Communication

Enantioselective Arylative Dearomatization of Indoles via Pd-catalyzed Intramolecular Reductive Heck Reactions

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Enantioselective Arylative Dearomatization of Indoles via Pd-catalyzed Intramolecular Reductive Heck Reactions

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Supporting Information Placeholder

ABSTRACT: A highly enantioselective intramolecular arylative dearomatization of indoles was developed via palladium-catalyzed reductive Heck reactions. The new strategy led to a series of optically active indolines bearing C2-quaternary stereocenters in modest to good yields and excellent enantioselectivities (up to 99% ee).

Enantioselective dearomatization of arenes has emerged as an important transformation approaching a variety of optically active alicyclic systems, which constitute key moieties of bioactive natural products and pharmaceuticals.[1] Thanks to the effort devoted to this field, many elegant catalytic asymmetric dearomatization (CADA) reactions have been developed, such as the asymmetric hydrogenation of heteroarenes,[2] oxidative dearomatizations and alkylative dearomatizations.[1d,e] In contrast, asymmetric arylative dearomatization has met with less success and still remained a challenging task. Among the few known methods, palladium-catalyzed cross-coupling of two aryl moieties that pioneered by the groups of Buchwald, Bedford, and You has been demonstrated as a reliable approach toward this challenge.[3,4] A few examples have appeared in their enantioselective versions. In 2009, Buchwald and co-workers developed an elegant Pd-catalyzed intramolecular enantioselective dearomatization reaction of anilines, delivering chiral 3,3-disubstituted-3a*H*-indoles in excellent enantioselectivities.[3a] Soon after, Buchwald and You independently reported arylative dearomatizations of phenols and indoles, while quite a few examples were tested in the enantioselective fashion.[3d,e] Notably, very recently, success has been achieved for the asymmetric arylative dearomatization of phenols by Tang and co-workers, accessing chiral phenanthrenone derivatives in high enantioselectivities.[3h] Obviously, all the aforementioned examples covering the racemic versions are only limited to aromatic substrates bearing free N-H or O-H bonds, such as aniline, indole, pyrrole, and phenol. Indeed, keto-enol tautomerism of such aromatic compounds under basic condition facilitates the dearomatization and subsequent carbon-carbon cross-coupling under Pd(0) catalyst. Undoubtedly, novel asymmetric dearomative arylation process based on the development of new strategies is highly attractive.

In recent years, transition-metal-catalyzed direct arylation of C_{Ar}-H bonds of (hetero)arenes offers an efficient access to biaryl compounds,[5] where Heck-type arylation has been proposed as a possible mechanism.[6] We envisaged that new arylative dearomatization reaction might be realized through an intramolecular reductive Heck reaction,[7] if suitable substituent was introduced onto the reactive site to prevent biaryl compound formation, and meanwhile the generated alkyl-palladium intermediate was trapped by proper hydride sources. Following this hypothesis, we investigated the intramolecular asymmetric arylative dearomatization of *N*-substituted indoles via palladium-catalyzed reductive Heck reactions (Figure 1).[8,9] The new dearomatization strategy provides a facile approach to chiral indolines bearing C2-quaternary stereocenters,[10] which are frequently occurring core structures of bioactive natural products, such as trigonoliimine C,[11] (-)-isatisine A,[12] and hinckdentine A.[13] Herein, we wish to present our findings of highly enantioselective Pd-catalyzed arylative dearomatization of a variety of indole derivatives.

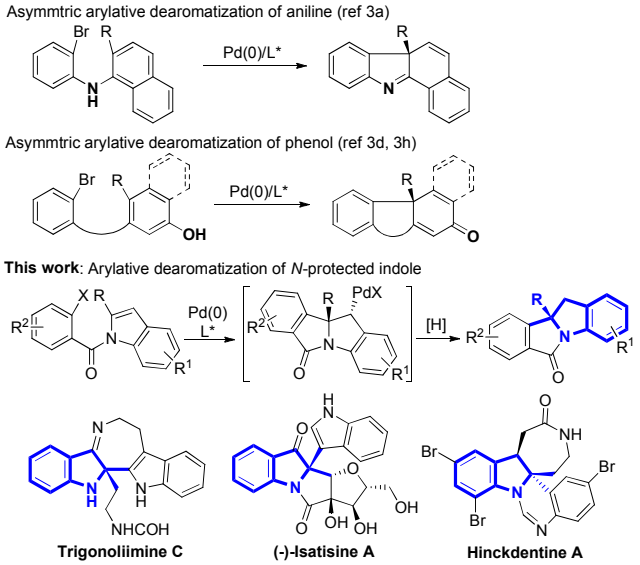
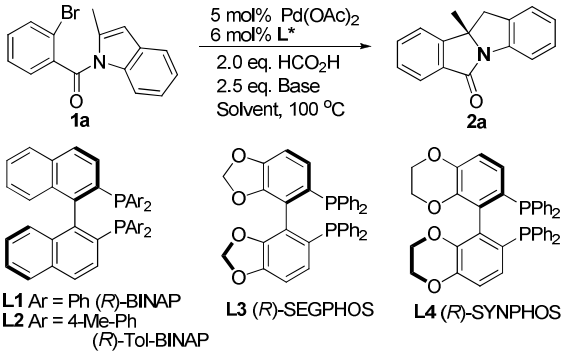


Figure 1. Methods for palladium-catalyzed asymmetric arylative dearomatizations and selected natural products containing C2-quaternary substituted indoline framework

At the outset, the asymmetric reductive Heck reaction of *N*-(2-bromobenzoyl)-2-methylindole **1a** was studied with HCO_2H/NEt_3 as a hydride source, $Pd(OAc)_2$ as a catalyst, and

(*R*)-BINAP as a ligand. As shown in Table 1, the reaction in THF or Toluene at 100 °C did not afford any arylative product (Table 1, entries 1-2). To our delight, the desired product **2a** was isolated in lower yields but with excellent enantioselectivities when the reactions were performed in CH_3CN or DCE (1,2-dichloroethane) (Table 1, entries 3-4). Gratifyingly, the yield was remarkably improved to 79% in methanol and the excellent enantioselectivity was retained (Table 1, entry 5). Comparable results were observed for reactions in EtOH and ^{i}PrOH (Table 1, entries 6-7). Other amines (TMEDA, DIPA, DABCO, and DBU) combined with HCO_2H were then examined as hydride sources in MeOH, which gave similar results as that with NEt_3 (Table 1, entries 8-11). However, the results were significantly improved when HCO_2Na was used as a hydride source, leading to product **2a** in 85% yield and 97% ee value (Table 1, entry 13). Subsequent ligand screening indicated that generally bidentate phosphines were efficient chiral ligands. The reactions with (*R*)-Tol-BINAP or (*R*)-SYNPHOS as ligands also provided indoline **2a** in good yields and excellent enantioselectivities, whereas relatively lower ee value was observed for (*R*)-SEGPHOS (Table 1, entries 14-16). Finally, lowering the temperature to 80 °C afforded **2a** in comparable results albeit with a longer reaction time (Table 1, entry 17). Therefore, the best results were obtained under the conditions: 5 mol% $Pd(OAc)_2$, 6 mol% (*R*)-BINAP, and 2.0 equiv. HCO_2Na in 2.0 mL methanol at 100 °C for 10 h.[14]

Table 1. Optimization of the reaction conditions[a]

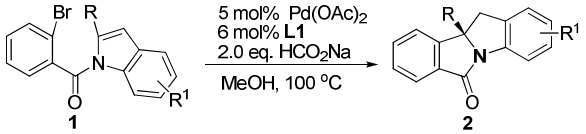


Entry	L*	Base	Solvent	Yield(%)[b]	Ee(%)[c]
1	**L1**	NEt_3	THF	<5	--
2	**L1**	NEt_3	Toluene	<5	--
3	**L1**	NEt_3	CH_3CN	36	96
4	**L1**	NEt_3	DCE	35	96
5	**L1**	NEt_3	MeOH	79	97
6	**L1**	NEt_3	EtOH	75	97
7	**L1**	NEt_3	^{i}PrOH	70	96
8	**L1**	TMEDA	MeOH	77	98
9	**L1**	DIPA	MeOH	80	97
10	**L1**	DABCO	MeOH	78	97
11	**L1**	DBU	MeOH	69	97
12[d]	**L1**	HCO_2NH_4	MeOH	80	93
13[d]	**L1**	HCO_2Na	MeOH	85	97
14[d]	**L2**	HCO_2Na	MeOH	82	97
15[d]	**L3**	HCO_2Na	MeOH	82	82
16[d]	**L4**	HCO_2Na	MeOH	81	98
17[d,e]	**L1**	HCO_2Na	MeOH	82	96

[a]Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), **L***(6 mol%), base (0.4 mmol), and the solvent (2.0 mL) indicated in a sealed Schlenk tube at 100 °C (oil bath) for 10 h. [b]Isolated yiled. [c]Determined by chiral HPLC. [d]In the absence of HCO_2H. [e]At 80 °C (oil bath) for 36 h.

Under the optimal reaction conditions, we then studied the scope of the reaction.[15] Substituent effect of indoles was examined and the results were shown in Table 2. Excellent enantioselectivities (92-99%) were exclusively observed for the new quaternary stereogenic centers generated from all the reactions. A range of C2-substituted indoles were well tolerated, showing a broad scope of the reaction. Modest to good yields and excellent enantioselectivities (over 97%) were obtained for the substrates bearing alkyl groups (methyl, benzyl, and cyclopropyl) (Table 2, entries 1, 2 and 16) or an ester group (Table 2, entry 3). The C2-substituted aromatic groups were also investigated (Table 2, entries 4-15), while the yields were influenced unfavorably by the steric effect. In comparison to the reactions of the substrates bearing *para*-substituted aryl groups, slightly lower yields were obtained for those containing *meta*-substituents on the benzene ring (Table 2, entries 10 and 11); and in particular, very poor yield (15%) was observed for the substrate **1l** with an *ortho*-methyl group (Table 2, entry 12). Likewise, yields were found to be a little lower for the substrates bearing electron-withdrawing substituents at the *para*-position on benzene ring (Table 2, entries 7-9). Notably, 2-naphthyl and heteroaromatic (2-furyl and 2-thienyl) groups were also tested in the reaction, affording the desired products in modest yields and excellent enantioselectivities (Table 2, entries 13-15). In addition, the influence of the substituted groups at C5 and C6 position of the indole ring was examined. Electron-donating groups furnished the arylation with good results in terms of yield and enantioselectivity (Table 2, entries 17 and 19-21). However, electron-withdrawing group was unfavorable for the reaction and the desired product were afforded in a relatively low yield but with excellent ee value (Table 2, entry 18). In addition, a novel pentacyclic chiral indoline **2v** was afforded in 55% yield and with 89% ee (Table 2, entry 22). It is worth noting that a gram-scale reaction of **1a**→**2a** was carried out to give the product in 81% yield and with 97% ee, showing the practice of this reaction (Eq. 1).

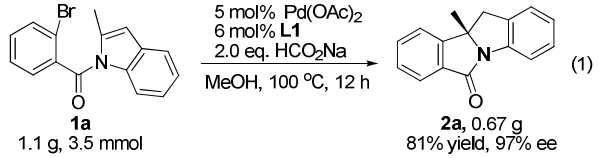
Table 2. Substituent effect of substrate **1**[a]



Entry	R, R[1]		Yield(%)[b]	Ee(%)[c]
1	Me, H (**1a**)	**2a**	85	97
2	Bn, H (**1b**)	**2b**	78	97
3	CO_2Me, H (**1c**)	**2c**	71	99
4	Ph, H (**1d**)	**2d**	81	97
5	4-MeO-C_6H_4, H (**1e**)	**2e**	88	92
6	4-Me-C_6H_4, H (**1f**)	**2f**	75	97
7	4-Cl-C_6H_4, H (**1g**)	**2g**	68	96

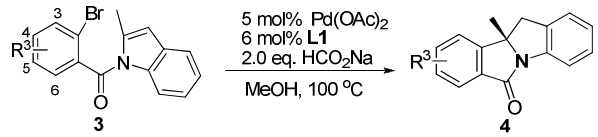
8	4-F-C_6H_4, H (**1h**)	**2h**	72	96
9	4-CF_3-C_6H_4, H (**1i**)	**2i**	64	98
10	3-Me-C_6H_4, H (**1j**)	**2j**	62	97
11	3-Cl-C_6H_4, H (**1k**)	**2k**	60	98
12	2-Me-C_6H_4, H (**1l**)	**2l**	15	94
13	2-Naphthyl, H (**1m**)	**2m**	68	97
14	2-Furyl, H (**1n**)	**2n**	67	98
15	2-Thienyl, H (**1o**)	**2o**	62	99
16	*c*-Propyl, 5-MeO (**1p**)	**2p**	89	97
17	Ph, 5-Me (**1q**)	**2q**	76	98
18	Ph, 5-Cl (**1r**)	**2r**	46	98
19	Ph, 5-MeO (**1s**)	**2s**	80	98
20	Ph, 5-^{i}Pr (**1t**)	**2t**	87	96
21	Ph, 6-MeO (**1u**)	**2u**	75	98
22	Ph, 6,7-$(CH)_4$ (**1v**)	**2v**	55	89

[a]Reactions conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), ligand **L1** (6 mol%), HCO_2Na (0.4 mmol) in MeOH (2.0 mL) at 100 °C (oil bath) for 16-36 h. [b]Isolated yield. [c]Determined by chiral HPLC.



The effect of substituents on the benzene ring of 2-bromobenzoyl was then investigated under the optimized reaction conditions. As shown in Table 3, desired products **4b**-**i** were obtained in modest to good yields and with excellent enantioselectivities for the reactions with substrates bearing either electron-donating or electron-withdrawing groups at the C4, C5, and C6 position (Table 3, entries 2-9). In contrast, substituent on C3 position of the bromobenzoyl moiety disfavored the reaction, owing to large steric hindrance. For example, the reaction of substrate **3a** containing a 3-methyl group occurred at 120 °C to afford the product **4a** in poor yield and with low ee value (Table 3, entry 1).

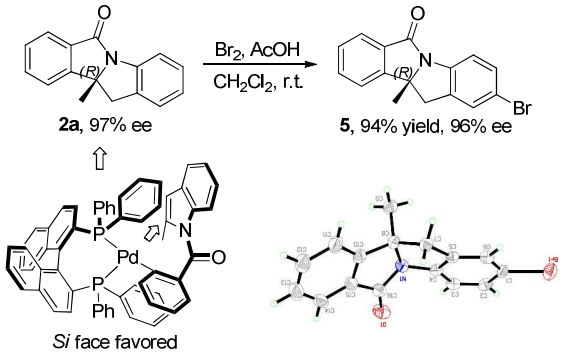
Table 3. Substituent effect of substrate **3**[a]



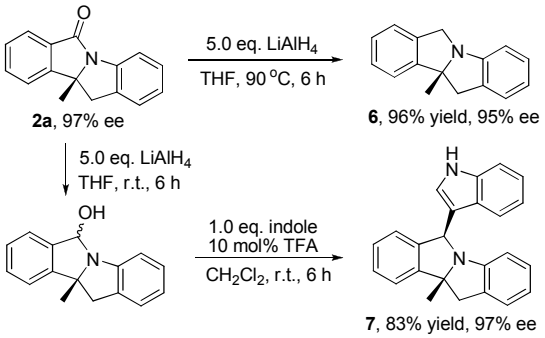
Entry	R^3	Product	Yield (%)[b]	Ee (%)[c]
1[d]	3-Me (**3a**)	**4a**	22	29
2	4-Me (**3b**)	**4b**	85	98
3	4-F (**3c**)	**4c**	73	97
4	5-MeO (**3d**)	**4d**	75	96
5	5-Me (**3e**)	**4e**	76	97
6	5-Cl (**3f**)	**4f**	73	99
7	5-F (**3g**)	**4g**	67	97
8	4,5-F_2 (**3h**)	**4h**	64	94
9	4,5-$(MeO)_2$ (**3i**)	**4i**	76	99

[a]Reactions conditions: **3** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), ligand **L1** (6 mol%), HCO_2Na (0.4 mmol) in MeOH (2.0 mL) at 100 °C (oil bath) for 10-16 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]At 120 °C (oil bath) for 20 h.

As shown in Scheme 1, the asymmetric induction model was proposed. The intramolecular aryl attack to indole was favored from Si face, leading to product **2a** in *R* configuration. This was consistent to the observed configuration of compound **5**, derived from the bromination of **2a**, based on the X-ray structural analysis of its single crystal. Subsequently, synthetic transformations of product **2a** were conducted (Scheme 2). A facile reduction of **2a** with $LiAlH_4$ in refluxing THF led to a tetracyclic indoline **6** in 96% yield and with 95% ee. However, the reduction occurred at room temperature furnished the corresponding hemiaminal, which was readily converted to adduct **7** as a single isomer in 83% yield and with complete preservation of enantiopurity by an acid-catalyzed addition of indole to the *in situ* formed iminium.



Scheme 1. Determination of the absolute configuration and the asymmetric induction model



Scheme 2. Synthetic transformations of product **2a**

In conclusion, we have developed a new strategy for the asymmetric arylative dearomatization of indoles via palladium-catalyzed reductive Heck reaction. A series of optically active tetracyclic indolines bearing C2-quaternary stereogenic centers were obtained in modest to good yields and with excellent enantioselectivities. The new methodology presented here offers new opportunities for the development of arylative dearomatization reactions. Investigations on further applications of this methodology in organic synthesis are currently underway in the laboratory.

ASSOCIATED CONTENT

Supporting Information

Full experimental and characterization data, including ^{1}H and ^{13}C NMR for all the new compounds, chiral HPLC spectra for the products, and crystal data are 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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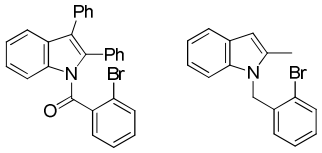
(14) No C7-arylation product was detected during optimization of the reaction conditions.

(15) The following substrates were failed to give the desired products under the optimal reaction conditions. 2,3-Diphenylindole-1*H*-indole was observed as the major byproduct for the former, while hydrodebromination reaction occurred for the latter.



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