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

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Supporting Information

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

Enantioselective dearomatization of arenes has emerged as an important transformation approaching a variety of optically active alicyclic systems that 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 remains a challenging task. Among the few known methods, palladium-catalyzed cross-coupling of two aryl moieties, which was 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 that delivers chiral 3,3-disubstituted-3a*H*-indoles with excellent enantioselectivities.[3a] Soon after, Buchwald and You independently reported arylative dearomatizations of phenols and indoles, and quite a few examples were tested in the enantioselective fashion.[3d,e] Notably, Tang and co-workers very recently achieved success in the asymmetric arylative dearomatization of phenols, providing access to chiral phenanthrenone derivatives with high enantioselectivities.[3h] Obviously, all of the aforementioned examples covering the racemic versions are limited only 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 conditions facilitates the dearomatization and subsequent carbon−carbon cross-coupling under Pd(0) catalysis. Undoubtedly, novel asymmetric dearomative arylation processes based on the development of new strategies would be highly attractive.

In recent years, transition-metal-catalyzed direct arylation of C_{Ar}−H bonds of (hetero)arenes has offered efficient access to biaryl compounds,[5] and Heck-type arylation has been proposed as a possible mechanism.[6] We envisaged that a new arylative dearomatization reaction might be realized through an intramolecular reductive Heck reaction[7] if a suitable substituent could be introduced at the reactive site to prevent biaryl compound formation and the generated alkylpalladium intermediate could be 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

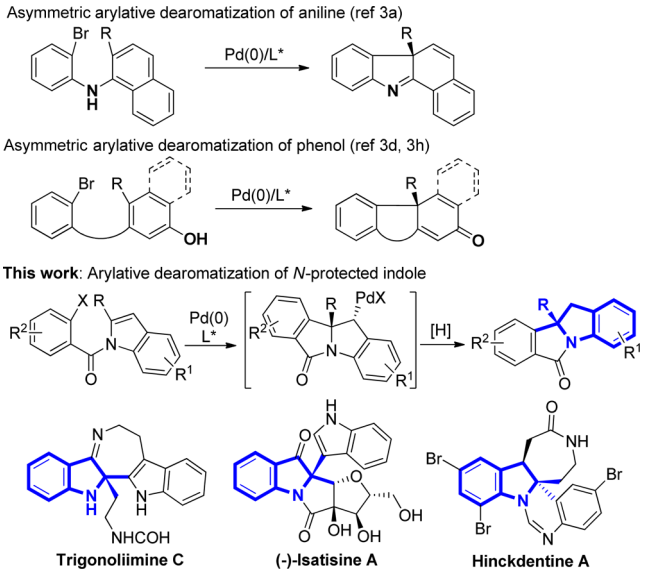

Figure 1. Methods for palladium-catalyzed asymmetric arylative dearomatizations and selected natural products containing a C2-quaternary substituted indoline framework.

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 present our findings on the highly enantioselective Pd-catalyzed arylative dearomatization of a variety of indole derivatives.

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 tetrahydrofuran (THF) or toluene at 100 °C did not afford any arylative product (entries 1 and 2). To our delight, the desired product **2a** was isolated in lower yield but with excellent enantioselectivity when the reaction was performed in CH_3CN

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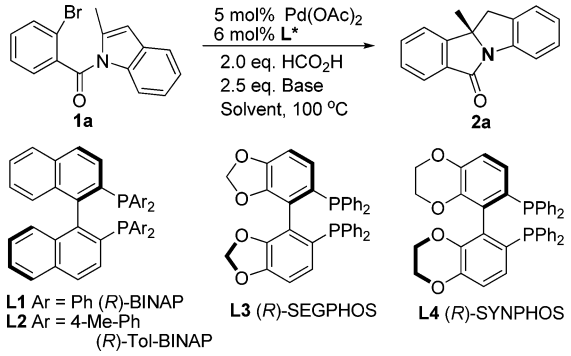
Table 1. Optimization of the Reaction Conditions[a]



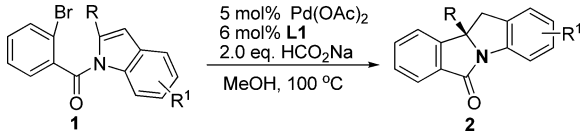
entry	L*	base	solvent	yield (%)[b]	ee (%)[c]
1	**L1**	NEt_3	THF	<5	–
2	**L1**	NEt_3	toluene	<5	–
3	**L1**	NEt_3	CH_3CN	36	96
4	**L1**	NEt_3	DCE	35	96
5	**L1**	NEt_3	MeOH	79	97
6	**L1**	NEt_3	EtOH	75	97
7	**L1**	NEt_3	^{i}PrOH	70	96
8	**L1**	TMEDA	MeOH	77	98
9	**L1**	DIPA	MeOH	80	97
10	**L1**	DABCO	MeOH	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 %), and base (0.4 mmol) in the indicated solvent (2.0 mL) in a sealed Schlenk tube at 100 °C (oil bath) for 10 h. [b]Isolated yields. [c]Determined by chiral HPLC. [d]In the absence of HCO_2H. [e]At 80 °C (oil bath) for 36 h.

or 1,2-dichloroethane (DCE) (entries 3 and 4). Gratifyingly, the yield was remarkably improved to 79% in methanol, and the excellent enantioselectivity was retained (entry 5). Comparable results were observed for reactions in EtOH and ^{i}PrOH (entries 6 and 7). Other amines (TMEDA, DIPA, DABCO, and DBU) combined with HCO_2H were then examined as hydride sources in MeOH and gave results similar to those with NEt_3 (entries 8–11). However, the results were significantly improved when HCO_2Na was used as the hydride source, as **2a** was obtained in 85% yield with 97% ee (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 with excellent enantioselectivities, whereas a relatively lower ee value was observed with (*R*)-SEGPHOS (entries 14–16). Finally, lowering the temperature to 80 °C afforded **2a** with comparable results, albeit with a longer reaction time (entry 17). Therefore, the best results were obtained using 5 mol % $Pd(OAc)_2$, 6 mol % (*R*)-BINAP, and 2.0 equiv HCO_2Na in 2.0 mL of methanol at 100 °C for 10 h.[14]

Under the optimal reaction conditions, we then studied the scope of the reaction.[15] The effect of indole substituents was examined, and the results are shown in Table 2. Excellent enantioselectivities (92–99%) were exclusively observed for the new quaternary stereogenic centers generated from all of the

Table 2. Effect of Indole Substituents[a]



entry	R, R^1 (**1**)	product	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]Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), ligand **L1** (6 mol %), and HCO_2Na (0.4 mmol) in MeOH (2.0 mL) at 100 °C (oil bath) for 16–36 h. [b]Isolated yields. [c]Determined by chiral HPLC.

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% ee) were obtained for substrates bearing alkyl groups (methyl, benzyl, and cyclopropyl) (entries 1, 2, and 16) or an ester group (entry 3). The C2-substituted aromatic groups were also investigated (entries 4–15), and the yields were influenced unfavorably by steric effects. In comparison with the reactions of the substrates bearing para-substituted aryl groups, slightly lower yields were obtained for those containing meta substituents on the benzene ring (entries 10 and 11), and a very poor yield (15%) was observed for substrate **1l** with an *o*-methyl group (entry 12). Likewise, the yields were found to be a little lower for the substrates bearing electron-withdrawing substituents at the para position on the benzene ring (entries 7–9). Notably, 2-naphthyl and hetero-aromatic (2-furyl and 2-thienyl) groups were also tested in the reaction and afforded the desired products in modest yields with excellent enantioselectivities (entries 13–15). In addition, the influence of substitution at C5 and C6 of the indole ring was examined. Electron-donating groups furnished the arylation products with good results in terms of yield and enantioselectivity (entries 17 and 19–21). However, an electron-withdrawing group was unfavorable for the reaction, and the desired product was obtained in a relatively low yield but with an excellent ee value (entry 18). In addition, the novel pentacyclic chiral indoline **2v** was obtained in 55% yield with 89% ee (entry 22). It is worth noting that a gram-scale reaction of **1a** to give **2a** was carried out and afforded the product in 81% yield with 97% ee (eq 1), showing the practicality of this reaction.

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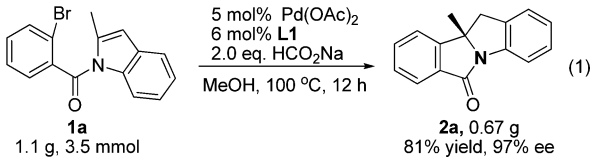
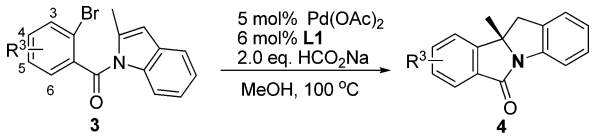


The effect of substituents on the benzene ring of the 2-bromobenzoyl moiety was then investigated under the optimized reaction conditions. As shown in Table 3, the desired

Table 3. Effect of Bromobenzoyl Substituents[a]



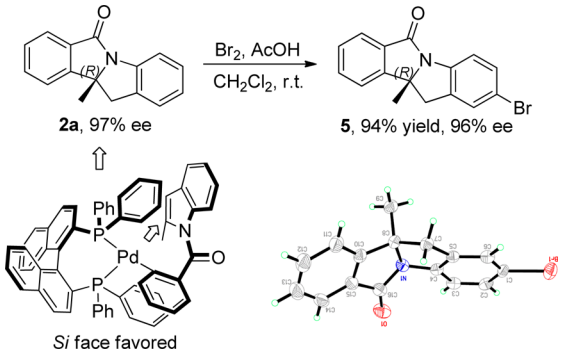
entry	R^3 (3)	product	yield (%)[b]	ee (%)[c]
1[d]	3-Me (**3a**)	**4a**	22	29
2	4-Me (**3b**)	**4b**	85	98
3	4-F (**3c**)	**4c**	73	97
4	5-MeO (**3d**)	**4d**	75	96
5	5-Me (**3e**)	**4e**	76	97
6	5-Cl (**3f**)	**4f**	73	99
7	5-F (**3g**)	**4g**	67	97
8	4,5-F_2 (**3h**)	**4h**	64	94
9	4,5-$(MeO)_2$ (**3i**)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

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

products **4b−i** were obtained in modest to good yields with excellent enantioselectivities for the reactions with substrates bearing either electron-donating or electron-withdrawing groups at C4, C5, or C6 (entries 2−9). In contrast, substitution at C3 of the bromobenzoyl moiety disfavored the reaction because of 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 with a low ee value (entry 1).

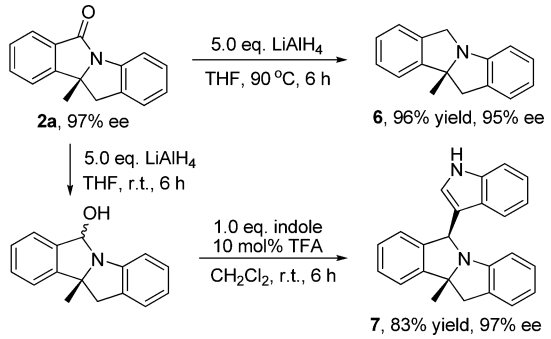
Scheme 1 shows a proposed asymmetric induction model. The intramolecular aryl attack on the indole is favored from the

Scheme 1. Determination of the Absolute Configuration and the Asymmetric Induction Model



Si face, leading to product **2a** in the *R* configuration. This is consistent with the observed configuration of compound **5** (derived from the bromination of **2a**) on the basis of X-ray structural analysis of its single crystal. Subsequently, synthetic

Scheme 2. Synthetic Transformations of Product 2a



transformations of product **2a** were conducted (Scheme 2). A facile reduction of **2a** with $LiAlH_4$ in refluxing THF led to tetracyclic indoline **6** in 96% yield with 95% ee. However, the reduction performed at room temperature furnished the corresponding hemiaminal, which was readily converted to adduct **7** as a single isomer in 83% yield with complete preservation of the enantiopurity by an acid-catalyzed addition of indole to the in situ-formed iminium.

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 with excellent enantioselectivities. The new methodology presented here offers new opportunities for the development of arylative dearomatization reactions. Investigations of further applications of this methodology in organic synthesis are currently underway in the laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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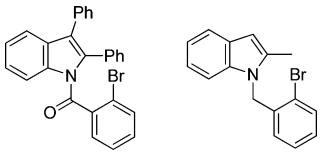
(14) No C7-arylation product was detected during optimization of the reaction conditions.

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



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