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Authors: Junliang Zhang, Huamin Wang, Junyou Zhang, and Youshao Tu

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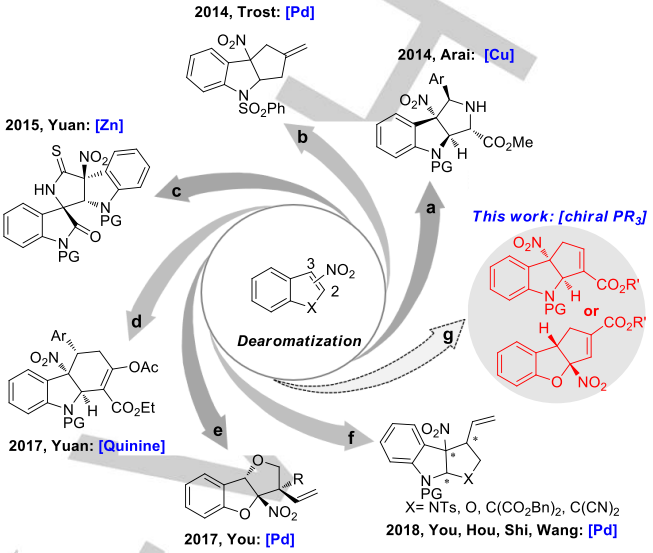
Phosphine-Catalyzed Enantioselective Dearomative [3 + 2]-Cycloaddition of 3-Nitroindoles and 2-Nitrobenzofurans

Huamin Wang[+], Junyou Zhang[+], Youshao Tu, and Junliang Zhang*

Abstract: *Over past years, the metal-catalyzed dearomative cycloaddition of 3-nitroindoles and 2-nitrobenzofurans have emerged as a powerful protocol to construct chiral fused heterocyclic rings. However, organocatalytic dearomative reaction of these two classes of heteroarenes has become a long-standing challenging task. Herein, we reported the first example of phosphine-catalyzed asymmetric dearomative 3-nitroindoles and 2-nitrobenzofurans was realized, which provide a new, facile, and efficient protocol for the synthesis of chiral 2,3-fused cyclopentannulated indolines and dihydrobenzofurans by reacting with allenoates and MBH carbonates, respectively via dearomative [3 + 2]-cycloaddition.*

Catalytic asymmetric dearomatization (CADA) of heteroarenes have emerged as one of the simple and powerful strategies to access enantio-enriched polycyclic frameworks.[1] Compared with the now well-received electron-rich heteroarenes,[2] the CADA reactions of electron-deficient nitro-heteroarenes was still very limited. In 2014, Arai et al. reported the first example of asymmetric dearomative 1,3-dipolar cycloaddition of electron-deficient indoles under the catalysis of copper complex (Scheme 1a).[3] Later, Trost and co-workers[4] developed a palladium/phosphoramidite catalyst system to achieve the asymmtric dearomative [3C+2C]-cycloaddition reaction of 3-nitroindole with trimethylenemethane (Scheme 1b). The group of Yuan investigated a series of enantioselective dearomative cycloaddition reactions of 3-nitroindoles and 2-nitrobenzofurans (Scheme 1c and 1d).[5] Recently, You and co-workers[6] disclosed a highly stereoselective palladium-catalyzed asymmetric dearomative [3+2]-cycloaddition of nitrobenzofurans with vinyl oxiranes (Scheme 1e). Shortly after, You,[7] Hou[8], Shi[9] and Wang[10] independently realized the palladium-catalyzed asymmetric dearomatization [3+2]-cycloaddition reaction of 3-nitroindoles with vinyl oxiranes, vinylazirdines and vinylcylopropanes (Scheme 1f). Despite these advances, reports for organocatalytic asymmetric dearomative cycloadditions of 3-nitroindoles and 2-nitrobenzofurans remain rare,[5a,5c] and therefore is still highly desirable.

Over the past decades, asymmetric phosphine-catalysis have emerged as a powerful tool for the construction of diverse chiral skeletons.[11-13] However, to the best of our knowledge, phosphine catalytic asymmetric dearomative cycloaddition of 3-



Scheme 1. Asymmetric dearomatizative cycloaddition of 3-nitroindoles and 2-nitrobenzofurans.

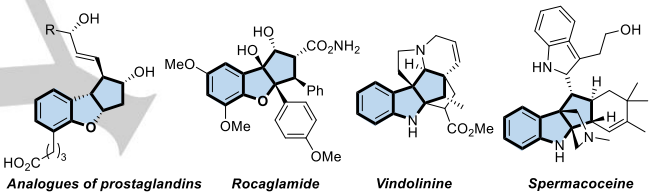
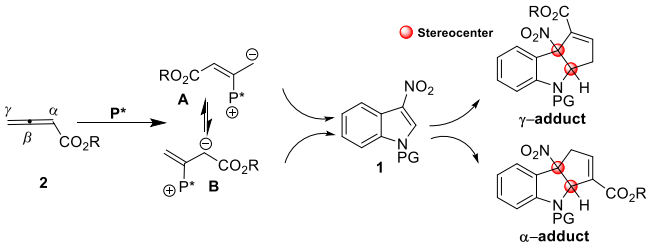


Figure 1. Relevant natural products and bioactive moleculars.

nitroindoles or 2-nitrobenzofurans has not been realized so far. This may be attributed to: (1) the high energetic barrier in dearomative cycloaddition;[14] (2) regioselectivity outcome of the cycloaddition; and (3) control of diastereo- and enantioselectivities. With regard to the high importance of chiral indolines and benzodihydrofurans (Figure 1)[15] and in continuation of our research program on asymmetric phosphine catalysis,[16] we became interest in the phosphine-catalyzed asymmetric dearomative cycloaddition of electron-deficient heteroarenes such as 3-nitroindoles and 2-nitrobenzofurans. We envisioned that zwitterionic intermediate (**A** or **B**), generated from the addition of phosphine to allenoate **2**, might react with 3-nitroindoles **1** via consecutive conjugate addition−α- or γ-addition, thereby leading to dearomative cycloaddition products (Scheme 2). Herein we present the first example of phosphine-catalyzed asymmetric dearomative [3+2]-cycloaddition of 3-nitroindoles and 2-nitrobenzofurans with allenoates and MBH carbonates, respectively, for highly enantioselective synthesis of chiral indolines and benzodihydrofurans (Scheme 1g).



Scheme 2. Designed phosphine-catalyzed dearomative cycloaddition.

[*] H. Wang, J. Zhang, Prof. Dr. J. Zhang*
Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University
Shanghai, 200062 (P. R. China)
Prof. Dr. J. Zhang*
Department of Chemistry
Fudan University
2005 Songhu Road, Shanghai, 200438 (P. R. China)
Y. Tu
College of Chemistry and Life Science, Advanced Institute of Materials Science, Changchun University of Technology,
2055 N. Yan'an Avenue, Changchun 130012 (P. R. China)
[+] These authors contributed equally to this work.
E-mail: junliangzhang@fudan.edu.cn

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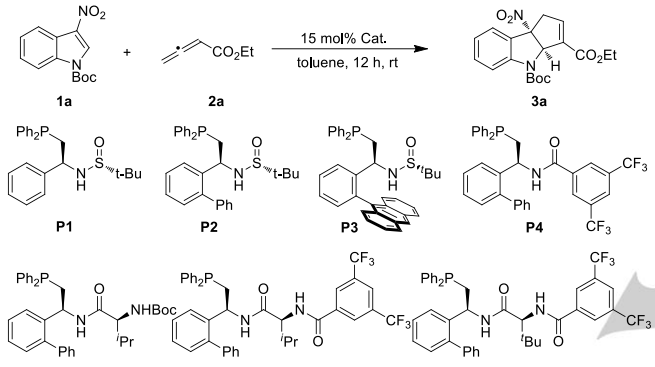
To test the above hypothesis, we investigated the reaction of 1-*tert*-butyloxycarbonyl-3-nitroindole **1a** and allenoate **2a** in toluene with 15 mol% of chiral phosphine catalyst at room temperature. When chiral sulfinamide derived **Xiao-Phos P1-P3**[16a,c] were used as the catalyst, the desired dearomatization product **2a** could be obtained in 20-34% NMR yields and with poor enantioselectivities (Table 1, entries 1-3). With the use of **Peng-Phos P4**[16e] bearing a 3,5-bis(trifluoromethyl)benzamide moiety as the catalyst, the yield and ee were elevated to 71% yield and 51% *ee*, respectively (Table 1, entry 4). Chiral dipeptidic phosphines **P5-P7** could deliver better yield and ee (Table 1, entries 5-7). With the use of **P7**, a systematic screening of solvent, additives, reaction temperature and catalyst loading was carried out (Table 1, entries 8-19). Finally, the best reaction conditions were determined: 15 mol% **P7**, mesitylene, 4 ÅMS, 0 °C, delivering 93% yield of **3a** with 95% ee (Table 1, entry 19).

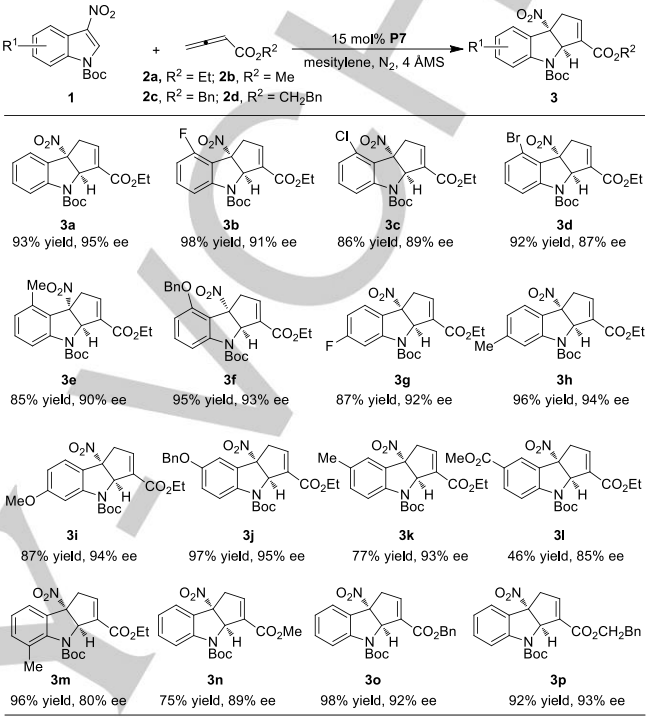
Table 1. Optimization of reaction conditions[a]



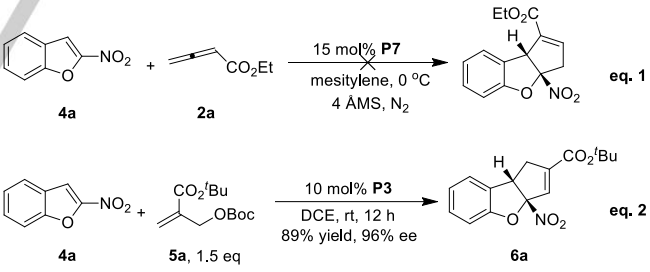
Entry	Cat.	Solvent	Yield (%)[b]	Ee (%)[c]
1	**P1**	toluene	20	19
2	**P2**	toluene	30	-3
3	**P3**	toluene	34	0
4	**P4**	toluene	70	51
5	**P5**	toluene	82	78
6	**P6**	toluene	87	87
7	**P7**	toluene	80	89
8	**P7**	DCM	78	65
9	**P7**	THF	50	41
10	**P7**	mesitylene	90	90
11	**P7**	*o*-xylene	45	89
12	**P7**	*m*-xylene	66	90
13	**P7**	*p*-xylene	N.R.	--
14	**P7**	cumene	N.R.	--
15	**P7**	acetone	N.R.	--
16	**P7**	$CHCl_3$	65	69
17[d]	**P7**	mesitylene	15	89
18[e]	**P7**	mesitylene	50	91
19[e,f]	**P7**	mesitylene	93	95

[a] Unless otherwise specified, all reactions were carried on 0.1 mmol scale in solvent (1.0 mL) and used 2.0 equiv of **2a**, 15 mol% catalyst under N_2, rt. [b] Determined by ^1H NMR. [c] Determined by HPLC analysis using a chiral stationary. [d] 10 mol % catalyst used. [e] at 0 °C. [f] 50 mg of 4 Å MS.

The scope of this phosphine-catalyzed asymmetric dearomative [3+2]-cycloaddition was then investigated (Scheme 3). Halogens (**1b**-**3d**, **3g**) or electron-donating groups (**1e**-**1k**, **1m**) at different positions on the indole ring are compatible, delivering the desired products in 77-96% yields with up to 95% ee. The absolute configuration of product **3f** was determined via single-crystal X-ray diffraction analysis.[17] However, ester-substituted nitroindole (**1l**) was less ideal, and the yield of the reaction dropped dramatically (**3l**, 46%). In addition, the allenoates bearing various ester group, namely methyl (**2b**), benzyl (**2c**) and phenethyl (**2d**), were well applicabe to the reaction, furnishing the cycloadducts **3n**-**3p** in 75-98% yields with 89-93% *ees*.



Scheme 3. Substrate scope for cycloaddition of 3-nitroindoles with allenoates. All reactions were carried on 0.1 mmol scale in mesitylene (1.0 mL) and used 2.0 equiv of **2**, 15 mol% **P7**, 50 mg of 4 Å MS under N_2, 0 °C; Isolated yields were reported; *Ee* values were determined by chiral HPLC analysis.



Inspired by the above result, we then tried to extend this phosphine-catalyzed asymmetric dearomative [3+2]-cycloaddition to the 2-nitrobenzofuran **4a,** but failed (eq. 1). After many attempts, we finally realized the phosphine catalyzed asymmetric dearomative [3+2]-cycloaddition of 2-nitrobenzofuran **4a** by the use of MBH carbonate **5a** as the 3C-component (eq. 2). The reaction scope was then investigated via variation of 2-nitrobenzofuran component under the catalysis of **P3** (**Scheme 4**). In general, 2-nitrobenzofurans bearing electron-donating and electron-withdrawing groups could undergo dearomative cycloaddition smoothly to afford the corresponding products **6b-6p** in 81-98% yields with 95-98% ees. The absolute configuration of the product was determined by X-ray crystal structural analysis of **3b**.[17] The variation of the ester moiety of MBH carbonates was also investigated and the isopropyl MBH carbonate still could deliver good result (**6r**, 96% ee), but the corresponding methyl or benzyl MBH carbonates gave only moderate yield of the products with relatively lower ee (**6q** and

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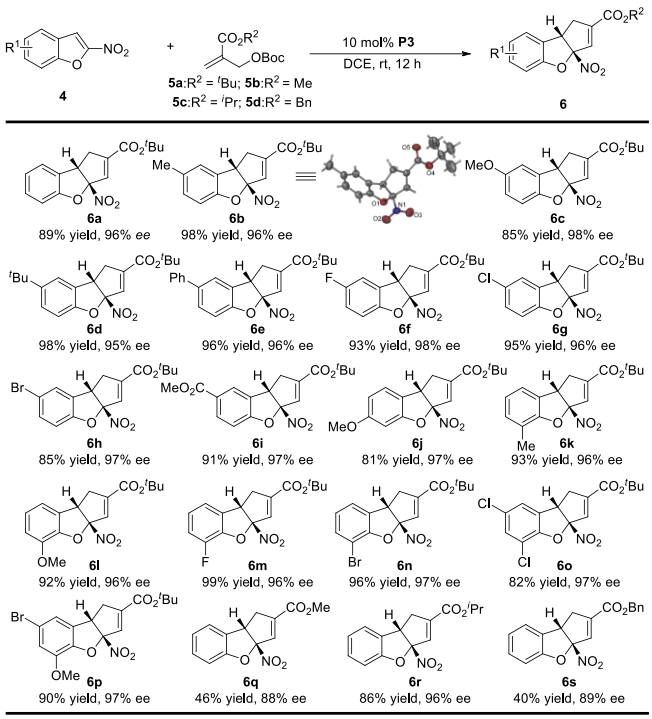
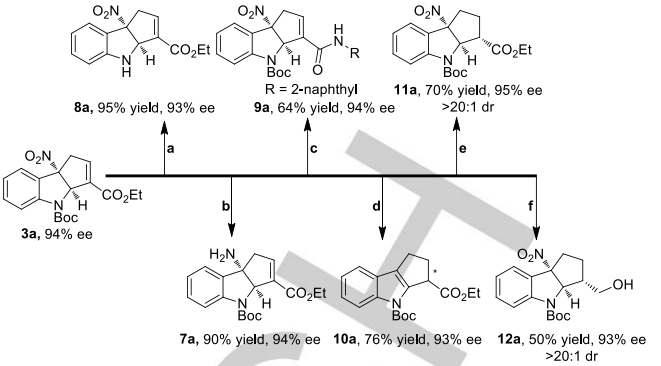
6s). Unfortunately, the substituted MBH carbonates could not be compatible with this transformation under various conditions.



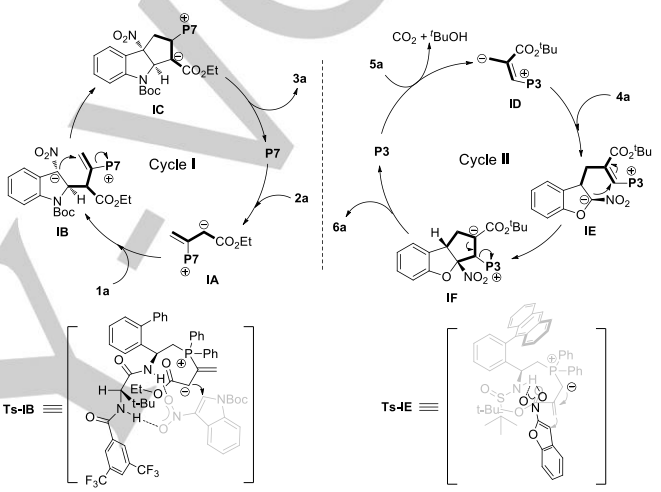
Scheme 4. Study the reaction scope. All reactions were carried on 0.2 mmol scale in dichloroethane (2.0 mL) and used 1.5 equiv of **5**, 10 mol% **P3** under N_2, rt.; Isolated yields were reported; *Ee* values were determined by chiral HPLC analysis.

A gram-scale reaction under the catalysis of 7.5 mol% **P3** was then performed, delivering 1.33 g of **6a** (88% yield) with 97% ee (see the SI). Synthetic transformations of **3a** were then conducted (**Scheme 5**). The nitro group of **3a** was efficiently reduced with Zn/HCl, delivering compound **7a** in 90% yield with 94% ee. The deprotection of Boc group with TFA in DCM could produce **8a** in 95% yield. In addition, amide **9a** was obtained by hydrolysis and amidation in 64% overall yield and 94% ee via a two-step procedure. The denitronation reaction was realized by treatment with $NiCl_2/NaBH_4$ in MeOH, furnishing the product **10a** was attained in 76% yield with 93% ee. Treating compound **3a** with $NaBH_4$ in EtOH could selectively furnish **11a** or **12a** by adjusting the reaction temperature.

According to the above results and literatures,[11-13] two plausible mechanisms and transition state stereoinduction models are depicted in Scheme 6. In the cycloaddition of 3-nitroindole/allenoate (cycle I), the conjugate addition of **P7** to allenoate **2a** would generate phosphonium intermediate **IA**, which upon subsequent conjugate addition to **1a** via the α-position to form advanced intermediate **IB**. Subsequent cyclization affords the intermediate **IC**, which then regenerates catalyst **P7** via elimination to give product **3a**. In the cycloaddition of 2-nitrobenzofuran/MBH carbonate (cycle II), the conjugated addition of allylic phosphonium ylide **ID**, in-situ generated from **P3** and MBH carbonate, to **4a** generates intermediate **IE**, which upon Michael addition to generate intermediate **IF**. Finally, the elimination of **P3** affords product **6a**. Meanwhile, we reasoned that the hydrogen-bonding interaction between the amide NH and the nitroarene facilitates a significant decrease the LUMO energy of the aromatic partner[18] and makes cycloaddition process smoothly.



Scheme 5. Scaled-Up version of the dearomative [3+2] annulation and transformation of the product **3a**. a) TFA, DCM; b) Zn, TMSCl, MeOH; c) 1) LiOH,THF/H_2O; 2) 2-Aminonaphthalene, EDCl, DMAP, DCM; d) $NiCl_2$, $NaBH_4$, MeOH; e) $NaBH_4$, EtOH, 0 °C; f) $NaBH_4$, EtOH, 0 °C to rt.



Scheme 6. Possible reaction mechanism and proposed transition states.

In summary, we have developed the first phosphine-catalyzed asymmetric dearomative [3 + 2]-cycloaddition of 3-nitroindoles and 2-nitrobenzofurans with allenoates and MBH carbonates, respectively, which provides a new, facile, and efficient protocol for the synthesis of chiral 2,3-fused cyclopentannulated indolines and dihydrobenzofurans in moderate to excellent yields with high enantioselectivities. Notably, to the best of knowledge, this work represents the first example of phosphine-catalyzed asymmetric dearomative cycloaddition reaction. Synthetic transformations of product were also showcased. The strategy disclosed in this report affords a new approach to synthetically valued chiral polycyclic structures, which might be potentially useful for organic synthesis and medicinal chemistry.

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Keywords: phosphine catalysis• dearomatization• cycloaddition• CADA• nitro-heteroarenes

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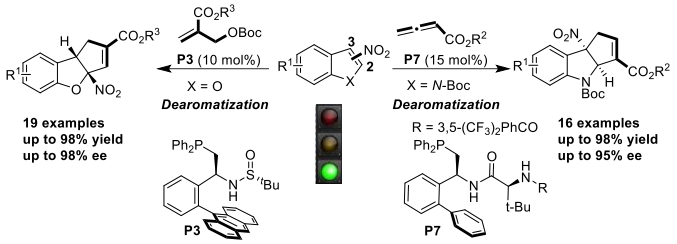

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Phosphine-Catalyzed Enantioselective Dearomative [3 + 2]-Cycloaddition of 3-Nitroindoles and 2-Nitrobenzofurans

The first example of phosphine-catalyzed asymmetric dearomative [3 + 2]-cycloaddition of 3-nitroindoles and 2-nitrobenzofurans was realized, which provides a new, facile, and efficient protocol for the synthesis of chiral 2,3-fused cyclopentannulated indolines and dihydrobenzofurans by reacting with allenoates and MBH carbonates, respectively