A Journal of the Gesellschaft Deutscher Chemiker

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# Accepted Article

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**To be cited as:** *Angew. Chem. Int. Ed.* 10.1002/anie.201705539
*Angew. Chem.* 10.1002/ange.201705539

**Link to VoR:** http://dx.doi.org/10.1002/anie.201705539
http://dx.doi.org/10.1002/ange.201705539

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10.1002/anie.201705539


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# Catalytic Enantioselective Aza-pinacol Rearrangement

Yuanyuan Yu,[+] Jingwen Li,[+] Long Jiang, Jing-Ren Zhang* and Liansuo Zu*

**Abstract:** The first catalytic enantioselective asymmetric aza-pinacol rearrangement is reported. The reactions are catalyzed by a chiral phosphoric acid through a highly-organized transition state involving a cyclic aza-*ortho*-xylylene intermediate to afford the indoline structures with good to excellent enantioselectivities. The synthetic utility has been demonstrated by the asymmetric synthesis of a key intermediate to natural product minfiensine and the identification of a chiral lead compound to repress antibiotic resistance.

The aza-pinacol rearrangement, analogue of the classic pinacol rearrangement, refers to the 1,2-alkyl, aryl, or hydride migration from a nitrogen-containing carbon to a vicinal hydroxylated carbon, generating imine or iminium as the product or transient intermediate.[1] While pinacol and related semipinacol rearrangements have been widely utilized in assembling complex carbonyl-containing molecules,[2] the development of aza-pinacol rearrangement as synthetic methods has been rather challenging. The synthetic difficulties mainly arise from the instability of the rearrangement product (imine or iminium), the weak driving force of the entire process, and the unpredictable side reactions associated with the highly reactive species (imine, iminium, or their tautomer enamine). So despite the synthetic potential of aza-pinacol rearrangement as powerful tactics in making nitrogen-containing heterocycles and natural alkaloids, by far there are only a few reported examples of aza-pinacol rearrangement.[1] With respect to the enantioselective asymmetric version of this reaction, only the group of Zhou has reported the asymmetric hydrogenation of the active intermediate generated from aza-pinacol rearrangement, in which the rearrangement itself is a racemic process.[3] Herein we report the first, to our knowledge, catalytic enantioselective asymmetric aza-pinacol rearrangement.

Inspired by the indoline core of a variety of natural alkaloids,[4] such as minfiensine, aspidophyline A, and calophyline A (Figure 1), we have recently developed a novel strategy based on aza-pinacol rearrangement and successfully demonstrated its synthetic utility in the chemical syntheses of minfiensine and calophyline A.[5] One remaining chemical problem in this project is to develop an asymmetric version of the aza-pinacol rearrangement, which will lay the foundation for the asymmetric synthesis of indoline natural products and medicinally important molecules (for example, analogs of the Wang's leads,[6] Figure 1).

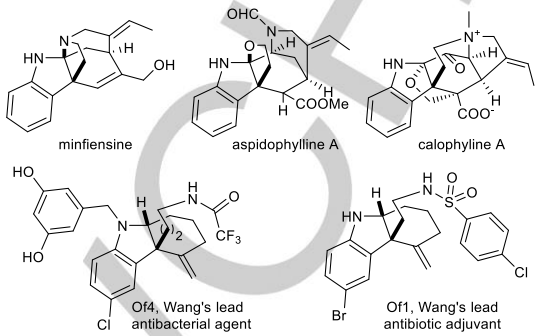
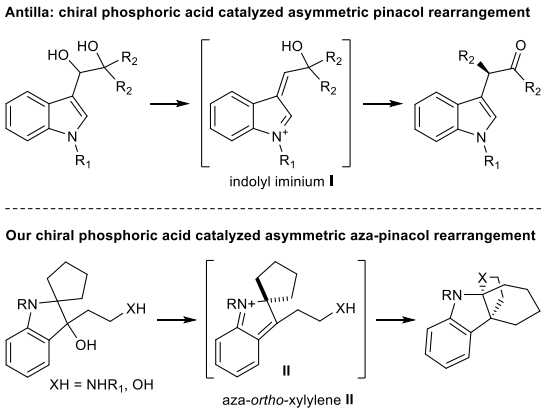



**Figure 1.** Representative indoline natural products and lead compounds.

Chiral phosphoric acid catalysis has emerged as powerful tactics for asymmetric synthesis.[7] While the phosphoric acid catalyzed asymmetric semipinacol rearrangement by Tu,[8a] vinylogous pinacol rearrangement and acyloin rearrangement by Zhu,[8b,8c] aza-semipinacol rearrangement by Burgi and Alexakis,[8d] and asymmetric syntheses of indoles and indolines by List[8e,8f] are truly inspiring, we were particularly inspired by the seminal work from the group of Antilla, who reported the first catalytic asymmetric pinacol rearrangement of indole derivatives (Scheme 1).[9] In their work, the indolyl iminium **I**[10] was proposed to interact with the chiral phosphoric acid, providing the chiral environment for the pinacol rearrangement. We envisioned that if cyclic aza-*ortho*-xylylene **II**, a putative intermediate in our aza-pinacol rearrangement, could be directed by chiral phosphoric acid, asymmetric induction might be delivered (Scheme 1). While asymmetric transformations involving aza-*ortho*-xylylenes, either acyclic or cyclic, have previously been achieved,[11,12] to our knowledge, such intermediates have not been utilized to facilitate asymmetric skeletal rearrangements.




**Scheme 1.** Aza-pinacol rearrangement via aza-*ortho*-xylylene intermediate.

[*] Y. Yu, L. Jiang, Prof. Dr. L. Zu
School of Pharmaceutical Sciences, Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Tsinghua University, Beijing 100084 (China)
E-mail: zuliansuo@biomed.tsinghua.edu.cn

J. Li, Prof. Dr. J.-R. Zhang
School of Medicine, Tsinghua University, Beijing 100084 (China)
E-mail: zhanglab@tsinghua.edu.cn

Prof. Dr. J.-R. Zhang, Prof. Dr. L. Zu
Collaborative Innovation Center for Biotherapy, West China Medical School, Sichuan University, Chengdu, 610041 (China)

[+] These authors contributed equally to this work.

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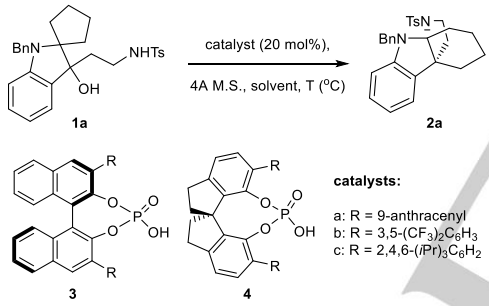
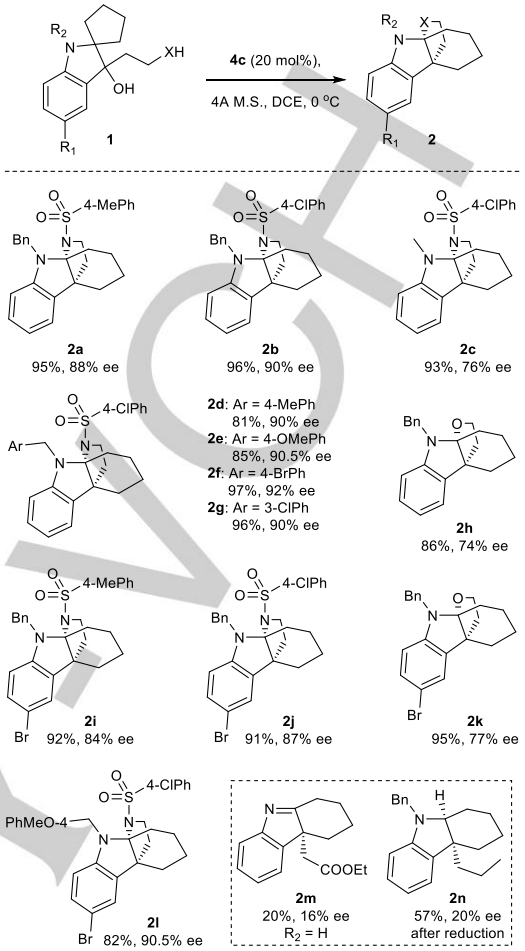
A model reaction of **1a** was carried out first to identify the optimized reaction conditions for the aza-pinacol rearrangement (Table 1). Both commercial available BINOL- and SPINOL-derived chiral phosphoric acids were screened for their abilities in promoting the skeletal rearrangement and controlling the absolute stereochemistry. In the presence of the (*R*)-BINOL-derived chiral phosphoric acids (**3a-c**), the reaction proceeded smoothly in toluene to furnish the desired product **2a** with varied yields and enantioselectivities (entry1-3). With this class of catalysts, the hindered **3c** was seen to provide the best results (95% yield, 77% ee). To our delight, the (*R*)-SPINOL-derived analogue (**4c**) catalyzed the rearrangement with improved enantioselectivity (80% ee, entry 5). Thus, **4c** became the choice of catalyst for further optimizations. Lowering the temperature of the reaction further increased the enantioselectivity, albeit with reduced reaction yields (entry 6-7). The switch of solvent from toluene to chlorinated solvents (DCM, DCE) led to the excellent results in terms of both yield and enantioselectivity (entry 8-9). Attempts to decrease the catalyst loading to 10 mol% did not affect the reaction yield, but lower enantioselectivity was observed (entry 10). It should be noted that using molecular sieves as an additive to remove $H_2O$ was essential for the success of the rearrangement.

**Table 1**. Catalysts optimization.[a]




| Entry | catalyst | solvent | T (°C) | Yield (%)[b] | ee[c] |
|---|---|---|---|---|---|
| 1 | **3a** | toluene | 23 | 60 | 0 |
| 2 | **3b** | toluene | 23 | 62 | -31 |
| 3 | **3c** | toluene | 23 | 95 | -77 |
| 4 | **4a** | toluene | 23 | 94 | 74 |
| 5 | **4c** | toluene | 23 | 94 | 80 |
| 6 | **4c** | toluene | -20 | 65 | 85 |
| 7 | **4c** | toluene | 0 | 79 | 84 |
| 8 | **4c** | DCM | 0 | 94 | 87 |
| 9 | **4c** | DCE | 0 | 95 | 88 |
| 10 | **4c** | DCE | 0 | 95 | 82[d] |

[a] The reaction was catalyzed by 20 mol% catalyst in the specified solvent (0.05 M). [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] Using 10 mol% catalyst. DCM = dicholoromethane, DCE = 1,2-dichloroethane, M. S. = molecular sieves.




**Scheme 2.** Substrate scope of the aza-pinacol rearrangements. DCE = 1,2-dichloroethane, M. S. = molecular sieves.

With the optimized reaction conditions identified, the substrate scope of the aza-pinacol rearrangement was next examined (Scheme 2). A variety of tertiary alcohols **1** with varied $R_1$, $R_2$, and pendent nucleophiles (XH) proved to be efficient substrates. The aza-pinacol rearrangement/cyclization cascade sequence proceeded smoothly, generating fused indolines **2** with excellent yields and good to excellent enantioselectivities. The absolute configuration of **2d** was determined by single-crystal X-ray diffraction.[13] The $R_2$ had a marked effect on enantioselectivity as exemplified by the different ees of **2b** ($R_2$ = Bn) and **2c** ($R_2$ = Me). Varying the electronic and steric properties of the Ar had little effect on both yield and enantioselectivities (**2d-g**). Both pyrrolidinoindolines and furoindolines (**2h**, **2k**) could be synthesized with good to excellent yields and ees. In addition, substrates bearing a bromine substituent ($R_1$ = Br) were investigated, generating indolines with synthetic handles for further elaboration (**2i-2l**). Considering the rich chemistry of aryl bromides for coupling reactions, the divergent syntheses of numerous derivatives could be possible. Substrates without pendent nucleophiles were also examined (**2m, 2n**). While low enantioselectivities were observed for these two substrates, the reactions served as

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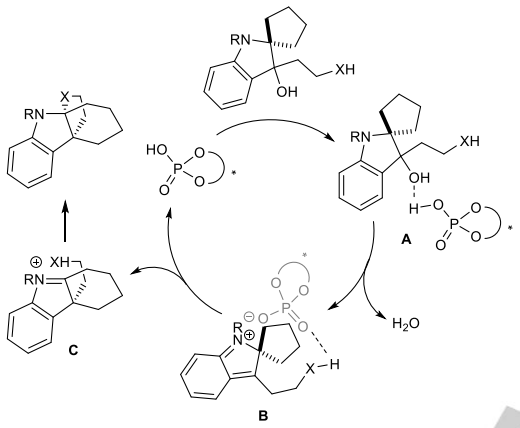
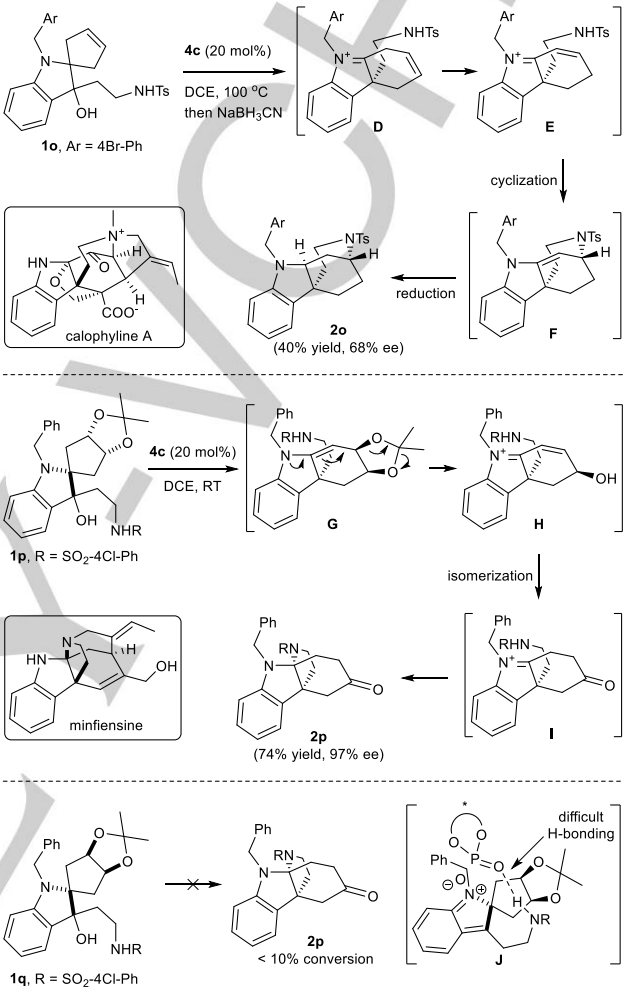
control experiments for the elucidation of the reaction mechanism, indicating that the formation of iminium ($R_2 \neq H$) and the pendent nucleophiles were essential for organizing the catalytic transition state.

Based on the above results, the reaction pathway for the aza-pinacol rearrangement was proposed (Scheme 3). Dehydration of the tertiary alcohol was facilitated by the chiral phosphoric acid via hydrogen bonding (**A**), resulting in the formation of aza-*ortho*-xylylene intermediate **B**. The orientation of the transition state was directed through potential two-site binding between the bifunctional chiral phosphate and **B**: electrostatic interaction via ion pair and hydrogen bonding with the pendent nucleophile. Subsequently, enantioselective aza-pinacol rearrangement (**C**) followed by ring closure delivered the fused indoline product.




**Scheme 3.** Proposed catalytic pathway.

To demonstrate the synthetic potential of the phosphoric acid catalyzed aza-pinacol rearrangement for natural products synthesis, complex substrates (**1o**-**1q**) were prepared and investigated (Scheme 4). High temperature was required for the rearrangement of **1o**, generating the core structure of natural product calophyline A (**2o**) after reduction with $NaBH_3CN$ in modest yield and enantioselectivity. The cascade reaction sequence included aza-pinacol rearrangement (**D**), alkene isomerization (**E**) and conjugate addition to afford intermediate **F**, the instability of which presumably weaken the driving force of the entire process. To our delight, the aza-pinacol rearrangement initiated cascade reaction of **1p**, involving aza-pinacol rearrangement and tautomerization (**G**), elimination of the ketal (**H**), isomerization (**I**) and cyclization, proceeded with remarkable efficiency (74% yield, 97% ee) under mild conditions to afford ketone **2p** directly. While this type of ketone with varied protecting groups have been extensively used as the key intermediate in the total synthesis of natural product minfiensine,[14] catalytic enantioselective asymmetric synthesis of the structure has been only previously achieved by Overman and Jiao using palladium catalysis.[14a,14b,14g] Our approach offer an organocatalytic alternative to this polycyclic ketone with minimized functional group elaboration. Surprisingly, substrate **1q** (the diastereomer of **1p**) was not reactive under identical conditions, presumably because the hydrogen bonding interaction between the chiral phosphate and the pendent nucleophile became difficult with the placement of the ketal in the same side (**J**). This result further supported the proposed transition state in Scheme 3.

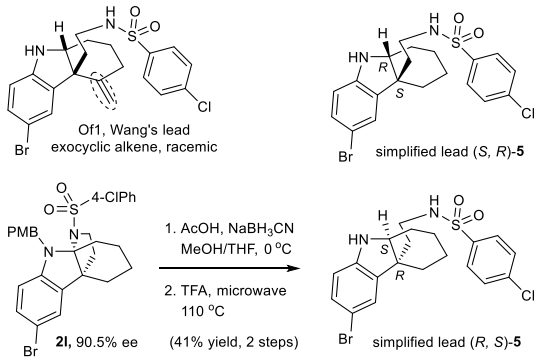



**Scheme 4.** Syntheses of the core structure of calophyline A and advanced intermediate to minfiensine. DCE = 1,2-dichloroethane.

The diverse biological activities of indoline natural products have served as the inspirations for the discovery of new lead compounds. Recently, the group of Wang has identified a potent lead compound Of1 (Scheme 5), which can be used as a resistance-modifying agent to resensitize methicillin-resistant *Staphylococcus aureus* (MASA) to β-lactam antibiotics.[6a,6b] Antibiotic-resistance threats have become a global problem that has need urgent attention.[15] While new classes of antibiotics have proven difficult to develop, the use of antibiotic adjuvants represents an appealing strategy because they can increase the life span of the currently used antibiotics and they are less susceptible to the development of new bacterial resistance.

In addition to the indoline core, the structure of Wang's lead compound Of1 contains an exocyclic alkene, which is the signature of the original synthesis via Gold-catalyzed indole-

alkyne cyclization.[6] We envisioned that our asymmetric aza-pinacol rearrangements could allow for the synthesis of a simplified version of Wang's lead without the exocyclic alkene and further examine the stereochemistry-based structure/activity relationship (SARs).




**Scheme 5.** Synthesis of the simplified lead compounds **5**. PMB = *p*-methoxylbenzyl, TFA = trifluoroacetic acid, THF = tetrahydrofuran.

From **2l**, the two step synthetic transformations involving reductive ring opening and deprotection delivered the simplified lead compound (*R, S*)-**5**. Similarly, (*S, R*)-**5** was prepared from the enantiomer of **2l**, which was obtained by the asymmetric aza-pinacol rearrangement using (*S*)-**4c** as the catalyst. Gratifyingly, both enantiomers of **5** were seen to potentiate the activity of several β-lactam antibiotics in a multidrug-resistant MARA strain BAA-1695 with the same level of potency as that of the Wang's lead compound (Of1), indicating that the exocyclic alkene might be not required for the bioactivity (Table 2). The (*S, R*)-**5** was 2-fold more active in potentiating the activity of amox/clav, cefazolin and meropenem, albeit no marked difference in MIC was seen for methicillin and oxacillin. Although no marked difference in MIC for (*R, S*)-**5** and (*S, R*)-**5** in potentiating the activity of methicillin toward the multidrug-resistant MARA strain was observed, further bacteria growth and killing experiments showed that the (*S, R*)-**5** was more active as a resistance-modifying agent in killing bacteria (see supporting information). The structural simplification and stereochemistry-based structure/activity relationship will further inspire the development of more potent compounds to repress antibiotic resistance.

**Table 2.** Selected potentiation results of **5** (20 μM).

| Entry | antibiotics | MIC [μg/mL] | MIC [μg/mL] [+ (*S, R*)-**5**] | MIC [μg/mL] [+ (*R, S*)-**5**] |
|---|---|---|---|---|
| 1 | Methicillin | 128 | 4-8 | 4-8 |
| 2 | Amox/clav | 8-16 | 2-4 | 4-8 |
| 3 | Cefazolin | 8-16 | 2-4 | 4-8 |
| 4 | Meropenem | 16-32 | 1-2 | 2-4 |
| 5 | Oxacillin | 16-32 | 8-16 | 8-16 |

In summary, we have developed the first phosphoric acid catalyzed enantioselective aza-pinacol rearrangement and demonstrated that a cyclic aza-*ortho*-xylylene intermediate could be utilized to facilitate asymmetric skeletal rearrangements. This method provides direct access to the indoline core of a variety of natural products and medicinally important lead compounds with good to excellent enantioselectivities. The synthetic utility has been demonstrated by the organocatalytic asymmetric synthesis of a key intermediate to natural product minfiensine and identification of a simplified version of Wang's lead to fight antibiotic-resistance.

## Acknowledgements

This work is supported by the "1000 Talents Recruitment Program" (for LZ), Tsinghua-Peiking University Center for Life Science, National Natural Science Foudation of China (Grant No 21302107 and 21672123 for LZ; 81671972 and 31530082 for J.-R.Z), Tsinghua University Research Program (No. 20161080058 for J.-R.Z), and Grand Challenges Exploration of the Bill and Melinda Gates Foundation (No. OPP1021992 for J.-R.Z).

**Keywords:** indoline • aza-pinacol• phosphoric acid •antibiotics• rearrangement

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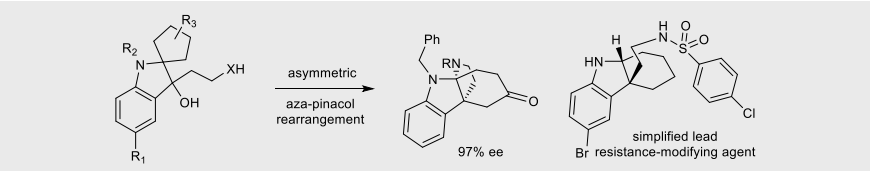


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