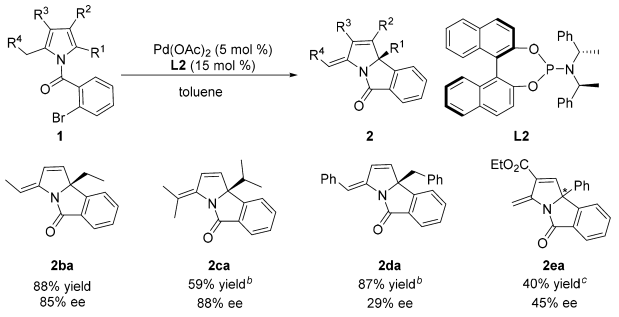
compatible with this reaction (**2ah**, 71% yield, 87% ee), and the Cl in the product would offer a handle for subsequent cross-coupling reactions. Aryl bromides bearing an electron-withdrawing substituent (CF_3, F, NO_2) at the *para* position led to decreased yields (**2ai**–**ak**) but comparable enantioselectivity (85–89% ee). Notably, the naphthyl group was also compatible, and the desired product **2al** was obtained in 89% yield with 79% ee. It is worth noting that cycloalkenyl *N*-acylpyrroles with different-sized rings also afforded the desired products in excellent yields and enantioselectivity (90–99% yield, 84–96% ee) (**2am**–**ao**). The absolute configuration of **2ac** was determined as *R* by X-ray crystallographic analysis of an enantiopure sample. The absolute configurations of other products were assigned by analogy.

Next, the effects of various substituents on the pyrrole ring were also investigated (Scheme 3). When the two methyl groups on the pyrrole ring were changed to ethyl or isopropyl groups, the desired products were obtained in reasonable yields with excellent enantioselectivity (**2ba**, 88% yield, 85% ee; **2ca**, 59% yield, 88% ee). When the dibenzyl-substituted substrate was used, the corresponding product was obtained in good yield but with low enantioselectivity (**2da**, 87% yield, 29% ee). When a trisubstituted pyrrole substrate was tested, the dearomatized product **2ea** was obtained in 40% yield with 45% ee.

Scheme 3. Substrate Scope: Variation on the Pyrrole Ring[a]



[a]Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), **L2** (0.03 mmol), and Cs_2CO_3 (0.24 mmol) in toluene (1.0 mL) at 70 °C. [b]**1** (0.1 mmol), $Pd(OAc)_2$ (0.005 mmol), **L2** (0.015 mmol), and Cs_2CO_3 (0.12 mmol) in toluene (1.0 mL) at 70 °C. [c]**1ea** (0.2 mmol) with DIPEA (0.4 mmol) instead of Cs_2CO_3 in toluene (1.0 mL) at 100 °C.

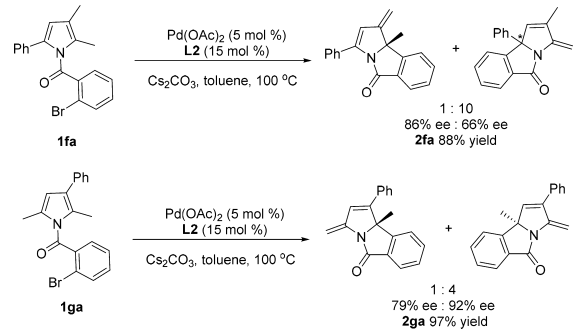
For substrates bearing multiple reaction sites, there will be regioselectivity issues. For substrate **1fa**, the reaction favored the formation of the product with an exocyclic enamine moiety (**2fa**, 1:10). For substrate **1ga**, the reaction preferred to occur at the less sterically hindered site (**2ga**, 1:4) (Scheme 4).

To demonstrate the practicality of this reaction further, a gram-scale reaction was carried out (Scheme 5). The intramolecular dearomatization of **1ac** (3.5 mmol) proceeded to afford **2ac** in 97% yield with 87% ee.

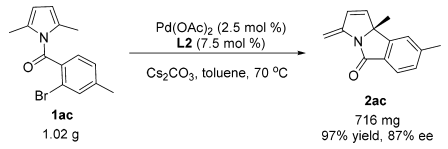
To test the utility of this method, transformations of the products were performed (Scheme 6). Product **2ac** underwent a hydroboration–oxidation reaction to afford **3ac** in 65% yield. Dearomatized product **2af** was transformed to **4af** by the Sonogashira reaction with ethynyltriisopropylsilane. It is worth noting that no erosion of enantiomeric purity was detected in either case.

In summary, we have developed the first Pd-catalyzed asymmetric intramolecular dearomatization of pyrroles via a Heck reaction. The reaction in general proceeded smoothly with excellent yields and enantioselectivity. A series of enantiomerically enriched pyrrolines bearing a quaternary stereogenic center were obtained efficiently and underwent useful transformations. Further studies on the application of this method in organic synthesis are currently underway in our laboratory.

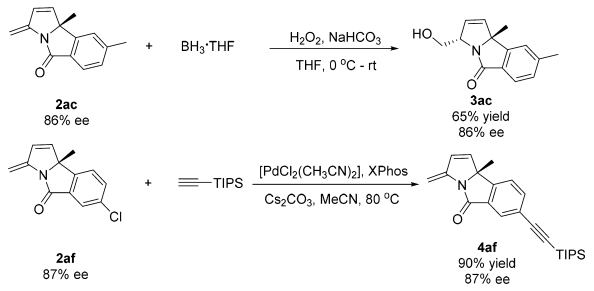
Scheme 4. Substrates with Multiple Reaction Sites



Scheme 5. Gram-Scale Reaction



Scheme 6. Transformations of the Products



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03425.

Experimental procedures, compound characterization data, and X-ray data for **2ac** (PDF)

Accession Codes

CCDC 1870088 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*slyou@sioc.ac.cn

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ORCID

Shu-Li You: 0000-0003-4586-8359

Notes

The authors declare no competing financial interest.

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