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Stereodivergent Synthesis of Tetrahydrofuroindoles via Pd-Catalyzed Asymmetric Dearomative Formal [3+2] Cycloaddition Reactions

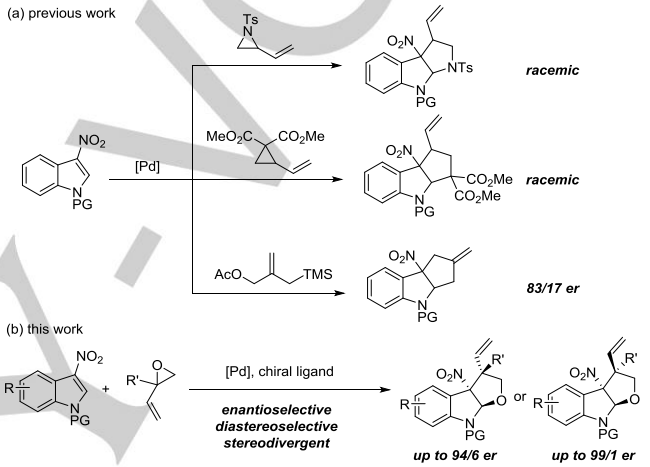
Qiang Cheng[a], Fang Zhang[a], Yue Cai[a], Yin-Long Guo[a]*, and Shu-Li You[a,b]*

Dedication ((optional))

Abstract: Stereodivergent synthesis of tetrahydrofuroindoles via palladium-catalyzed asymmetric dearomative formal [3+2] cycloaddition of nitroindoles with epoxybutenes was developed. Polarity of solvent was found to play as the key role on the switch of diastereoselectivity. In toluene, good to excellent yields (70-99%), diastereo- (87/13->95/5 dr) and enantioselectivity (85/15-94/6 er) were obtained regardless of the properties of substituents on nitroindoles. In acetonitrile, tetrahydrofuroindoles of another diastereoisomer were produced with good to excellent yields (75-98%) and stereoselectivity (78/22-93/7 dr, 93/7-99/1 er). Mechanistic studies were conducted to illustrate the origin of the diastereodivergency. The kinetic experiments indicate that the rate-determining step of this reaction has been altered in different solvents. The ESI-MS experiments also support the existence of the key palladium-complex intermediates and the catalytic cycle of the reaction.

Asymmetric construction of polysubstituted fused rings provides convenient accesses to various natural products and pharmaceuticals, and their analogs.[1] Thus methodologies have been developed for the synthesis of polycyclic systems, among which catalytic asymmetric dearomatization (CADA) reactions have recently emerged as a powerful tool to convert simple arenes to fused and spiro ring structures.[2] However, most of the reported CADA reactions are based on the nucleophilicity of electron-rich arenes,[3] which leads to substrate scope limitation that arenes with electron-deficient substituents are frequently unreactive. Reversing the electronic properties of arenes by decorating with electron-withdrawing substituents, by converting arenes to Michael acceptors, will bring with novel reactivity.

Stereodivergent synthesis performs as a powerful tool for the access to the full set of stereoisomers of multiple stereogenic center containing compounds from the same substrate, which has attracted much attention recently.[4] Although strategies including dual catalysis, switching of solvents or additives, change of substrates, and using different catalysts have been achieved for this goal, investigations for more convenient and reliable methods are still urgent.[5]



Scheme 1. Dearomatization of 3-nitroindoles via palladium-catalyzed [3+2] cycloaddition reactions.

Recently, 3-nitroindole was reported as a suitable substrate for several dearomative transformations.[6] Merging dearomatization of 3-nitroindole with palladium-catalyzed asymmetric [3+2] cycloaddition would lead to multiple substituted fused indolines (Scheme 1a). However, challenges such as the high energetic barrier for dearomatization, as well as the control of enantio- and diastereoselectivity, will be encountered. Two recent elegant examples using vinylaziridines and vinylcyclopropanes were reported in racemic form.[6k,6l] Another pioneering example by Trost and coworkers provided a trial of asymmetric catalysis, albeit with moderate enantioselectivity (83/17 er).[6b] Recently, our group reported a Pd-catalyzed asymmetric dearomative formal [3+2] cycloaddition reaction of nitrobenzofurans, while stereodivergent process could not be realized yet.[7] Herein, we report an asymmetric dearomatization of 3-nitroindoles via palladium-catalyzed formal [3+2] cycloaddition reactions, solvent induced stereodivergency, and related mechanistic studies (Scheme 1b).

We initiated our studies with 1-tert-butyloxycarbonyl-3-nitroindole **1a** and racemic 2-vinyloxirane **2a** as model substrates combined with Pd_2dba_3/**L** as the catalyst and toluene as solvent. The detailed ligand screening can be found in the supporting information (Table S1). It should be noted that phosphinooxazoline (PHOX) ligands[8] were found to be efficient for this reaction. To our delight, ligand **L1** decorated with fluorine and trifluoromethyl groups provided the best results (Table S1,

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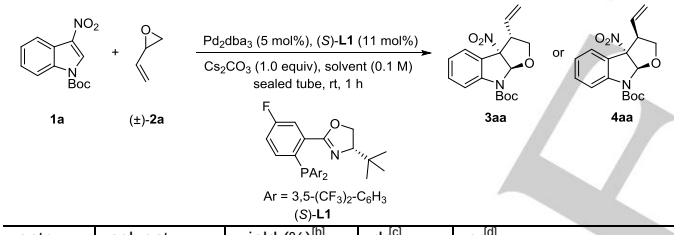
entry 11; Table 1, entry 1). Next, a detailed optimization of reaction conditions was conducted. Examination of solvents such as *p*-xylene, Et_2O, THF, dioxane and DCM showed comparable or no better results (Table 1, entries 2-6). To our surprise, when acetonitrile, a much polar solvent, was used, the diastereoselectivity was reversed compared to that in toluene (Table 1, entry 7). To further illustrate the relationship between the polarity of the solvent and diastereoselectivity of the reaction, polar solvents like DMF and DMSO were also applied. As expected, **4aa** was obtained as the major product in these two solvents (Table 1, entries 8, 9). Thus, a diastereodivergent phenomenon induced by polarity of solvent was discovered, and is further discussed later (vide infra). Finally, toluene was proved to be the best solvent for the formation of **3aa** (Table 1, entry 1), while acetonitrile was favorable for the formation of **4aa** (90% yield, 15/85 dr, 99/1 er, Table 1, entry 7). It is noteworthy that the best result was observed for **3aa** when $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ was used (89% yield, >95/5 dr, 94/6 er, Table 1, entry 10). In addition, Cs_2CO_3 was an indispensable additive for the reaction favoring the formation of **3aa** (Table 1, entry 11). With acetonitrile as solvent, palladium sources made no much difference, and Pd_2dba_3 gave better results (Table 1, entries 7 and 12). Furthermore, additive was not essential for the formation of **4aa**, while Cs_2CO_3 promoted the reaction obviously (Table 1, entry 13).

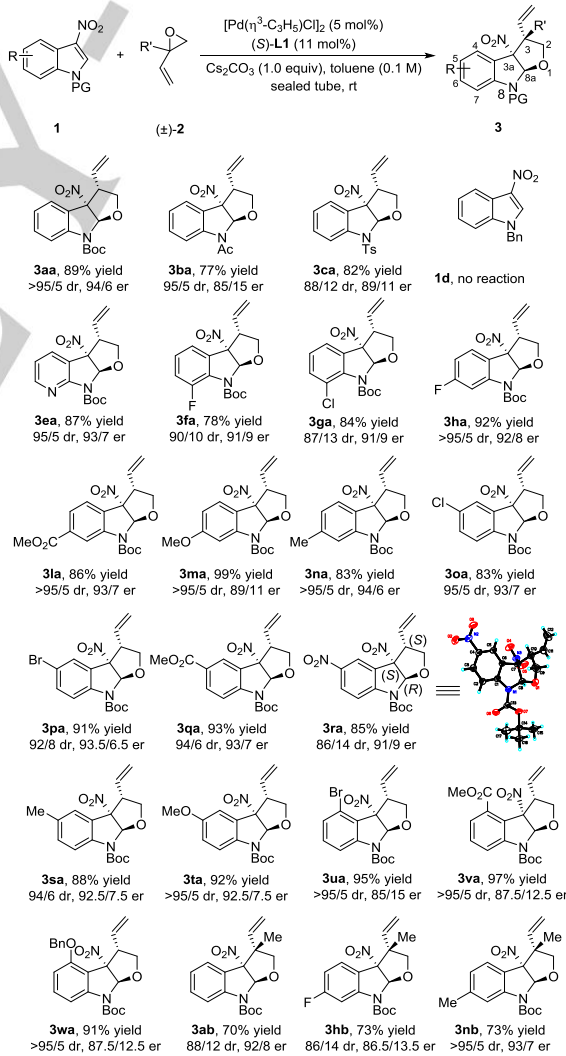
Table 1. Effect of solvents and optimization of other reaction conditions.[a]



entry	solvent	yield (%)[b]	dr[c]	er[d]	
				3aa	**4aa**
1	toluene	80	91/9	94/6	98/2
2	*p*-xylene	93	89/11	90/10	99/1
3	Et_2O	82	94/6	91/9	99/1
4	THF	77	62/38	78/22	97.5/2.5
5	Dioxane	96	89/11	88/12	95/5
6	DCM	84	52/48	79/21	92/8
7	MeCN	90	15/85	33/67	99/1
8	DMF	45	28/72	42/58	94/6
9	DMSO	47	18/82	31/69	97.5/2.5
10[e]	toluene	89	>95/5	94/6	n.d.
11[e,f]	toluene	0	n.d.	n.d.	n.d.
12[e]	MeCN	75	20/80	35/65	98/2
13[f]	MeCN	70	15/85	30/70	99/1

[a] Reaction conditions: 5 mol% of Pd_2dba_3, 11 mol% of **L1**, 0.1 mmol of **1a**, 0.13 mmol of **2a**, 0.1 mmol of Cs_2CO_3 in solvent (1 mL), sealed tube, rt. [b] Isolated yield of **3aa** and **4aa**. [c] Determined by ^{1}H NMR of crude reaction mixture. [d] Determined by HPLC analysis. [e] $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ was used as Pd source. [f] Reaction without Cs_2CO_3. n.d. = not determined.

With the optimal conditions established for **3aa** (Table 1, entry 10) and **4aa** (Table 1, entry 7), we launched the substrate scope investigation. In toluene, various electron-withdrawing groups on *N*-1 of nitroindole could be accommodated, leading to good to excellent yields, diastereo- and enantioselectivity (Scheme 2, **3aa**-**3ca**), while electron-donating benzyl group failed (Scheme 2, **1d**). Attention was then paid to the groups on the indole ring. To our delight, all reactions with substrates bearing substituents on different positions proceeded smoothly in good to excellent yields (70-99%) and stereoselectivity (86/14->95/5 dr, 85/15-94/6 er). 4-Substituted nitroindoles displayed lower enantioselectivity, but better diastereoselectivity (Scheme 2, **3ua**-**3wa**). On the other hand, substituents with varied electronic properties ranging from electron-donating methyl and methoxyl group to electron-withdrawing ester and even nitro group were well tolerated, indicating a wider group tolerance than traditional dearomatization reactions of indoles functioning as nucleophiles. In addition, halides, including the bromide group, survived in this palladium-catalyzed process (Scheme 2, **3fa**-**3ha**, **3oa**, **3pa**, **3ua**, **3hb**). To further explore scope, substituted vinyl epoxides were applied. We are pleased to obtain products bearing vicinal quaternary stereogenic carbon centers with good to excellent yields, diastereo- and enantioselectivity (Scheme 2, **3ab**, **3hb**, **3nb**). Furthermore, the absolute configuration of **3ra** was determined as 3*S*,3a*S*,8a*R* by an X-ray crystallographic analysis of a single crystal of the enantiopure sample.[9]



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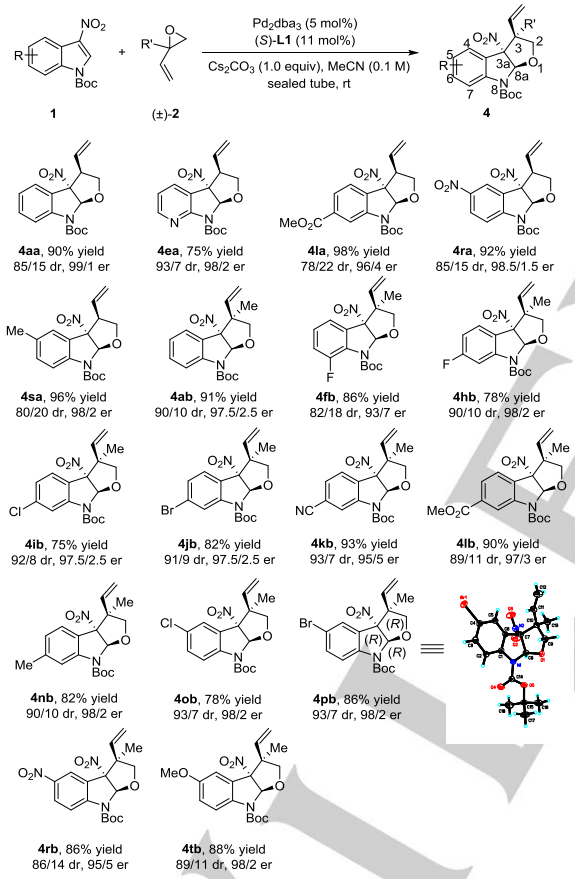
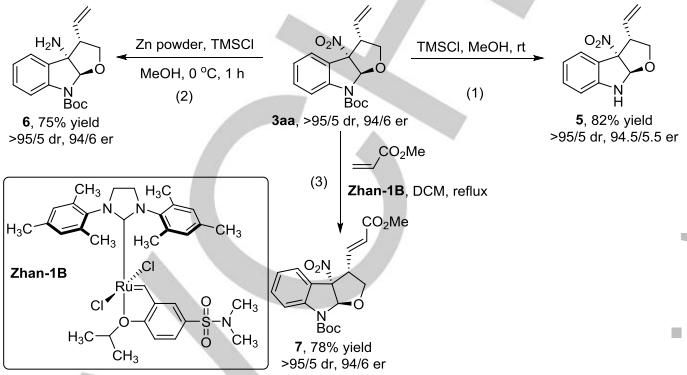
Scheme 2. Reaction scope in toluene. Reaction conditions: 5 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 11 mol% of **L1**, 0.2 mmol of **1**, 0.26 mmol of **2**, 0.2 mmol of Cs_2CO_3 in toluene (2 mL), sealed tube , rt.

Compared with toluene, reactions in acetonitrile occurred faster to produce the diastereoisomer **4** with higher enantioselectivity (Scheme 3). Of particular note, methyl substituted epoxybutene **2b** produced dearomatized products with higher diastereoselectivity. Substrates bearing either an EWG (CO_2Me, NO_2, CN, F, Cl, Br) or EDG (Me, OMe) provided **4** with good to excellent yields (75-98%), moderate to good diastereoselectivity (78/22-93/7 dr), and excellent enantioselectivity (93/7-99/1 er). In addition, the absolute configuration of **4pb** was determined as 3*R*,3a*R*,8a*R* by an X-ray crystallographic analysis of a single crystal of the enantiopure sample.[9]



Scheme 3. Reaction scope in acetonitrile. Reaction conditions: 5 mol% of Pd_2dba_3, 11 mol% of **L1**, 0.2 mmol of **1**, 0.26 mmol of **2**, 0.2 mmol of Cs_2CO_3 in acetonitrile (2 mL), sealed tube, rt.

To illustrate the potential application of this reaction, several transformations of product **3aa** were carried out. Firstly, the Boc group on nitrogen was easily removed by TMSCl in MeOH at room temperature (Scheme 4, equation (1)). In addition, the nitro group could also be readily reduced with Zn and TMSCl at 0 °C to afford **6** (Scheme 4, equation (2)). Cross-metathesis reaction of **3aa** with methyl acrylate in the presence of **Zhan-1B** catalyst occurred smoothly with other functional groups untouched (Scheme 4, equation (3)). It is worth noting that all reactions proceeded without erosion of stereomeric purity.



Scheme 4. Transformations of **3aa**.

Although palladium-catalyzed [3+2] cycloaddition reaction has been studied extensively, its mechanism is still not fully understood. The challenge lied on the difficulty in isolation of the unstable intermediates that are essential for drawing a possible catalytic cycle. Nevertheless, ESI-MS is a direct and reliable method for the characterization of reaction intermediates in situ, which benefits from the gentle ionization process that delivers minimal fragmentation.[10] We next tried to capture the key reaction intermediates by monitoring the reaction with SAESI-MS instrument in the cation mode (Figure S5, see the supporting information for details). When the reaction in toluene was monitored after ten minutes, an ion of m/z 854.0680 was obtained (Figure S5a), indicating the existence of intermediate **A** or **B** (Figure 2). The SAESI-MS/MS spectra further support the structure of this ion (Figure S5b). In addition, a relatively weak signal of m/z 1116.1650 was also observed (Figure S5a). The SAESI-MS/MS spectra showed unambiguously the constituents of this ion (Figure S5c), indicating the existence of intermediate **C** (Figure 2). In addition, the experimental isotopic distributions of the palladium-containing species matched the theoretical isotopic distributions (Figure S5d). To our surprise, the positive ions of the intermediates in both solvents were observed with barely no difference (Figure S6), indicating that two reaction systems might share the same reaction intermediates.

With these key intermediates identified (Figure 2), a Hammett plot was put forward as a tool to investigate the rate determining steps. Under the optimal reaction conditions, various substituted nitroindoles were applied as substrates. The reactions were monitored by ^1H NMR or HPLC to determine the kinetic behaviors (Figure 1, see the supporting information for details). The observed Hammett plots strongly suggest that in toluene (Figure 1a), as $\rho > 0$, the rate limiting step is an anion building step, that is the Michael addition process. Oppositely, in acetonitrile (Figure 1b), allylic cyclization step is supported as the rate limiting step, as $\rho < 0$.

Finally, with all the mechanistic information in hand, a possible catalytic cycle was proposed (Figure 2). Coordination and oxidative addition of a palladium catalyst to the epoxybutene **2a** leads to ring-opened intermediate **B**. The following steps varied depending on the solvent. In toluene, as drawn in red (path a), a rate determining Michael addition type dearomatization process, which may be derived from a decreased nucleophilicity due to the formation of a tight ion pair in a nonpolar solvent, leads to intermediate **C** followed by a fast cyclization to form the final product **3aa**. On the other hand, in acetonitrile, intermediate **C** is easy to be formed, while the next ring closing becomes rate limiting step due to the stabilization of the zwitterion by the polar solvent. This provides time for π-σ-π inversion of the allylic palladium complex and leads to the formation of diastereoisomer **4aa**, where the configuration of the allylic stereogenic center is inversed compared with **3aa**.

In summary, we have developed a palladium-catalyzed diastereo- and enantioselective dearomative formal [3+2] cycloaddition reaction. A stereodivergent synthesis of tetrahydrofuroindoles was realized via tuning the polarity of solvents in this kind of reactions. The mechanistic studies supported that reactions in different solvents would proceed in the same pathway with different rate limiting steps, leading to a reversed stereocontrol. The ESI-MS studies have been carried out to present a full picture of the reaction processes. These results indicate some general explanation of stereoselectivity for palladium-catalyzed asymmetric [3+2] cycloaddition reactions.

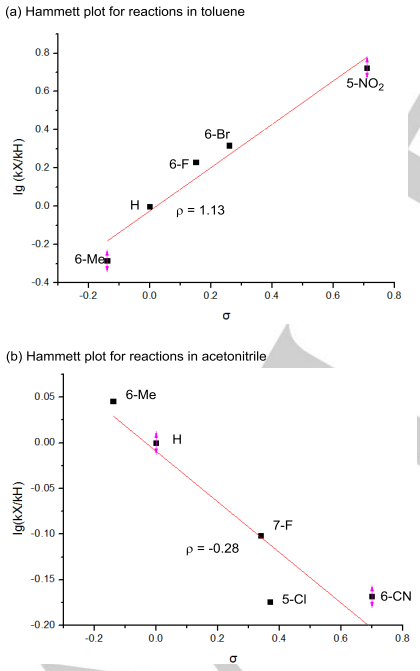


Figure 1. Hammett plots of reactions in toluene (a) and acetonitrile (b).

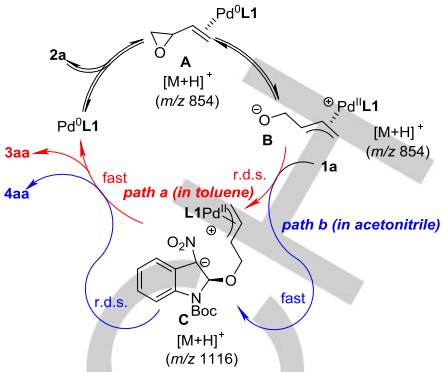


Figure 2. Proposed reaction mechanism.

Acknowledgements

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Keywords: cycloaddition • dearomatization • indole • mechanism • stereodivergent

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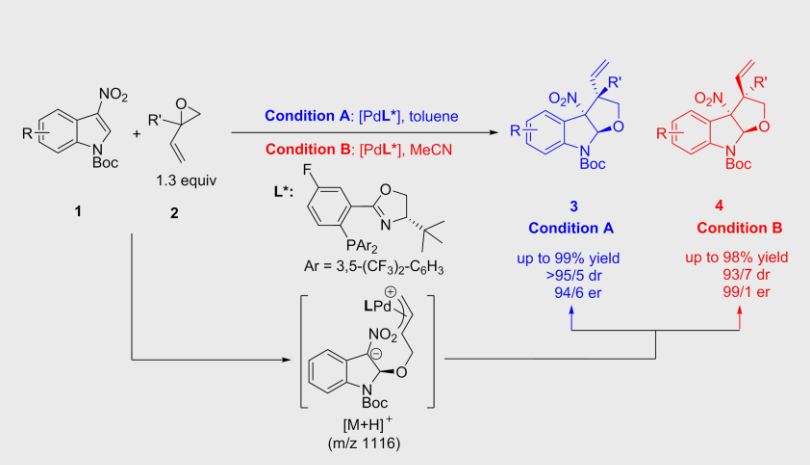

Stereodivergent synthesis of tetrahydrofuroindoles via palladium-catalyzed asymmetric dearomative formal [3+2] cycloaddition of nitroindoles with epoxybutenes was developed. Polarity of solvent was found to play as the key role on the switch of diastereoselectivity. In toluene, good to excellent yields (70-99%), diastereo- (87/13->95/5 dr) and enantioselectivity (85/15-94/6 er) were obtained regardless of the properties of substituents on nitroindoles. In acetonitrile, tetrahydrofuroindoles of another diastereoisomer were produced with good to excellent yields (75-98%) and stereoselectivity (78/22-93/7 dr, 93/7-99/1 er). Mechanistic studies were conducted to illustrate the origin of the diastereodivergency. The kinetic experiments indicate that the rate-determining step of this reaction has been altered in different solvents. The ESI-MS experiments also support the existence of the key palladium-complex intermediates and the catalytic cycle of the reaction.