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Highly Regio- and Enantioselective Synthesis of Polysubstituted 2*H*-Pyrroles via Pd-Catalyzed Intermolecular Asymmetric Allylic Dearomatization of Pyrroles

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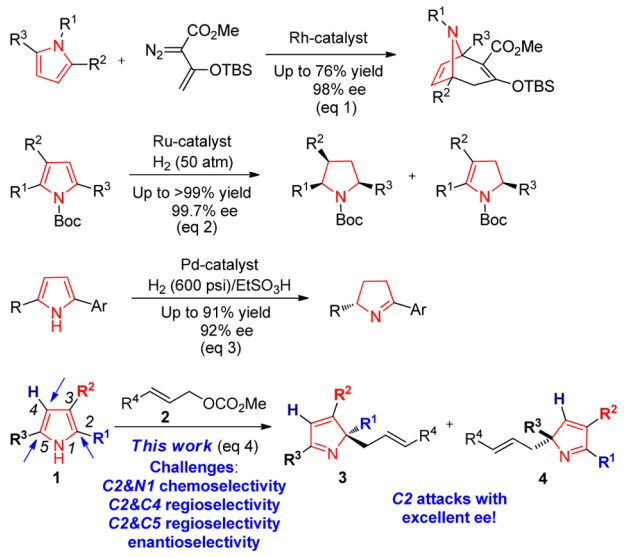
Supporting Information

ABSTRACT: A highly efficient synthesis of chiral polysubstituted 2*H*-pyrrole derivatives via a Pd-catalyzed intermolecular asymmetric allylic dearomatization reaction of pyrroles is presented. With the commercially available palladium precursor and chiral ligand, the polysubstituted 2*H*-pyrrole products containing a chiral quaternary carbon center were obtained with up to 97% ee and >95/5 regioselectivity.

As one of the most important electron-rich heterocycles, the pyrrole moiety is embedded in numerous biologically active natural products and pharmaceutical agents.[1] However, the documented enantioselective Friedel−Crafts type alkylation reactions of pyrroles are much fewer than those of indoles,[2] likely due to the regioselectivity issue caused by the similar nucleophilicity between the 2- and 3-positions of pyrroles.[3] In this regard, rare examples were reported using electron-rich pyrroles as *C*-nucleophiles in transition-metal-catalyzed allylic alkylation reactions,[4−6] although electron-deficient pyrroles have been well demonstrated to be *N*-nucleophiles over the past decade.[7] In 2006, Bandini, Umani-Ronchi, and their co-workers reported the first example of a Pd-catalyzed intramolecular asymmetric Friedel−Crafts type allylic alkylation reaction of pyrroles.[5a] Later, Du and co-workers disclosed the first Pd-catalyzed intermolecular asymmetric Friedel−Crafts type allylic alkylation reaction of pyrroles with a novel olefin-phosphine ligand.[6a,b]

In addition to the above elegant studies, pyrroles can also serve as prochiral nucleophiles in catalytic asymmetric dearomatization reactions, furnishing various highly functionalized pyrrolines or pyrrolidines.[8,9] Recently, we described efficient syntheses of chiral spiro-2*H*-pyrroles via an Ir-catalyzed intramolecular asymmetric allylic dearomatization reaction of pyrroles.[8] The dearomatization was achieved in excellent regio- and enantioselective control due to the intramolecular design which led to the reduction of the number of possible transition states and ring-size directed reactivity. However, the reactivity and selectivity toward an intermolecular reaction remain unsettled problems. Notably, [4 + 3] cycloaddition and hydrogenation reactions have been proven successful for the intermolecular asymmetric dearomatization of pyrroles.[10−12] In 2007, Reddy and Davies reported an elegant synthesis of chiral tropanes via Rh-catalyzed [4 + 3] cycloaddition from simple pyrroles (eq 1, Scheme 1).[10a] Soon after, Kuwano and co-workers reported the Ru-catalyzed asymmetric hydrogenative dearomatization of 2,3,5-trisubstituted pyrroles, providing a straightforward route for the synthesis of 4,5-dihydropyrroles and pyrrolidines (eq 2, Scheme 1).[11] Very recently, Zhou, Fan, and their co-workers presented an efficient asymmetric construction of chiral 1-pyrrolines via Pd-catalyzed partial hydrogenation of simple pyrroles (eq 3, Scheme 1).[12] With a Brønsted acid as an activator, chiral 2,5-disubstituted 1-pyrrolines were obtained with excellent ee. Nevertheless, the enantioselective intermolecular alkylative dearomatization of pyrroles is rare and challenging due to the multiselectivity issues including the chemoselectivity (C2 and N1), regioselectivity (C2 and C4, C2 and C5), and enantioselectivity (eq 4, Scheme 1). Herein, for the first time we report a highly regio- and enantioselective synthesis of polysubstituted 2*H*-pyrroles containing a chiral quaternary carbon center via a Pd-catalyzed intermolecular asymmetric allylic dearomatization reaction of multisubstituted pyrroles (eq 4, Scheme 1).

Scheme 1. Transition-Metal-Catalyzed Intermolecular Asymmetric Dearomatization Reactions of Pyrroles



At the outset, 2,5-dimethyl-pyrrole (**1a**) and cinnamyl carbonate (**2a**) were chosen as the model substrates to

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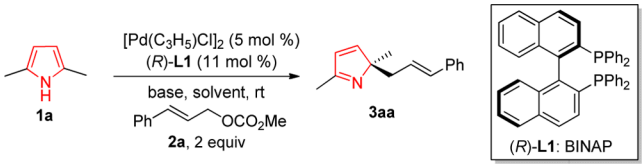
investigate the reaction conditions. In the presence of 5 mol % of $[Pd(C_3H_5)Cl]_2$, 11 mol % of (*R*)-BINAP,[13] and 1.0 equiv of Cs_2CO_3, the reaction of **1a** and **2a** in dioxane for 4 h gave 2*H*-pyrrole **3aa** in 69% yield and 83% ee (entry 1, Table 1).

Table 1. Investigation of Reaction Conditions[a]



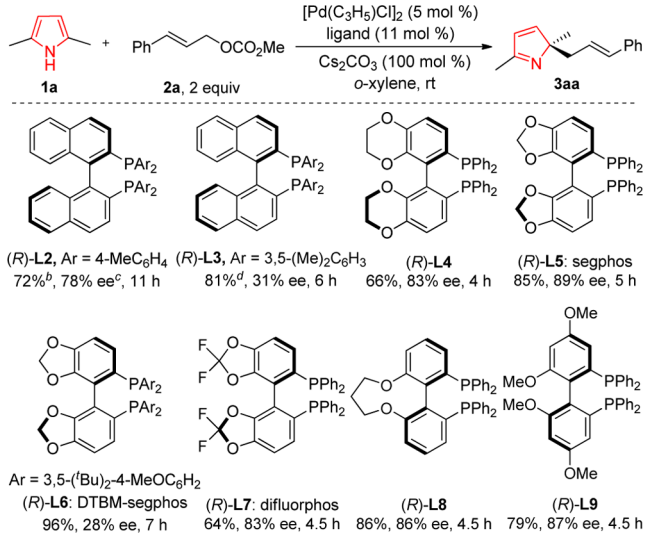
entry	base	solvent	*t* (h)	yield (%)[b]	ee (%)[c]
1	Cs_2CO_3	dioxane	4	69	83
2	K_2CO_3	dioxane	11	50	78
3	Na_2CO_3	dioxane	16	35	70
4	Li_2CO_3	dioxane	16	30	70
5	K_3PO_4	dioxane	16	35	75
6	Et_3N	dioxane	22	70	79
7	DBU	dioxane	22	68	79
8	–	dioxane	22	71	77
9	Cs_2CO_3	THF	12	35	70
10	Cs_2CO_3	DCE	12	24	46
11	Cs_2CO_3	toluene	7	82	81
12	Cs_2CO_3	*o*-xylene	7	78	83
13	Cs_2CO_3	cyclohexane	12	67	76

[a]Reaction conditions: 5 mol % of $[Pd(C_3H_5)Cl]_2$, 11 mol % of (*R*)-**L1**, 0.2 mmol of **1a**, 0.4 mmol of **2a**, and 0.2 mmol of base in 2.0 mL of solvent at rt. [b]Isolated yield. [c]Determined by HPLC analysis.

Encouraged by these results, further optimization of the reaction conditions was carried out. Various inorganic and organic bases such as K_3PO_4, K_2CO_3, Na_2CO_3, Li_2CO_3, Et_3N, and DBU were screened (entries 2–7, Table 1), and Cs_2CO_3 was found to be the optimal base. Notably, the reaction also occurred smoothly with slightly decreased ee in the absence of an additional base (entry 8, Table 1). Next, investigation of various solvents (entries 9–13, Table 1) led to the identification of *o*-xylene as being ideal (78% yield, 83% ee, entry 12, Table 1). Several commercially available chiral ligands were then tested (Scheme 2).[14] Surprisingly, the increase in the steric hindrance of the aromatic substituents on the phosphine led to the decreased ee of **3aa** (**L2**–**L3**, Scheme 2). Then, examination of biphenyl type axially chiral bisphosphine ligands disclosed that (*R*)-segphos (**L5**) was the best choice for the reaction process (**L4**–**L9**, Scheme 2). Interestingly, the same steric effect of the chiral phosphine ligands was also observed in the segphos series (**L5**–**L6**, Scheme 2). According to the observations made in the optimization studies, the best conditions were identified as the following: reaction of **1a** and **2a** in *o*-xylene (0.1 M) with 5 mol % of $[Pd(C_3H_5)Cl]_2$, 11 mol % of (*R*)-**L5**, and 1.0 equiv of Cs_2CO_3 at rt. Under these conditions, 2*H*-pyrrole **3aa** was obtained in 85% yield and 89% ee (Scheme 2).

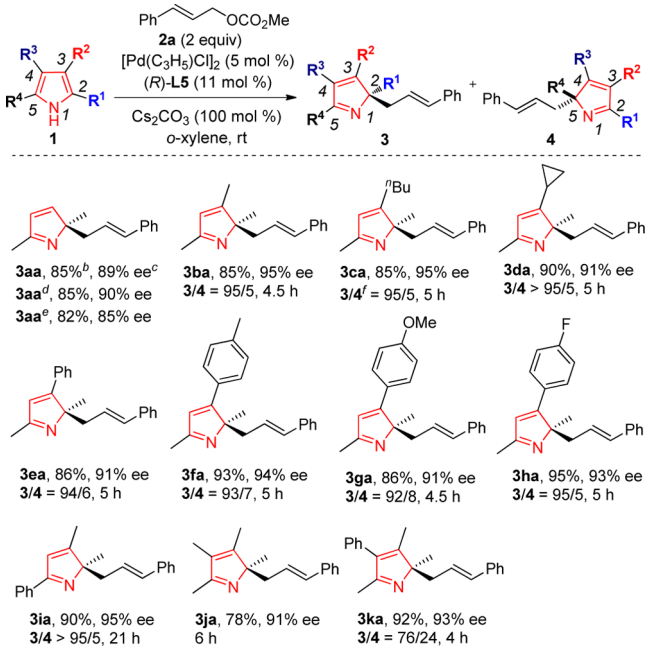
With the optimized reaction conditions in hands, various pyrrole derivatives **1b**–**k** were reacted with cinnamyl carbonate (**2a**) to examine the generality of the dearomatization process (Scheme 3). Notably, the reaction of methyl (1-phenylallyl) carbonate and **1a** under the optimized reaction conditions for 3.5 h gave product **3aa** in 82% yield with 85% ee, which are similar to the results with cinnamyl carbonate. These results suggest that the reaction proceeds through the Pd-*pi*-allyl

Scheme 2. Investigation of Chiral Ligands[a]



[a]Reaction conditions: 5 mol % of $[Pd(C_3H_5)Cl]_2$, 11 mol % of ligand, 0.2 mmol of **1a**, 0.4 mmol of **2a**, and 0.2 mmol of Cs_2CO_3 in 2.0 mL of *o*-xylene at rt. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Toluene was used as the solvent.

Scheme 3. Reaction Substrate Scope: Pyrroles[a]



[a]Reaction conditions: 5 mol % of $[Pd(C_3H_5)Cl]_2$, 11 mol % of (*R*)-**L5**, 0.2 mmol of **1**, 0.4 mmol of **2a**, and 0.2 mmol of Cs_2CO_3 in 2.0 mL *o*-xylene at rt. The ratio of **3**/**4** was determined by ^1H NMR analysis of the crude reaction mixture. [b] Isolated yield of **3** and **4**. [c] Ee of **3** was determined by HPLC analysis. [d] Reaction conditions: 1 mol % of $[Pd(C_3H_5)Cl]_2$, 2.2 mol % of (*R*)-**L5**, 0.5 mmol of **1a**, 1.0 mmol of **2a**, and 0.5 mmol of Cs_2CO_3 in 5.0 mL of *o*-xylene at rt for 5 h. [e] Methyl (1-phenylallyl) carbonate was used as the electrophile. [f] Determined by GC analysis of the crude reaction mixture.

intermediate. When 2,3,5-trimethyl-pyrrole (**1b**) was used, the reaction occurred smoothly in excellent regioselectivity (95/5) and enantioselectivity (95% ee) to give **3ba**. The excellent regioselectivity favoring the attack at the more sterically

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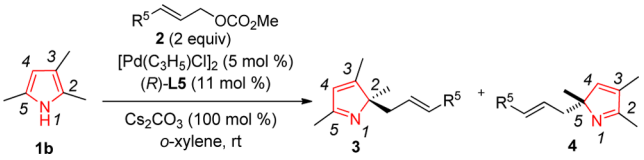
hindered C2 of **1b** might be attributed to the resonance and stereoelectronic effects, which make C2 more nucleophilic.[15] By switching the 3-methyl substituent to the *n*-butyl (**1c**), cyclopropyl (**1d**), or phenyl (**1e**) group, the reaction also proceeded smoothly to give the corresponding desired products in excellent regio- and enantioselectivity (85−90% yield, 94/6 − >95/5 r.r., 91−95% ee, **3ca**−**3ea**, Scheme 3). 3-Aryl 2,5-dimethyl-pyrrole containing an electron-donating group (*p*-Me, *p*-OMe; **1f**−**1g**) or an electron-withdrawing group (*p*-F; **1h**) on the benzene ring led to the corresponding dearomatized products in excellent regioselectivity (92/8−95/5), yields and enantioselectivity (86−95% yield, 91−94% ee, **3fa**−**3ha**, Scheme 3). Interestingly, when 2,3-dimethyl-5-phenyl-pyrrole (**1i**) was utilized, the reaction occurred smoothly in excellent yield and ee with exclusive formation of **3ia** (90% yield, 95% ee, Scheme 3). Moreover, the steric bulky 2,3,4,5-tertmethyl-pyrrole (**1j**) was well tolerated in the reaction (78% yield, 91% ee, **3ja**, Scheme 3). It is noteworthy that the 2,4,5-trimethyl-3-phenyl pyrrole (**1k**) could also undergo the dearomatization reaction with moderate regioselectivity and excellent enantioselectivity [**3ka**/**4ka** = 76/24, 93% ee (**3ka**), Scheme 3]. Gratifyingly, when the reaction was run with 1 mol % of $[Pd(C_3H_5)Cl]_2$ and 2.2 mol % of (*R*)-**L5** on 0.5 mmol scale, **3aa** was obtained with an excellent yield and ee (85% yield, 90% ee, Scheme 3). The structures of all the major regioisomers (**3**) were confirmed unambiguously by 2D-NOESY analysis.[16]

In addition, reactions of **1b** with various substituted allylic carbonates **2** were also carried out. The results are summarized in Table 2. Reactions of allylic carbonates containing *para*-methylphenyl and *para*-methoxyphenyl groups (**2b**−**c**) occurred smoothly to give the desired products (**3bb**−**bc**) in good yields with excellent enantioselectivity (74−84% yield, 93/7−94/6 r.r., 92−93% ee, entries 2−3, Table 2). Cinnamyl carbonates containing an electron-withdrawing group (*p*-F, *p*-Cl, *p*-Br; **2d**-**f**) could be well reacted to afford the dearomatized products (**3bd**−**bf**) in good yields with excellent regio- and enantioselectivity (71−78% yield, 93/7−95/5 r.r., 88−92% ee, entries 4−6, Table 2). The reaction of 2-thienyl allylic carbonate (**2g**) with **1b** afforded product **3bg** in 77% yield with 97% ee (94/6 r.r., entry 7, Table 2). When crotyl carbonate (**2h**) and allylic carbonate (**2i**) were used, the reaction also proceeded smoothly in moderate yields with excellent ee (57−67% yield, >95/5 r.r., 88−94% ee, entries 9−10, Table 2). Notably, the reaction of **2g** with **1b** on the 1.6 mmol scale gave **3bg** in 75% yield with 97% ee (entry 8, Table 2). The structure and stereochemistry of the product were confirmed unambiguously by an X-ray crystallographic analysis of a crystal of enantiopure **3bg**. The absolute configuration was determined as (*R*).

To test the practicality of the methodology, a gram-scale synthesis of chiral 2*H*-pyrrole was carried out. The intermolecular allylic dearomatization of **1i** and **2a** on the 3.8 mmol scale gave the desired product **3ia** in 88% yield and 92% ee (Scheme 4).

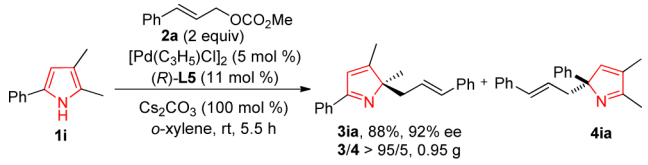
Table 2. Reaction Substrate Scope: Electrophiles[a]



entry	2, R^5	*t* (h)	3/4[b]	product	yield (%)[c]	ee (%)[d]
1	**2a**, Ph	4.5	95/5	**3ba**	85	95
2	**2b**, 4-Me-C_6H_4	5	94/6	**3bb**	84	92
3	**2c**, 4-MeO-C_6H_4	5	93/7	**3bc**	74	93
4	**2d**, 4-F-C_6H_4	5	93/7	**3bd**	78	91
5	**2e**, 4-Cl-C_6H_4	5	93/7	**3be**	71	92
6	**2f**, 4-Br-C_6H_4	5	95/5	**3bf**	74	88
7	**2g**, 2-thienyl	5	94/6	**3bg**	77	97
8[e]	**2g**, 2-thienyl	5.5	94/6	**3bg**	75	97
9[f]	**2h**, Me	5	>95/5	**3bh**	67	94
10[f]	**2i**, H	5	>95/5	**3bi**	57	88

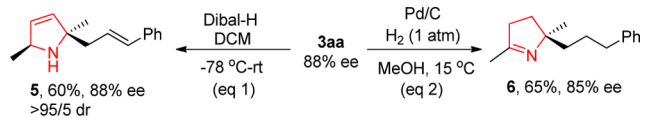
[a]Reaction conditions: 5 mol % of $[Pd(C_3H_5)Cl]_2$, 11 mol % of (*R*)-**L5**, 0.2 mmol of **1b**, 0.4 mmol of **2**, and 0.2 mmol of Cs_2CO_3 in 2.0 mL of *o*-xylene at rt. [b]Determined by ^1H NMR analysis of the crude reaction mixture. [c]Isolated yield of **3** and **4**. [d]Ee of **3** was determined by HPLC analysis. [e]The reaction was performed on 1.6 mmol scale. [f]The ratio of **3**/**4** was determined by GC analysis of the crude reaction mixture.

Scheme 4. A Gram-Scale Synthesis of 3ia



To further demonstrate the synthetic utility of the newly developed methodology, several transformations of the 2*H*-pyrrole derivatives were carried out. The imine group could be easily reduced with Dibal-H, affording chiral pyrroline **5** in 60% yield and excellent diastereoselectivity (>95/5 dr, 88% ee, eq 1, Scheme 5). Selective hydrogenation of the C=C bond was achieved when Pd/C was chosen as the catalyst, providing the imine derivative **6** in 65% yield and 85% ee (eq 2, Scheme 5).[17] No notable loss of the enantiomeric purity was observed in both cases.

Scheme 5. Product Transformation



In summary, we have developed a highly efficient synthesis of enantioenriched polysubstituted 2*H*-pyrrole derivatives via the first Pd-catalyzed intermolecular asymmetric allylic dearomatization reaction of pyrroles. With the commercially available palladium precursor and chiral ligand **L5**, the substituted 2*H*-pyrrole products containing a chiral quaternary carbon center were obtained with up to 97% ee under mild reaction conditions. Interestingly, the reactions occurred smoothly and good to excellent regioselectivities were obtained when the tri- and tetra-substituted pyrrole derivatives were used. Moreover, to the best of our knowledge, it is the first example involving the multisubstituted pyrroles as prochiral nucleophiles in Pd-catalyzed asymmetric allylic alkylation reactions. Further applications of the highly enantioenriched 2*H*-pyrrole derivatives and investigation of the reaction mechanism are currently underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analysis data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) For details, see the Supporting Information.

(17) The ee and relative configuration of product **5** were determined by the corresponding acetyl protected derivative **7**. For details, see the Supporting Information.