ChemPubSoc Europe

DOI: 10.1002/chem.201603049

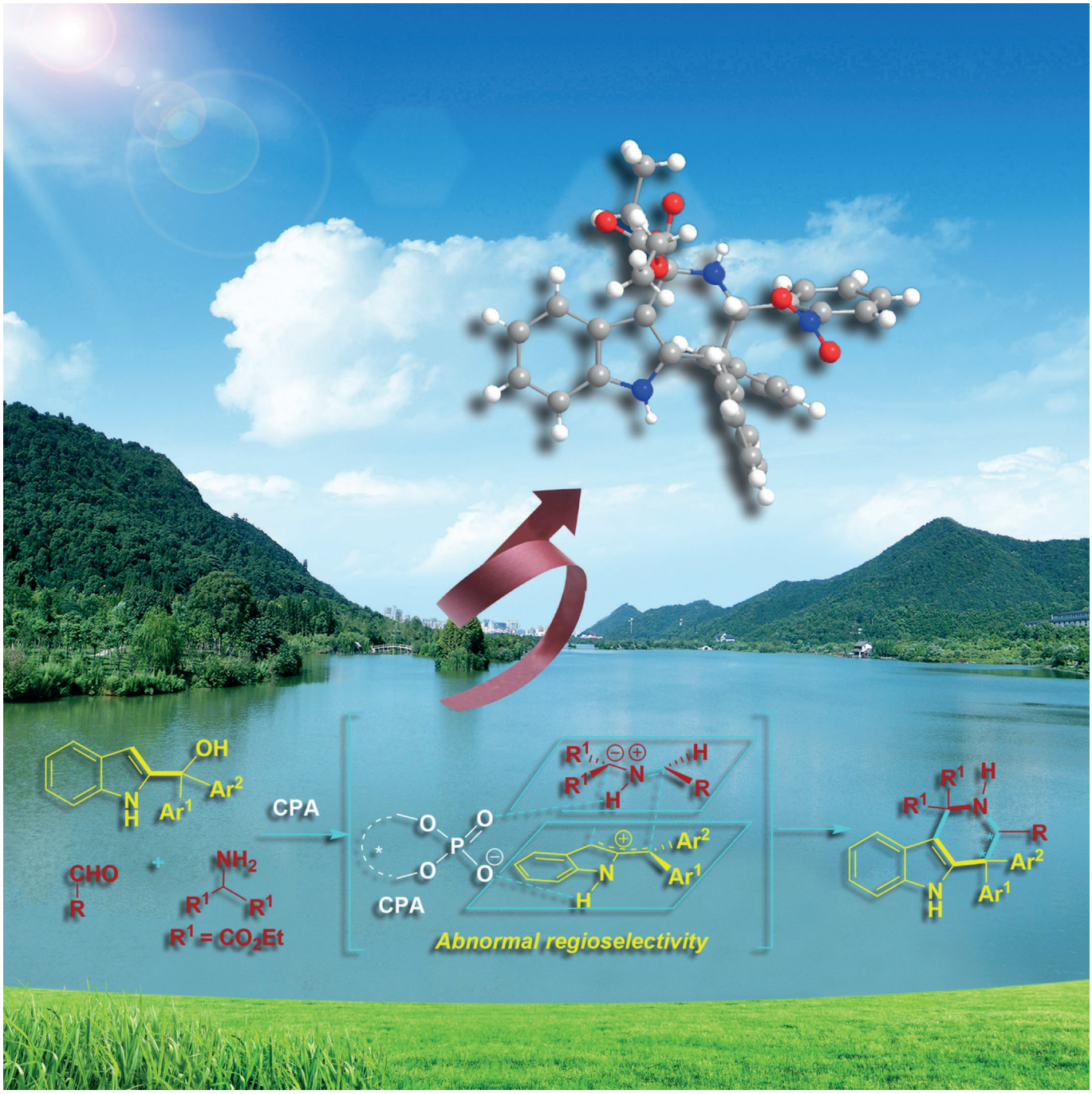
CHEMISTRY
A European Journal
Communication

Heterocycles

Catalytic Enantioselective and Regioselective [3+3] Cycloadditions Using 2-Indolylmethanols as 3C Building Blocks

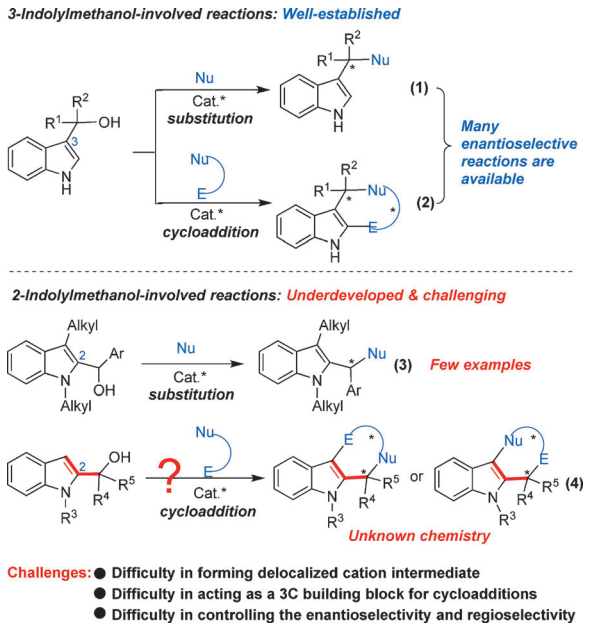
Xiao-Xue Sun, Hong-Hao Zhang, Guo-Hao Li, Ying-Ying He, and Feng Shi*[a]

In memory of Professor Richard F. Heck



Abstract: The first catalytic asymmetric cycloaddition using 2-indolylmethanols as 3C building blocks has been established by a chiral phosphoric acid-catalyzed enantioselective and regioselective [3+3] cycloaddition of 2-indolylmethanols with azomethine ylides, which constructed biologically important tetrahydro-γ-carboline frameworks in high yields and excellent enantioselectivities (up to 83% yield, 99:1 e.r.). This reaction not only represents the first application of 2-indolylmethanols as 3C building blocks in catalytic asymmetric cycloadditions, but also has established an abnormal regioselectivity in indolylmethanol-involved transformations.

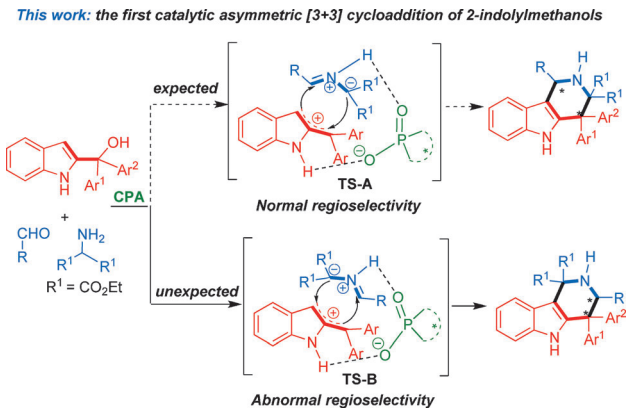
The catalytic asymmetric synthesis of enantioenriched indole derivatives has aroused great concern in the community of chemistry because chiral indole frameworks constitute the core structures of many important natural products and pharmaceuticals.[1] Among different approaches, indolylmethanol-involved catalytic asymmetric reactions have recently emerged as powerful methods for synthesizing optically pure indole derivatives (Scheme 1).[2–5] Particularly, 3-indolylmethanols have proven to be versatile reactants for catalytic asymmetric substitutions [Eq. (1)][3] or cycloadditions [Eq. (2)] [4] in the presence of chiral catalysts, and many enantioselective transformations involving 3-indolylmethanols have been established.[2–4]



Scheme 1. Profile of indolylmethanol-involved catalytic asymmetric reactions.

However, in sharp contrast, 2-indolylmethanols have scarcely been utilized for catalytic asymmetric reactions in spite of the fact that this class of reactants has promising applications in the synthesis of natural products and chiral indole derivative.[6] Until recently, Han and co-workers pioneered the catalytic asymmetric substitutions of 2-indolylmethanols using indoles[5a] or enamides[5b] as nucleophiles (Nu) in the presence of chiral Brønsted acid [Eq. (3)]. Despite this pioneering work, 2-indolylmethanol-involved catalytic asymmetric reactions are rather limited and are confined to several examples of enantioselective substitutions.[5] More importantly, the chemistry of catalytic asymmetric cycloadditions using 2-indolylmethanols as 3C building blocks still remains unknown [Eq. (4)]. Very surprisingly, even racemic cycloadditions involving 2-indolylmethanols have sporadically been reported in the literature.[6d,e,7] The underdevelopment of 2-indolylmethanol-involved enantioselective reactions, especially enantioselective cycloadditions, is largely ascribed to the great challenges in such transformations. The first one is the difficulty of 2-indolylmethanol in forming resonant intermediates of carbocation, vinyliminium and delocalized cation, which are key intermediates for 2-indolylmethanol-involved reactions. The second one is the difficulty of 2-indolylmethanol in acting as a 3C building block for cycloadditions. The last one is the difficulty in controlling the enantioselectivity and regioselectivity of the catalytic asymmetric cycloadditions, because there are two possible cycloaddition modes with reversed regioselectivity [Eq. (4)]. Therefore, developing catalytic asymmetric cycloadditions of 2-indolylmethanols is of great significance and becomes an urgent task.

To fulfill this task and as our continuous interest in synthesizing chiral indole derivatives, we designed a chiral phosphoric acid (CPA)[1e,8] catalyzed [3+3] cycloaddition of 2-indolylmethanols with azomethine ylides[9–11] which was generated in situ from aldehydes and amino ester (Scheme 2). In this design, CPA as an acidic catalyst not only facilitates the transformation of 2-indolylmethanols into resonant intermediates of carbocation, vinyliminium and delocalized cation, but also accelerates the generation of azomethine ylides from aldehydes and



Scheme 2. Design of the catalytic asymmetric cycloadditions of 2-indolylmethanols and observed abnormal regioselectivity.

[a] X.-X. Sun, H.-H. Zhang, G.-H. Li, Y.-Y. He, Prof. Dr. F. Shi
Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, School of Chemistry and Chemical Engineering
Jiangsu Normal University, Xuzhou, 221116 (P. R. China)
E-mail: fshi@jsnu.edu.cn

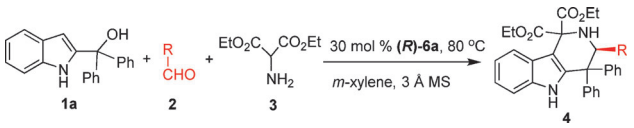
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201603049.

amino ester. More importantly, CPA anion as a chiral catalyst could simultaneously activate both of the two intermediates (delocalized cation and azomethine ylide) by dual hydrogen-bonding interaction, which played a crucial role in controlling the reactivity, enantioselectivity and regioselectivity of the designed [3+3] cycloaddition. So, this design will not only confront the great challenges in catalytic asymmetric cycloadditions of 2-indolylmethanols, but also provide an efficient strategy for constructing biologically important tetrahydro-γ-carboline frameworks[12] with optical purity. Very interestingly, during our investigation, it was found that the [3+3] cycloaddition occurred with an abnormal regioselectivity via a possible transition state (**TS-B**) rather than the anticipated **TS-A**. It should be mentioned that in previous transformations of indolylmethanols [Eq. (1)–(3)], the nucleophiles always attacked the carbon which was adjacent to the OH group of indolylmethanols, which resulted in a normal regioselectivity.[2–5]

Herein, we report the first catalytic asymmetric cycloaddition using 2-indolylmethanols as 3C building blocks, which makes use of chiral phosphoric acid-catalyzed enantioselective and regioselective [3+3] cycloaddition of 2-indolylmethanols with azomethine ylides in situ generated from aldehydes and amino ester, leading to the construction of biologically important tetrahydro-γ-carboline framework at high yields and excellent enantioselectivities (up to 83% yield, 99:1 e.r.).

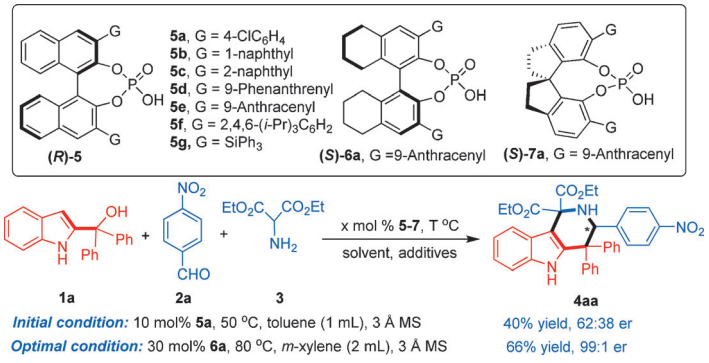
Initially, the reaction of 2-indolylmethanol **1a**, 4-nitrobenzaldehyde **2a**, diethyl 2-aminomalonate **3** was tentatively employed as a model reaction to testify the possibility of the designed [3+3] cycloaddition (Scheme 3). Gratifyingly and surprisingly, in the presence of CPA **5a**, the designed [3+3] cycloaddition occurred in an unexpected abnormal regioselectivity, although the generated tetrahydro-γ-carboline product **4aa** was in a low yield of 40% and poor enantioselectivity of 62:38 e.r. To further improve the enantioselectivity and the yield, a series of BINOL, H_8-BINOL and SPINOL-derived CPAs **5**–**7** were screened for the reaction, which found that CPA **6a** was the best catalyst in terms of the enantioselectivity. Besides, different reaction parameters such as solvents, additives, temperature, molar ratio and the catalyst loading were carefully evaluated to find the most suitable reaction conditions (see the Supporting Information for details). Finally, the best enantioselectivity (99:1 e.r.) was obtained by using *m*-xylene as solvent at a higher temperature of 80 °C.

Table 1. Generality of aldehydes **2**.[a]



Entry	4	R (2)	Yield [%][b]	e.r.[c]
1	**4aa**	4-$NO_2C_6H_4$ (**2a**)	66	99:1
2	**4ab**	4-CNC_6H_4 (**2b**)	81	99:1
3	**4ac**	4-$CO_2MeC_6H_4$ (**2c**)	51	97:3
4	**4ad**	4-$CF_3C_6H_4$ (**2d**)	54	97:3
5	**4ae**	4-FC_6H_4 (**2e**)	63	97:3
6	**4af**	4-ClC_6H_4 (**2f**)	64	96:4
7	**4ag**	4-BrC_6H_4 (**2g**)	66	98:2
8	**4ah**	3-$CF_3C_6H_4$ (**2h**)	79	99:1
9	**4ai**	3-FC_6H_4 (**2i**)	59	97:3
10	**4aj**	3-BrC_6H_4 (**2j**)	58	97:3
11	**4ak**	2-$NO_2C_6H_4$ (**2k**)	72	96:4
12	**4al**	2-CNC_6H_4 (**2l**)	56	96:4
13	**4am**	3-Cl,4-FC_6H_3 (**2m**)	72	99:1
14	**4an**	3-F,4-ClC_6H_3 (**2n**)	69	99:1
15	**4ao**	Ph (**2o**)	58	93:7
16	**4ap**	4-MeC_6H_4 (**2p**)	64	91:9
17	**4aq**	3-$MeOC_6H_4$ (**2q**)	65	90:10
18	**4ar**	2-$MeOC_6H_4$ (**2r**)	78	87:13
19	**4as**	2-thiophenyl (**2s**)	61	92:8
20	**4at**	3-thiophenyl (**2t**)	78	95:5
21[d]	**4au**	cyclopentyl (**2u**)	62	90:10

[a] Unless indicated otherwise, the reaction was carried out at the 0.1 mmol scale in *m*-xylene (2 mL) with 3 Å MS (100 mg) at 80 °C for 15 h, and the mole ratio of **1a**:**2**:**3** was 1:1.2:1.1. [b] Isolated yield. [c] The e.r. value was determined by HPLC. [d] Catalyzed by (*R*)-**5b** in ethyl acetate with 5 Å MS at 30 °C for 17 h.



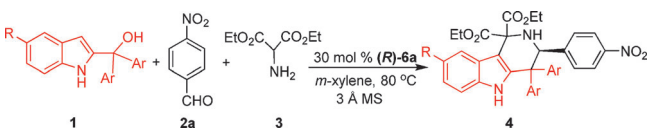
Scheme 3. Catalysts and model reaction utilized to optimize the conditions.

With the optimal conditions known, we then investigate the generality of this catalytic asymmetric [3+3] cycloaddition of 2-indolylmethanols. Firstly, the substrate scope of aldehydes **2** was examined. As shown in Table 1, a wide range of aromatic, heteroaromatic and aliphatic aldehydes were amenable to the [3+3] cycloaddition, which delivered the tetrahydro-γ-carboline products **4** in generally good yields and excellent enantioselectivities. In detail, a variety of aromatic aldehydes bearing electronically poor, neutral or rich substituents could smoothly participate in the reaction (entries 1–18). Clearly, electronically poor benzaldehydes appear to be competent substrates (entries 1–14), which offered the [3+3] cycloaddition products in uniformed excellent enantioselectivities (96:4 to 99:1 e.r.). Besides, it seemed that the position of the substituents had no evident effect on the enantioselectivity, because either *para*- (entries 1–7), *meta*- (entries 8–10) or *ortho*- (entries 11 and 12) substituted benzaldehydes could participate in the reaction in similarly satisfying enantioselectivities. However, the electronic nature of the substituents had a remarkable influence on the enantioselectivity due to the fact that electronically neutral and rich benzaldehydes were inferior to electronically poor ones with regard to the enantioselectivity (entries 1–14 vs. 15–

18). It should be mentioned that electronically rich benzaldehydes often exhibited low reactivity or low enantioselective control in CPA-catalyzed cycloadditions of azomethine ylide, which should be largely ascribed to the difficulty in forming azomethine ylides from such aldehydes and the low reactivity of the generated azomethine ylides in cycloadditions.[13] So, the successful utilization of electronically rich benzaldehydes in the [3+3] cycloaddition would greatly enlarge the applicability of this approach. More importantly, heteroaromatic aldehydes as exemplified by **2s**–**2t** also proved to be suitable substrates, which smoothly underwent the [3+3] cycloaddition at good yields and high enantioselectivities (entries 19 and 20). Notably, aliphatic aldehydes normally showed extremely low reactivity (much lower than electron-rich benzaldehydes) in azomethine ylide-involved cycloadditions.[9g,13a,14] So, the application of aliphatic aldehydes in such reactions is very challenging. After suitably adjusting the reaction conditions, cyclopentanecarbaldehyde **2u** as an aliphatic aldehyde could take part in the [3+3] cycloaddition to give the corresponding product **4au** at a good yield of 62% and a high enantioselectivity of 90:10 e.r., which would further expanded the substrate scope of the reaction.

Secondly, the applicability of 2-indolylmethanols **1** was investigated by the reactions with 4-nitrobenzaldehyde **2a** and diethyl 2-aminomalonate **3** under the optimal conditions (Table 2). As shown in entries 1–4, several 2-indolylmethanols

Table 2. Applicability of 2-indolylmethanols **1**.[a]



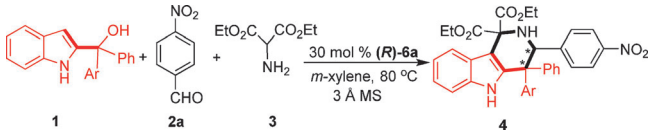
Entry	4	R/Ar (1)	Yield [%][b]	e.r.[c]
1	**4aa**	H/Ph (**1a**)	66	99:1
2	**4ba**	H/4-FC_6H_4 (**1b**)	57	98:2
3	**4ca**	H/3-FC_6H_4 (**1c**)	46	99:1
4	**4da**	H/3-MeC_6H_4 (**1d**)	83	97:3
5	**4ea**	Br/Ph (**1e**)	77	99:1

[a] Unless indicated otherwise, the reaction was carried out at the 0.1 mmol scale in *m*-xylene (2 mL) with 3 Å MS (100 mg) at 80 °C for 15 h, and the mole ratio of **1**:**2a**:**3** was 1:1.2:1.1. [b] Isolated yield. [c] The e.r. value was determined by HPLC.

1 linking different aromatic (Ar) groups could serve as suitable substrates in the [3+3] cycloadditions, which generated the tetrahydro-γ-carboline products **4** in excellent enantioselectivities (97:3 to 99:1 e.r.). Moreover, the applicability of substituted 2-indolylmethanols was exemplified by C-7 bromo-substituted substrate **1e**, which successfully participated in the [3+3] cycloaddition to give product **4ea** at a high yield and an excellent enantioselectivity (entry 5).

In addition, several unsymmetrical 2-indolylmethanols **1** were employed as substrates to the [3+3] cycloadditions with 4-nitrobenzaldehyde **2a** and diethyl 2-aminomalonate **3** (Table 3). Gratifyingly, the substrates bearing two different

Table 3. Using unsymmetrical 2-indolylmethanols **1** as substrates.[a]

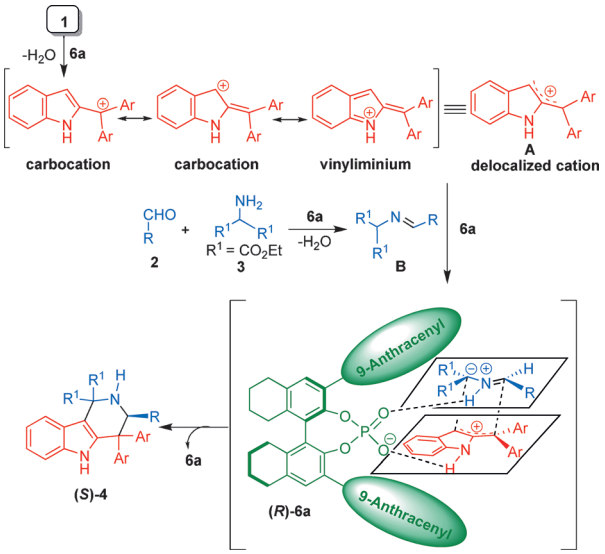


Entry	4	Ar	Yield [%][b]	d.r.[c]	e.r. (major/minor)[d]
1	**4fa**	4-FC_6H_4 (**1f**)	50	55:45	98:2/98:2
2	**4ga**	4-ClC_6H_4 (**1g**)	44	56:44	97:3/95:5
3	**4ha**	4-MeC_6H_4 (**1h**)	64	53:47	94:6/96:4
4	**4ia**	3-MeC_6H_4 (**1i**)	79	71:29	99:1/99:1
5	**4ja**	2-MeC_6H_4 (**1j**)	54	>95:5	95:5/–
6[e]	**4ka**	1-naphthyl (**1k**)	37	85:15	84:16/–

[a] Unless indicated otherwise, the reaction was carried out at the 0.1 mmol scale in *m*-xylene (2 mL) with 3 Å MS (100 mg) at 80 °C for 15 h, and the mole ratio of **1**:**2a**:**3** was 1:1.2:1.1. [b] Isolated yield. [c] The d.r. value was determined by ^{1}H NMR. [d] The e.r. value was determined by HPLC. [e] Performed in toluene at 50 °C for 19 h.

phenyl groups could smoothly participate in the desired [3+3] cycloaddition to give the corresponding products **4** at moderate to good yields and excellent enantioselectivities (entries 1–5). It seemed that the position of the substituents on the aryl group imposed some effect on the diastereoselectivity of the reaction. In detail, 2-indolylmethanols **1f**–**1h** bearing a *para*-substituted aryl group exhibited the lowest capability in controlling the diastereoselectivity, whereas 2-indolylmethanol **1i** bearing a *meta*-substituted aryl group could give the corresponding product in a moderate diastereoselectivity. Notably, 2-indolylmethanol **1j** bearing an *ortho*-substituted aryl group was much superior to others in controlling the diastereoselectivity, which gave the [3+3] cycloaddition product in the highest diastereoselectivity of >95:5 d.r. This phenomenon might be associated with the steric effect of *ortho*-substituted aryl group, which was beneficial to the diastereoselectivity during the process of cycloaddition. When 2-indolylmethanol **1k** bearing a bulky 1-naphthyl substituent was employed to the reaction with 4-nitrobenzaldehyde **2a** and diethyl 2-aminomalonate **3** under the original standard conditions, only trace of the product was observed. So, we modulated the reaction condition by lowering the reaction temperature to 50 °C and using toluene as a solvent. Under this reaction condition, the [3+3] cycloaddition product **4ka** could be generated in a good diastereoselectivity of 85:15 d.r. and a considerable enantioselectivity of 84:16 e.r. (entry 6). However, because of the bulky size of 1-naphthyl group, this substrate **1k** exhibited much lower reactivity, which might account for the low yield of the reaction.

The absolute configuration of product *ent*-**4ak** (99:1 e.r. after recrystallization) generated in the presence of **(*S*)-6a** was unambiguously determined to be (*R*) by single crystal X-ray diffraction analysis (see the Supporting Information for details).[15] So, the absolute configurations of product **4ak** and other products **4** in Tables 1 and 2 produced in the presence of **(*R*)-6a** were assigned to be (*S*) by reasoning and analogy. Based on the experimental results, we suggested a possible reaction pathway and activation mode to explain the chemistry and the



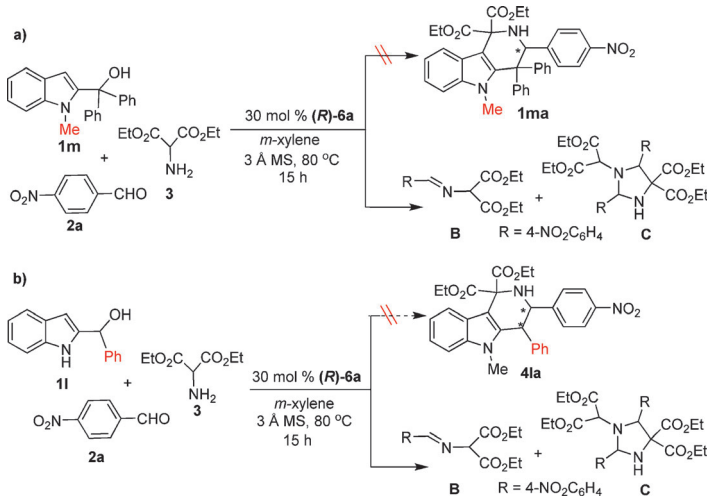
Scheme 4. Suggested reaction pathway and activation mode.

stereochemistry of the [3+3] cycloaddition (Scheme 4). Initially, in the presence of CPA **6a**, 2-indolylmethanols **1** were converted into cation intermediates with resonant structures of carbocation, vinyliminium and delocalized cation **A**. At the same time, CPA **6a** promoted the condensation of aldehydes **2** with amino ester **3** to generate the aldimine intermediates **B**, which served as precursors of azomethine ylide. Then, the anion of CPA **6a** simultaneously activated both the azomethine ylide and the delocalized cation via dual hydrogen-bonding interaction, which facilitated an enantioselective [3+3] cycloaddition between the two intermediates to afford the tetrahydro-γ-carboline products **4** with (*S*)-configuration. The rigid structure of H_8-BINOL backbone and the bulky 3,3′-(9-anthracenyl) substituents of CPA **6a** created a chiral environment, which contributed greatly to the obtained excellent enantioselectivity. The observed abnormal regioselectivity might be associated with the steric repulsion between the two ester groups (R^1) of the azomethine ylide and the two bulky Ar groups of the delocalized cation. Besides, the [3+3] cycloaddition was tentatively suggested to undergo a concerted reaction pathway, because no stepwise-addition products were detected in the reaction process.

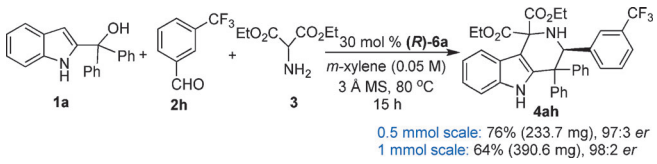
To verify the suggested activation mode of CPA to 2-indolylmethanols, a control experiment was carried out, which utilized *N*-methyl protected 2-indolylmethanol **1m** as a substrate under the standard conditions (Scheme 5a). As expected, no [3+3] cycloaddition occurred. Instead, only a small amount of aldimine **B** and homo-1,3-diplolar cycloaddition product **C**[13c] were generated via the condensation of aldehyde **2a** with amino ester **3**. This result indicated that the indole N–H group of 2-indolylmethanols played a crucial role in controlling the reactivity of the [3+3] cycloaddition by forming a hydrogen bond with CPA. Besides, we also employed 2-indolylmethanol **1l** bearing one aryl substituent to the reaction with 4-nitrobenzaldehyde **2a** and diethyl 2-aminomalonate **3** under the standard conditions. However, no [3+3] cycloaddition product **4la** was generated, while a large amount of homo-1,3-diplolar cycloaddition product **C** along with aldimine **B** was produced. This result indicated that this type of 2-indolylmethanols bearing one aryl substituent could hardly generate a carbocation intermediate as stable as that generated from 2-indolylmethanols bearing two aryl substituents.

Moreover, the [3+3] cycloaddition of 2-indolylmethanol **1a**, aldehyde **2h** and amino ester **3** was performed on a 0.5 and 1 mmol scale under the standard conditions (Scheme 6). The two large-scale reactions proceeded smoothly to generate the tetrahydro-γ-carboline product **4ah** in good yields and excellent enantioselectivities, demonstrating the utility of this reaction.

Finally, a preliminary derivatization of compound **4ea** was performed by Suzuki coupling with 4-chlorophenylboronic acid, which smoothly furnished the product **8** in a high yield of 86% and a perfect enantioselectivity of >99.5:0.5 e.r. (Scheme 7).

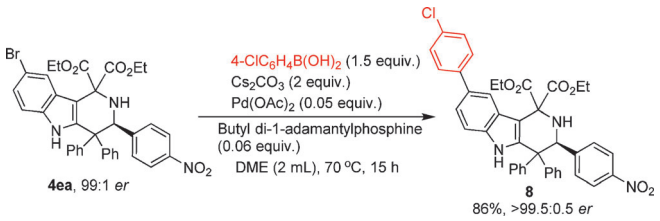


Scheme 5. Control experiments.



Scheme 6. Large scale synthesis.

In summary, we have established the first catalytic asymmetric cycloaddition using 2-indolylmethanols as 3C building blocks, which makes use of chiral phosphoric acid-catalyzed enantioselective and regioselective [3+3] cycloaddition of 2-indolylmethanols with azomethine ylides, leading to the construction of biologically important tetrahydro-γ-carboline framework at high yields and excellent enantioselectivities (up



Scheme 7. Preliminary derivation.

to 83% yield, 99:1 e.r.). This reaction not only represents the first application of 2-indolylmethanols as 3C building blocks in catalytic asymmetric cycloadditions, but also has established an abnormal regioselectivity in indolylmethanol-involved transformations. More importantly, this approach has settled the great challenges in 2-indolylmethanol-involved catalytic asymmetric cycloadditions, which will open a new window for developing 2-indolylmethanol-involved catalytic enantioselective transformations.

Experimental Section

General procedure for the synthesis of [3+3] cycloaddition products

After a solution of aldehydes **2** (0.12 mmol), amino ester **3** (0.11 mmol), the catalyst (*R*)-**6a** (0.03 mmol), and 3 Å molecular sieves (100 mg) in *m*-xylene (1 mL) was stirred at 25 °C for 1 h, the solution of 2-indolylmethanols **1** (0.1 mmol) in *m*-xylene (1 mL) was added. After being stirred at 80 °C for 15 h, the reaction mixture was filtered to remove molecular sieves and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford pure products **4**.

Acknowledgements

We are grateful for financial supports from NSFC (21372002 and 21232007), PAPD, Natural Science Foundation of Jiangsu Province (BK20160003).

Keywords: asymmetric catalysis · azomethine ylide · cycloaddition · enantioselectivity · organocatalysis

[1] For some reviews, see: a) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190 – 2201; b) M. Zeng, S.- L. You, *Synlett* **2010**, 1289 – 1301; c) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev.* **2010**, *39*, 4449 – 4465; d) R. Dalpozzo, *Chem. Soc. Rev.* **2015**, *44*, 742 – 778; e) H. Wu, Y.-P. He, F. Shi, *Synthesis* **2015**, *47*, 1990 – 2016.

[2] For a recent review: a) Y. Chen, L. Wang, J. Xiao, *Asian J. Org. Chem.* **2014**, *3*, 1036 – 1052.

[3] For enantioselective substitutions of 3-indolylmethanols: a) Q.-X. Guo, Y.-G. Peng, J.-W. Zhang, L. Song, Z. Feng, L.-Z. Gong, *Org. Lett.* **2009**, *11*, 4620 – 4623; b) F.-L. Sun, M. Zeng, Q. Gu, S.-L. You, *Chem. Eur. J.* **2009**, *15*, 8709 – 8712; c) P. G. Cozzi, F. Benfatti, L. Zoli, *Angew. Chem. Int. Ed.* **2009**, *48*, 1313 – 1316; *Angew. Chem.* **2009**, *121*, 1339 – 1342; d) J. Xiao, K. Zhao, T.-P. Loh, *Chem. Asian J.* **2011**, *6*, 2890 – 2894; e) J. Xiao, *Org. Lett.* **2012**, *14*, 1716 – 1719; f) J. Xiao, K. Zhao, T.-P. Loh, *Chem. Commun.* **2012**, *48*, 3548 – 3550; g) L. Song, Q.-X. Guo, X.-C. Li, J. Tian, Y.-G. Peng, *Angew. Chem. Int. Ed.* **2012**, *51*, 1899 – 1902; *Angew. Chem.* **2012**, *124*, 1935 – 1938; h) C. Guo, J. Song, J.-Z. Huang, P.-H. Chen, S.-W. Luo, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2012**, *51*, 1046 – 1050; *Angew. Chem.* **2012**, *124*, 1070 – 1074; i) J. Song, C. Guo, A. Adele, H. Yin, L.-Z. Gong, *Chem. Eur. J.* **2013**, *19*, 3319 – 3323; j) B. Xu, L.-L. Shi, Y.-Z. Zhang, Z.-J. Wu, L.-N. Fu, C.-Q. Luo, L.-X. Zhang, Y.-G. Peng, Q.-X. Guo, *Chem. Sci.* **2014**, *5*, 1988 – 1991; k) Y. Liu, H.-H. Zhang, Y.-C. Zhang, Y. Jiang, F. Shi, S.-J. Tu, *Chem. Commun.* **2014**, *50*, 12054 – 12057; l) W. Tan, B.-X. Du, X. Li, X. Zhu, F. Shi, S.-J. Tu, *J. Org. Chem.* **2014**, *79*, 4635 – 4643; m) Z.-L. Guo, J.-H. Xue, L.-N. Fu, S.-E. Zhang, Q.-X. Guo, *Org. Lett.* **2014**, *16*, 6472 – 6475; n) X.-D. Tang, S. Li, R. Guo, J. Nie, J.-A. Ma, *Org. Lett.* **2015**, *17*, 1389 – 1392; o) X.-X. Sun, B.-X. Du, H.-H. Zhang, L. Ji, F. Shi, *ChemCatChem* **2015**, *7*, 1211 – 1221; p) F. Jiang, Y.-C. Zhang, X. Yang, Q.-N. Zhu, F. Shi, *Synlett* **2016**, *27*, 575 – 580.

[4] For enantioselective cyclizations of 3-indolylmethanols: a) B. Han, Y.-C. Xiao, Y. Yao, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2010**, *49*, 10189 – 10191; *Angew. Chem.* **2010**, *122*, 10387 – 10389; b) B. Xu, Z.-L. Guo, W.-Y. Jin, Z.-P. Wang, Y.-G. Peng, Q.-X. Guo, *Angew. Chem. Int. Ed.* **2012**, *51*, 1059 – 1062; *Angew. Chem.* **2012**, *124*, 1083 – 1086; c) J. Huang, S. Luo, L.-Z. Gong, *Acta. Chim. Sin.* **2013**, *71*, 879 – 883; d) F. Shi, R.-Y. Zhu, W. Dai, C.-S. Wang, S.-J. Tu, *Chem. Eur. J.* **2014**, *20*, 2597 – 2604; e) W. Dai, H. Lu, X. Li, F. Shi, S.-J. Tu, *Chem. Eur. J.* **2014**, *20*, 11382 – 11389; f) C. Zhang, L.-X. Zhang, Y. Qiu, B. Xu, Y. Zong, Q.-X. Guo, *RSC Adv.* **2014**, *4*, 6916 – 6919; g) W. Tan, X. Li, Y.-X. Gong, M.-D. Ge, F. Shi, *Chem. Commun.* **2014**, *50*, 15901 – 15904; h) F. Shi, H.-H. Zhang, X.-X. Sun, J. Liang, T. Fan, S.-J. Tu, *Chem. Eur. J.* **2015**, *21*, 3465 – 3471; i) C. Lebée, A. O. Kataja, F. Blanchard, G. Masson, *Chem. Eur. J.* **2015**, *21*, 8399 – 8402.

[5] For enantioselective substitutions of 2-indolylmethanols: a) S. Qi, C.-Y. Liu, J.-Y. Ding, F.-S. Han, *Chem. Commun.* **2014**, *50*, 8605 – 8608; b) C.-Y. Liu, F.-S. Han, *Chem. Commun.* **2015**, *51*, 11844 – 11847; c) Y.-X. Gong, Q. Wu, H.-H. Zhang, Q.-N. Zhu, F. Shi, *Org. Biomol. Chem.* **2015**, *13*, 7993 – 8000.

[6] a) T.-H. Fu, A. Bonaparte, S. F. Martin, *Tetrahedron Lett.* **2009**, *50*, 3253 – 3257; b) X. Zhong, Y. Li, F.-S. Han, *Chem. Eur. J.* **2012**, *18*, 9784 – 9788; c) X. Zhong, S. Qi, Y. Li, J. Zhang, F.-S. Han, *Tetrahedron* **2015**, *71*, 37343740; d) B. A. Granger, I. T. Jewett, J. D. Butler, B. Hua, C. E. Knezevic, E. I. Parkinson, P. J. Hergenrother, S. F. Martin, *J. Am. Chem. Soc.* **2013**, *135*, 12984 – 12986; e) X. Zhong, Y. Li, J. Zhang, F.-S. Han, *Org. Lett.* **2015**, *17*, 720 – 723.

[7] a) T. Yokosaka, H. Nakayama, T. Nemoto, Y. Hamada, *Org. Lett.* **2013**, *15*, 2978 – 2981; b) X. Zhong, Y. Li, J. Zhang, W.-X. Zhang, S.-X. Wang, F.-S. Han, *Chem. Commun.* **2014**, *50*, 11181 – 11184; c) K.-S. Cao, H.-X. Bian, W.-H. Zheng, *Org. Biomol. Chem.* **2015**, *13*, 6449 – 6452. During our preparation of this manuscript, Schneider reported a catalytic asymmetric [3+2] cycloaddition using 3-subsituted 2-indolylmethanol as a NCC building block: d) K. Bera, C. Schneider, *Chem. Eur. J.* **2016**, *22*, 7074 – 7078.

[8] For some reviews: a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744 – 5758; b) M. Terada, *Chem. Commun.* **2008**, *35*, 4097 – 4112; c) M. Terada, *Synthesis* **2010**, 1929 – 1982; d) J. Yu, F. Shi, L.-Z. Gong, *Acc. Chem. Res.* **2011**, *44*, 1156 – 1171; e) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047 – 9153. For some recent prominent examples: f) K. Saito, H. Miyashita, T. Akiyama, *Org. Lett.* **2014**, *16*, 5312 – 5315; g) K. Saito, Y. Moriya, T. Akiyama, *Org. Lett.* **2015**, *17*, 3202 – 3205; h) W. Zhao, Z. Wang, B. Chu, J. Sun, *Angew. Chem. Int. Ed.* **2015**, *54*, 1910 – 1913; *Angew. Chem.* **2015**, *127*, 1930 – 1933; i) Z. B. Wang, F. J. Ai, Z. Wang, W. X. Zhao, G. Y. Zhu, Z. Y. Lin, J. W. Sun, *J. Am. Chem. Soc.* **2015**, *137*, 383 – 389.

[9] For early reports on metal-catalyzed asymmetric [3+2] cycloadditions of azomethine ylide: a) J. M. Longmire, B. Wang, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13400 – 13401; b) A. S. Gothelf, K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2002**, *41*, 4236 – 4238; *Angew. Chem.* **2002**, *114*, 4410 – 4412. For early reports on organocatalytic asymmetric [3+2] cycloadditions of azomethine ylide: c) J. L. Vicario, S. Reboredo, D. Badía, L. Carrillo, *Angew. Chem. Int. Ed.* **2007**, *46*, 5168 – 5170; *Angew. Chem.* **2007**, *119*, 5260 – 5262; d) I. Ibrahem, R. Rios, J. Vesely, A. Cordova, *Tetrahedron Lett.* **2007**, *48*, 6252 – 6257; e) M.-X. Xue, X.-M. Zhang, L.-Z. Gong, *Synlett* **2008**, 691 – 694; f) Y.-K. Liu, H. Liu, W. Du, L. Yue, Y.-C. Chen, *Chem. Eur. J.* **2008**, *14*, 9873 – 9877; g) X.-H. Chen, W.-Q. Zhang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 5652 – 5653.

[10] For metal-catalyzed asymmetric [3+3] cycloadditions of azomethine ylide: a) M.-C. Tong, X. Chen, H.-Y. Tao, C.-J. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 12377 – 12380; *Angew. Chem.* **2013**, *125*, 12603 – 12606; b) H. Guo, H. Liu, F.-L. Zhu, R. Na, H. Jiang, Y. Wu, L. Zhang, Z. Li, H. Yu, B. Wang, Y. Xiao, X.-P. Hu, M. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 12641 – 12645; *Angew. Chem.* **2013**, *125*, 12873 – 12877.

[11] For catalytic asymmetric [6+3] cycloadditions of azomethine ylide: a) M. Potowski, J. O. Bauer, C. Strohmann, A. P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed.* **2012**, *51*, 9512 – 9516; *Angew. Chem.* **2012**, *124*, 9650 – 9654; b) Z.-L. He, H.- L. Teng, C.-J. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 2934 – 2938; *Angew. Chem.* **2013**, *125*, 3006 – 3010; c) H.-L. Teng, L. Yao, C.-J. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 4075 – 4080; d) Q.-H. Li, L. Wei, C.-J. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 8685 – 8692.

[12] a) S. A. A. Ebrik, A. Legrand, B. Rigo, D. Couturier, *J. Heterocycl. Chem.* **1999**, *36*, 997 – 1000; b) V. G. Nenaydenko, V. Y. Kabakov, PCT Int. Appl., **2011**, WO 2011014098A1 20110203.

[13] a) W.-J. Liu, X.-H. Chen, L.-Z. Gong, *Org. Lett.* **2008**, *10*, 5357 – 5360; b) F. Shi, G.-J. Xing, W. Tan, R.-Y. Zhu, S. Tu, *Org. Biomol. Chem.* **2013**, *11*, 1482 – 1489; c) R.-Y. Zhu, C.-S. Wang, F. Jiang, F. Shi, S.-J. Tu, *Tetrahedron: Asymmetry* **2014**, *25*, 617 – 624.

[14] J. Yu, L. He, X.-H. Chen, J. Song, W.-J. Chen, L.-Z. Gong, *Org. Lett.* **2009**, *11*, 4946 – 4949.

[15] CCDC 1471316 (*ent*-**4 ak**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Received: June 27, 2016
Published online on ■■ ■■, 0000

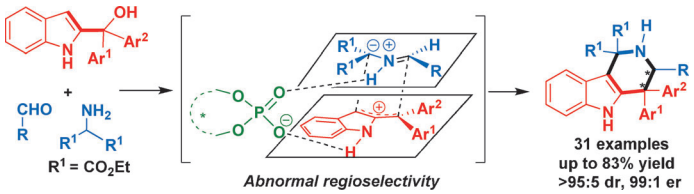
COMMUNICATION

Heterocycles

*X.-X. Sun, H.-H. Zhang, G.-H. Li, Y.-Y. He, F. Shi**

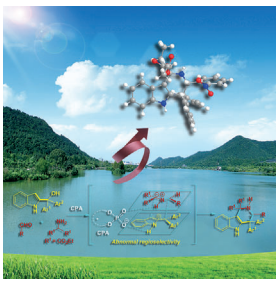
■■ – ■■

Catalytic Enantioselective and Regioselective [3+3] Cycloadditions Using 2-Indolylmethanols as 3C Building Blocks



Abnormally selective: The first catalytic asymmetric cycloaddition using 2-indolylmethanols as 3C building blocks has been established by chiral phosphoric acid-catalyzed enantioselective and regioselective [3+3] cycloaddition of 2-indolylmethanols with azomethine ylides, which constructed biologically important tetrahydro-γ-carboline framework in high yields and excellent enantioselectivities (up to 83% yield, 99:1 e.r.).

Asymmetric Catalysis



Due to the great challenges in 2-indolylmethanol-involved enantioselective cycloadditions, 2-indolylmethanols have scarcely been utilized for catalytic asymmetric cycloadditions. In their Communication on page ■■ ff., F. Shi and co-workers demonstrate the first catalytic asymmetric [3+3] cycloaddition of 2-indolylmethanols with azomethine ylides using a chiral phosphoric acid catalyst. Notably, this reaction proceeds with an abnormal regioselectivity, which provides easy access to enantioenriched tetrahydro-γ-carboline frameworks.