Discovery and enantiocontrol of axially chiral urazoles via organocatalytic tyrosine click reaction

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Axially chiral compounds play an important role in areas such as asymmetric catalysis. The tyrosine click-like reaction is an efficient approach for synthesis of urazoles with potential applications in pharmaceutical and asymmetric catalysis. Here we discover a class of urazole with axial chirality by restricted rotation around an N–Ar bond. By using bifunctional organocatalyst, we successfully develop an organocatalytic asymmetric tyrosine click-like reaction in high yields with excellent enantioselectivity under mild reaction conditions. The excellent remote enantiocontrol of the strategy originates from the efficient discrimination of the two reactive sites in the triazoleidone and transferring the stereochemical information of the catalyst into the axial chirality of urazoles at the remote position far from the reactive site.
Urazoles are important heterocyclic compounds with potential pharmaceutical applications and valuable utilities in the area of protein modification chemistry due to the simplicity of chemical synthesis and ease of optimization of reaction conditions. In addition, oxidation of urazoles gives rise to a very useful class of persistent cyclic hydrazyl radicals for versatile transformations. Consequently, there is a large demand for easy access to a broad variety of these compounds. In this regard, the tyrosine click reaction provides a straightforward strategy to access such compounds under mild conditions as illustrated in Fig. 1a, in which a class of cyclic diazodicarboxamides (triazodiones) reacted selectively and rapidly with the phenol side chain of tyrosine as first developed by the Barbas group for the application in bioconjugate chemistry. Although the development of other methodologies towards the synthesis of these compounds has also been reported, to the best of our knowledge, there is no report involving the direct construction of chiral urazoles in a catalytic enantioselective manner. Inspired by a developing research field on atropisomeric compounds possessing an N–Ar bond in arylurazoles, we speculated that the utility of bifunctional organocatalysts could be expected by distinguishing the two nonequivalent reactive nitrogen centres and transferring the central chirality of the catalyst into the axial chirality far from the reaction site. As part of our continued interest in the area of synthesis of axially chiral compounds and asymmetric catalysis, herein, we would like to exhibit the remote control of the axial chirality of urazoles by using a desymmetrization strategy via organocatalytic tyrosine click reaction of 4-aryl-1,2,4-triazole-3,5-dione (ATAD). The key feature of our strategy is the ability of a bifunctional organocatalyst to transfer its axial chirality to distant position.

**Figure 1 | Synthesis of urazoles via tyrosine click reaction and discovery of axial chirality and strategy for remote enantiocontrol.** (a) Synthesis of urazoles via tyrosine click reaction (Barbas’ discovery). (b) Discovery of urazoles with axial chirality. (c) Our strategy for remote enantiocontrol of axial chirality of urazoles.
stereochemical information to a remote position and thereafter efficiently control its axial chirality.

Results
Discovery of urazoles with axial chirality. In 2006, the Jørgensen group discovered a new class of axially chiral skeleton A via asymmetric amination of 8-amine-2-naphthol with azodicarboxylates (Fig. 1b)\(^{40,41}\). Motivated by this pioneering discovery, we synthesized the compounds B and C through tyrosine click reaction and imagined that such compounds should have axial chirality due to the significant restricted rotation between nitrogen atom and the directly attached phenol ring or naphthol ring (Fig. 1b). Disappointedly, they did not display axial chirality based on the chiral stationary high-performance liquid chromatography (HPLC) analysis presumably because of the relatively low rotational barrier of the N–Ar bond. To further screen different aryl substituents of triazodiones, we are pleased to find that urazole D with a steric bulky substituent (t-butyl group) in the ortho position of the phenyl ring shows apparently axial chirality. As such, a class of urazoles with axial chirality was discovered (Fig. 1b).

Optimization of reaction conditions involving naphthols. To investigate the feasibility of our hypothesis, we initiated to conduct the tyrosine click reaction of naphthol (1a) with 4-(2-tert-butylphenyl)-3H-1,2,4-triazole-3,5-dione (2a) by using

| Entry | Solvent | Catalyst | Time (min) | Yield (%)\(^{\dagger}\) | ee (%)\(^{\ddagger}\) |
|-------|--------|---------|-----------|----------------|---------------|
| 1     | DCM    | C1      | <5        | 57             | 25            |
| 2     | DCM    | C2      | <5        | 59             | 5             |
| 3     | DCM    | C3      | <5        | 68             | 75            |
| 4     | DCM    | C4      | <5        | 65             | 11            |
| 5     | DCM    | C5      | <5        | 63             | - 9           |
| 6     | DCM    | C6      | <5        | 61             | - 45          |
| 7     | DCM    | C7      | <5        | 68             | 91            |
| 8     | DCM    | C8      | <5        | 66             | - 43          |
| 9     | Toluene| C7      | 90        | 65             | 90            |
| 10    | Et\(_2\)O| C7    | 30        | 82             | 99            |
| 11\(\dagger\) | Et\(_2\)O| C7    | 90        | 70             | 98            |
| 12\(\dagger\) | Et\(_2\)O| C7    | 90        | 70             | 98            |

DCM, dichloromethane; HPLC, high-performance liquid chromatography.
*Reactions were performed with 1a (0.10 mmol), 2a (0.12 mmol) and catalyst (10 mol%) in 2.0 ml solvent.
\(\dagger\)Isolated yield.
\(\ddagger\)Determined by HPLC analysis on a chiral stationary phase.
\(\dagger\)Reaction was conducted with 5 mol% catalyst.
\(\dagger\)3 mol% catalyst was used.
Takemoto catalyst (C1)42 in dichloromethane (DCM) at room temperature. To our delight, the desired product 3a was obtained in almost quantitative yield in less than 5 min, albeit without any enantioselectivity. Using the analysis of chiral HPLC, the urazole compound 3a was confirmed to be atropisomeric and two peaks corresponding to the enantiomers were observed on the chiral HPLC at room temperature without any change during the analysis timescale. In the absence of organocatalyst, the reaction also proceeded very smoothly (less than 5 min for the model reaction) in quantitative yield, indicating that the strong background reaction might be the major challenge for efficiently realizing enantioselective transformation. With these initial results in hand and to improve the enantioselectivity, we turned our attention to decrease the reaction temperature to —78 °C. Gratifyingly, the reaction proceeded completely within just 5 min and the desired product was obtained in 57% isolated yield with 25% enantioselectivity excess (ee). We next investigated different bifunctional thiourea-tertiary amine catalysts (Table 1, entries 2–5). Among the tested catalysts, Takemoto catalyst C3 with a cyclic tertiary amine proved to be very promising, with the ee value up to 75%. Considering that the additional aromatic stacking interaction might be involved in the transition states, catalysts C6 and C7 with an axial binaphthyl moiety were tested43. Catalyst C7 displayed an excellent enantiocontrol (entry 7), while catalyst C6 with opposite configuration of diamine gave rise to poor enantioselectivity (entry 6). As shown in entry 8, the diamine skeleton in the catalyst had a great influence on the asymmetric induction. Of the solvents tested for the reaction catalysed by C7, diethyl ether proved optimal with respect to the enantioselectivity (Table 1, entry 10). It is noteworthy that the reaction proceeded smoothly without having any affect on enantioselectivity (99% ee) and with an improved chemical yield up to 82% when 5 mol% of catalyst was used (entry 11).

**Substrate scope.** After the optimal reaction condition being established, we set out to explore the substrate scope with respect to various phenols and 2-naphthols as reactants (Table 2). All of the investigated reactions were complete within 60 min and gave products in moderate to good yields (51–85%) and with excellent enantioselectivities (90–99% ee). As regarding the use of a variety of 2-naphthols, bearing electron-withdrawing (Table 2, products 3b–3f) and electron-donating (Table 2, products 3g–3h) groups, the reaction of these 2-naphthols with 2a gave the expected products with very high stereoselectivities. These results indicated that there was only limited influence on stereoselectivity regardless of the electronic properties of the substituents at the different positions on the aromatic ring. It is noteworthy that the use of 4-substituted phenol, such as 4-tert-butyl-phenol and 4-phenyl-phenol, also afforded the desired products 3i and 3j in excellent stereocontrol with a modified reaction conditions, respectively, demonstrating that the substrate scope could not be only limited to naphthols.

**Table 2 | Substrate scope of naphthols or phenols*.**

| Reaction | Yield | ee  |
|----------|-------|-----|
| 3a       | 82%   | 99% |
| 3b       | 85%   | 99% |
| 3c       | 81%   | 99% |
| 3d†‡     | 61%   | 98% |
| 3e       | 76%   | 97% |
| 3f       | 71%   | 99% |
| 3g       | 81%   | 97% |
| 3h       | 70%   | 98% |
| 3i†‡     | 51%   | 94% |
| 3j†‡     | 60%   | 90% |

DCM, dichloromethane; HPLC, high-performance liquid chromatography.

*Reactions were performed with 1 (0.1 mmol), 2a (0.12 mmol) and catalyst C7 (5 mol%) in 2.0 ml Et2O. Isolated yields and the ee values were determined with HPLC analysis using the chiral stationary phase.

†Reactions were performed with 20 mol% catalyst C7 in 2.0 ml solvent.

‡In DCM at —78 °C.

†In toluene at —40 °C.
Next, we explored the generality of the reaction with regard to variation of ATADs. A broad range of ATADs containing different substituents at the aromatic ring reacted smoothly with 2-naphthol 1a to produce the corresponding axially chiral urazoles with high efficiency and excellent enantiocontrol (Table 3). The electronic and position properties of the aromatic ring substituents did not affect the selectivities of the tyrosine click reactions. It should be pointed out that the ortho group is not only restricted to tert-butyl group or iodo, and the bromo or phenyl group at the ortho position could also be obtained with excellent enantioselectivities (3p and 3q). It should be emphasized that the presence of I or Br is very convenient to do the further transformation for diversity-oriented synthesis and drug discovery due to the high reactivity in many transition metal-catalysed reactions44. Experiments on the configurational stability of the product were carried out by heating a solution of 3a in toluene or MeCN at 80 °C for 12 h. Chiral HPLC analysis showed that the ee value of 3a did not have any effect. Therefore, the obtained axially chiral compounds may have potential wide applications as asymmetric organocatalysts/ligands.

Optimization of reaction conditions involving indoles. To expand the synthetic utility of this methodology and further develop the application of the very reactive ATAD, we next focused our attention on more challenging nucleophiles. Although much progress has been made in the development of organocatalytic asymmetric intermolecular transformation by using indoles as nucleophiles45,46, to the best of our knowledge, only few examples involving 2-substituted indoles as nucleophile have been reported with good enantiocontrol, which is probably ascribed to the interrupted interaction between the substrates and the organocatalyst47. We envisaged that the very reactive and multifunctional electrophile ATAD might provide new possibility to proceed such a remote control process with good stereoselectivity with bifunctional organocatalysts. To our delight, by using the standard reaction conditions (Table 4, entry 1), we found that the reaction of 2-phenylindole 4a with 4-(2-tert-butylphenyl)-3H-1,2,4-triazole-3,5-dione (2a) proceeded smoothly by simply using the catalyst C6, giving the desired product 5a in 74% yield with 15% ee. However, after making great efforts on investigation of the optimized reaction conditions, we could not improve the enantioselectivity by using thiourea-tertiary amine organocatalyst (see Supplementary Table 1 for details). On the basis of these findings and own comprehension on the phosphoric acid catalysis48–50, we envisioned that phosphoric acid might perform bifunctional action to activate indole and ATAD simultaneously and control the enantioselectivity51–54. As shown in Table 4, phosphoric acid...
catalyst proved to be a suitable organocatalyst for this transformation. On optimizing the reaction conditions through variation of the phosphoric acid catalysts, solvents and catalyst loadings (Table 4, entries 3–15), the following protocol was proved to be optimal: reaction of \(4a\) and \(2a\) with the molar ratio of 1.0:1.2 by using phosphoric acid \(CP5\) (5 mol%) as catalyst in DCM/Et\(_2\)O (1/1) at \(-78^\circ\)C for 10 min, \(5a\) was obtained in excellent yield with 97% ee (Table 4, entry 15). It should be noted that the chiral spiro-phosphoric acid catalyst displayed better enantioselectivity than the BINOL-derived catalyst if the substituent in the 3 and 3' positions is the same (entries 6 and 12; entries 10 and 13; entries 11 and 15).

| Entry | Solvent | Catalyst (10%) | Time | Yield (%) | ee (%) |
|-------|---------|----------------|------|-----------|--------|
| 1     | Et\(_2\)O | C6             | 48 h | 69        | 5      |
| 2     | Et\(_2\)O | C7             | 24 h | 74        | -15    |
| 3     | Et\(_2\)O | CP1            | 10 h | 96        | 89     |
| 4     | DCM     | CP1            | <5 min | 99    | 68     |
| 5     | Toluene | CP1            | 60 min | 94  | 60     |
| 6     | DCM/Et\(_2\)O (1/1) | CP1               | 10 min | 99    | 95     |
| 7     | DCM/Et\(_2\)O (1/2) | CP1               | 20 min | 98    | 95     |
| 8     | DCM/Et\(_2\)O (1/1) | CP2             | 10 min | 99    | 95     |
| 9     | DCM/Et\(_2\)O (1/1) | CP3             | 10 min | 98    | 37     |
| 10    | DCM/Et\(_2\)O (1/1) | CP4             | 10 min | 99    | 85     |
| 11    | DCM/Et\(_2\)O (1/1) | CP5             | 10 min | 99    | 97     |
| 12    | DCM/Et\(_2\)O (1/1) | CP6             | 10 min | 96    | -77    |
| 13    | DCM/Et\(_2\)O (1/1) | CP7             | 10 min | 96    | -47    |
| 14    | DCM/Et\(_2\)O (1/1) | CP8             | 10 min | 97    | -79    |
| 15    | DCM/Et\(_2\)O (1/1) | CP9             | 10 min | 98    | -95    |
| 16    | DCM/Et\(_2\)O (1/1) | CP10            | 10 min | 99    | -89    |
| 17    | DCM/Et\(_2\)O (1/1) | CP5 (5%)        | 10 min | 99    | 97     |
| 18    | DCM/Et\(_2\)O (1/1) | CP5 (3%)        | 10 min | 99    | 95     |
| 19     | DCM/Et\(_2\)O (1/2) | CP5 (1%)        | 40 min | 99    | 95     |

Substrate scope with indoles as nucleophiles. Having identified the optimized reaction conditions, the reaction was extended to include various 2-substituted indoles and triazoleidine compounds with catalyst \(CP5\). As shown in Table 5, the reaction proceeded smoothly to give the desired product \(5a\)–5m in very high yield (86–96%) and excellent enantioselectivity (84–97% ee). It should be noted that the electronic nature, bulkiness or positions of the substituents on the cyclic diazo compounds and substituted indoles have only minimal effect on efficiencies and enantioselectivities. In addition to aromatic groups, alkyl substituents on indole were used to acquire the desired products (5l and 5m) with excellent yields and...
good stereoselectivities in just less than 5 min (Table 5, entries 12–13).

**Preliminary evaluation as chiral ligands.** To verify the stability of such axial compounds, we heated the obtained product 5a in MeCN at 80 °C for 12 h and no ee erosion was observed. Thus, this kind of axially chiral compounds displayed a high rotation energy about the N–Ar bond, indicating that the chiral urazoles may have potential applications in the field of asymmetric organocatalysts and Lewis acid catalysis. To really investigate the potential application of the resultant axially chiral urazoles in the field of asymmetric catalysis, we chose the addition of N-methylindole (8) to N-methylsatin (9) as a model reaction and evaluated the potential application in the asymmetric catalysis (see Supplementary Table 2). Gratifyingly, the reaction proceeded completely within 8 h at 5 °C and the desired product (10) was obtained in 96% yield with 62% ee (Fig. 2a), demonstrating that the newly developed axially chiral urazoles have the potential application in asymmetric synthesis. Further work encompassing the application of axially chiral urazoles as ligands or catalysts for enantioselective reactions is currently in progress in our laboratory.

**Gram-scale synthesis of enantiopure urazoles.** To further demonstrate the utility of the tyrosine click-like reaction, gram-scale syntheses of products 3a and 5a were carried out. As displayed in Fig. 2b, there was almost no change in reactivity and stereoselectivity, suggesting that this method should have the potential for large-scale chemical production (also see Supplementary Note 3). It should be worth highlighting that the reaction by using 2-phenyl indole as nucleophile was proceeded very smoothly, with only 1 mol% of phosphoric acid catalyst CP5. The absolute configuration of 3p was attributed to be αS and 5f was assigned to be αR using X-ray diffraction analysis of their methylation derivatives 6p and 7f (Fig. 2c, see also Supplementary Fig. 1).

**Table 5 | The substrate scope by using indoles as nucleophiles**

| Entry | R   | R1  | R2  | Time (min) | 5   | Yield (%) | ee (%) |
|-------|-----|-----|-----|-----------|-----|-----------|-------|
| 1     | H   | Ph  | H   | 10        | 5a  | 96        | 97    |
| 2     | H   | 4-F-Ph | H | 15     | 5b  | 95        | 96    |
| 3     | H   | 4-Cl-Ph | H | 20    | 5c  | 95        | 92    |
| 4     | H   | Ph  | Br  | 15     | 5d  | 94        | 94    |
| 5     | H   | Ph  | Ph  | 15     | 5e  | 90        | 96    |
| 6     | Br  | Ph  | H   | 10     | 5f  | 92        | 93    |
| 7     | Br  | 4-F-Ph | H | 15    | 5g  | 92        | 93    |
| 8     | Br  | 4-Cl-Ph | H | 20    | 5h  | 93        | 91    |
| 9     | Ph  | Ph  | H   | 10     | 5i  | 92        | 94    |
| 10    | Ph  | 4-F-Ph | H | 20    | 5j  | 91        | 95    |
| 11    | Ph  | 4-Cl-Ph | H | 20    | 5k  | 86        | 92    |
| 12    | H   | Isopropyl | H | <5   | 5l  | 95        | 90    |
| 13    | H   | Methyl | H | <5   | 5m  | 95        | 84    |

**Methods**

**General information.** Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. Flash column chromatography was performed using Tsingdao silica gel (60, particle size 0.040–0.063 mm). Visualization on TLC was achieved by the use of ultraviolet light (254 nm). NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz for 1H NMR, 100 MHz for 13C NMR and 376 MHz for 19F NMR in CDCl3 or acetone-d6, with tetramethylsilane as internal standard. Chemical shifts are reported in p.p.m., and coupling constants are given in Hz.
Data for $^1$H NMR are recorded as follows: chemical shift (p.p.m.), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (Hz) and integration. Data for $^{13}$C NMR are reported in terms of chemical shift (δ, p.p.m.). High-resolution mass spectra were recorded on a LC-TOF spectrometer (Micromass). Enantiomeric excess was determined on Agilent HPLC using the DAICEL CHIRAL column. For preparation of 4-aryl-l,2,4-triazoline-3,5-diones, see Supplementary Note 1.

Racemic compounds were obtained without catalyst.

**General procedure for synthesis of axially chiral urazoles 3.** In a Schlenk tube, 4-aryl-l,2,4-triazoline-3,5-diones 2 (0.12 mmol) and catalyst C7 (5 mol%, 0.005 mmol) were dissolved in Et₂O (2 ml; also see Supplementary Note 2). The solution was stirred for 10 min at −78 °C before 2-naphthols and phenols 1 (0.10 mmol) were added. The resulting solution was stirred until the red colour disappeared. After monitored with TLC, the reaction mixture was acidified with 6 N HCl and concentrated. Then, the obtained crude material was purified using silica gel column chromatography (CH₂Cl₂ to CH₂Cl₂/Acetone = 10/1) to afford the pure products 3. In some cases, reactions were performed with 20 mol% of catalyst C7 in 2.0 ml solvent, for 3d in DCM at −78 °C; 3i and 3j in dry toluene at −40 °C.

**General procedure for synthesis of axially chiral urazoles 5.** In a Schlenk tube, 4-aryl-l,2,4-triazoline-3,5-diones 2 (0.12 mmol) and catalyst CP5 (5 mol%, 0.005 mmol) were dissolved in DCM/Et₂O = 1/2, −78 °C, 40 min before 2-substituted indole 4 (0.10 mmol) was added. The resulting solution was stirred under this condition until the purple colour disappeared. After being monitored with TLC, the reaction mixture was concentrated, and then purified using silica gel column chromatography (CH₂Cl₂/Acetone = 20/1) to afford the pure products 5.

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Author contributions
J.-W.Z. performed experiments. D.-J.C. took part in the initial reaction development. J.-H.X. and C.S. helped with characterizing all new compounds. B.T. and X.-Y.L. conceived and directed the project and wrote the paper.

Additional information
Accession codes: The X-ray crystallographic coordinates for structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC 1439772 and CCDC 1440020. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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