CPA-catalyzed multicomponent reaction of anilines, aldehydes, and azetidinones: Rapid access to enantiopure-fused azetidines

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**SUMMARY**

The wide occurrence of enantiopure-fused azetidines in various bioactive molecules leads to a great demand for their efficient synthetic methods. However, so far, organocatalytic protocols have been rather limited. Here we develop a chiral phosphoric acid (CPA)-catalyzed multicomponent reaction of anilines, aldehydes, and azetidinones to access tetrahydroquinoline-fused azetidines with three contiguous stereocenters. Noteworthy features include complete diastereocontrol, high enantioselectivity, good yields, and broad functional group tolerance. Successful implementation of this strategy relies on dual activation of imine and enamine intermediates with CPA. This work not only contributes an efficient organocatalytic assembly of chiral fused azetidines but also provides a paradigm for designing other asymmetric multicomponent reactions.

**INTRODUCTION**

Fused azetidines are privileged structural motifs found in a wide range of naturally occurring alkaloids (e.g., gelsemoxonine and calydaphninone) and drugs (e.g., penicillin and clavulanic acid), as shown in Figure 1A.1–3 Azetidines fused to pyrrolidine and piperidine have been demonstrated to be potent neuronal nicotinic receptor agonists.4,5 Therefore, selective construction of fused azetidines has attracted immense attention over the past decades.6–11 Specifically, much progress has been made regarding their enantioselective synthesis.12–15 However, compared with asymmetric transition-metal catalysis,16–21 organocatalytic assembly of enantiopure fused azetidines avoiding heavy metal residue issues lags far behind. In 2011, an important kinetic resolution of racemic fused azetidines was reported (Figure 1B).22,23 The high enantioselectivities of this resolution resulted from the sacrifice of half premade azetidines. Under N-heterocyclic carbene (NHC) catalysis, another elegant protocol was developed through bimolecular annulations of enals and unsaturated ketimines (Figure 1C).24–26 Despite these advances, exploration of other asymmetric organocatalytic approaches for accessing chiral fused azetidines from simple substrates is still highly desirable.

The catalytic asymmetric multicomponent reaction (MCR), featuring simultaneous generation of multiple stereocenters in a single step, is one of the most powerful tools for rapid assembly of molecular complexity from simple substrates.27–29 Because of our ongoing interest in this area,30,31 we selected commercially available aniline, benzaldehyde, and cycloketone as starting materials to study their multicomponent Mannich reaction (Figure 2A).32–35 With diphenyl phosphate as the catalyst, the ring
size of cycloketones had a significant effect on chemoselectivity. For cyclohexanone, Mannich and Aldol adducts (I, II) were observed, whereas only the Aldol reaction took place (III) in the case of cyclopentanone. When N-tosyl 3-azetidinone was involved, an unexpected tetrahydroquinoline-fused azetidine IV was obtained with an endo/ exo ratio of 2/1. Aided by phosphoric acid, the in-situ-formed enamine and imine intermediates could react easily to yield the Mannich adduct. The exo-cyclic C=N bond increases the strain energy of the four-membered ring, and subsequent strain-release drives the Friedel-Crafts attack of the N-phenyl ring onto the C=N bond to furnish product IV.\textsuperscript{36} Given the importance of such a tricyclic framework, tremendous effort was directed toward this serendipitous finding. However, facile formation of various reactive intermediates, such as imine, enamine, and self- and cross-Aldol adducts, likely makes the final system uncontrollable and complex. Thus, achieving high levels of chemo-, diastereo-, and enantiocontrol is by no means an easy task. Here, by employing chiral phosphoric acid (CPA) as the catalyst, a highly stereoselective MCR of anilines, aldehydes, and azetidinones is developed, which provides rapid entry to enantiopure tetrahydroquinoline-fused azetidines (Figure 1D).

RESULTS AND DISCUSSION

Optimization of reaction conditions
At the outset, commonly used BINOL (1,1’-bi-2-naphthol)-derived CPA A1 was employed as a potential catalyst to induce the chirality of fused azetidine (Figure 2B). The reaction took place readily, leading to the expected product 4a in 20% ee and 2/1 dr. H8-BINOL-type CPA A2 provided comparable results. When changing the catalyst to 4-methylphenyl-substituted CPA A3, which can better form a chiral pocket, the enantioselectivity improved to 86%. 4-Chlorophenyl-substituted CPA

Figure 1. Synthesis of enantiopure-fused azetidines via asymmetric organocatalysis
(A) Representative natural products and bioactive molecules that contain fused azetidines.
(B) Asymmetric kinetic resolution of racemic fused azetidines.
(C) Bimolecular assembly of enantiopure-fused azetidines via chiral N-heterocyclic carbene (NHC) catalysis.
(D) Multicomponent assembly of enantiopure-fused azetidines via chiral phosphoric acid (CPA) catalysis.
Boc, tert-butoxycarbonyl.
(A4) slightly increased the selectivity. In the case of biphenyl-substituted CPA (A5), 4a was obtained in 74% yield with 90% ee and 4/1 dr. However, the bulky tri-isopropyl on the phenyl ring (A6) might hamper activation of enamine and imine intermediates, resulting in a significant decline in efficiency. 9-Anthryl- and -phenanthryl-derived CPAs did not give positive results. The reactions in other solvents, including CH3CN, tetrahydrofuran (THF), and 1,2-dichloroethane (DCE), all delivered the target product in decreased ee. Subsequently, a variety of protecting groups on the nitrogen atom of 3-azetidinone were surveyed (Figure 2C). Use of 4-tBu phenylsulfonyl substrate could not enhance the diastereoselectivity (4b). In comparison, the acetyl and benzyl groups led to high dr but with moderate yields and ee (4c and 4d). N-9-fluorenylmethoxycarbonyl (Fmoc) and -tert-butoxycarbonyl (Boc) azetidinones underwent transformation with exclusive diastereoselectivity (4e and 4f).
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2 \[\text{ArNH}_2\] + \[\text{O}\_R\] + \[\text{ArCHO}\] \[\text{A5 (2.5 mol\%)\] \[\text{Toluene, 60 °C}\]

4i, 83%
90% ee, >20/1 dr

4j, 67%
91% ee, >20/1 dr

4k, 83%
95% ee, >20/1 dr

4l, 72%
99% ee, >20/1 dr

4m, 80%
99% ee, >20/1 dr

4n, 74%
91% ee, >20/1 dr

4o, 34%
88% ee, >20/1 dr

4p, 88%
90% ee, >20/1 dr

4q, 58%
90% ee, >20/1 dr

4r, 62%
94% ee, >20/1 dr

4s, 56%
82% ee, >20/1 dr

5a, 87%
98% ee, >20/1 dr

5b, 93%
91% ee, >20/1 dr

5c, 93%
91% ee, >20/1 dr

5d, 81%
88% ee, >20/1 dr

5e, 81%
91% ee, >20/1 dr

5f, 85%
92% ee, >20/1 dr

5g, 77%
97% ee, >20/1 dr

5h, 97%
92% ee, >20/1 dr

5i, 51%
91% ee, >20/1 dr

5j, 93%
97% ee, >20/1 dr

5k, 77%
97% ee, >20/1 dr

5l, 40%
87% ee, >20/1 dr

5m, 83%
97% ee, >20/1 dr

5n, 74%
97% ee, >20/1 dr

5o, 74%
84% ee, 9/1 dr

5p, 58%
98% ee, >20/1 dr
but the latter produced a better yield (88%) and enantioselectivity (94% ee). Moreover, oxetanone and cyclobutanone were accommodated with the transformation as well, but with decreased enantio- and diastereoselectivity (4g and 4h).

**Substrate scope**

Having established the optimal reaction conditions, we then explored the generality of this enantioselective MCR. A variety of anilines bearing different substituents were first examined, and the results are summarized in Figure 3. With biphenyl-substituted H8-BINOL-derived CPA A5 as the catalyst, electron-donating para-substituted anilines (-Me and -OMe) worked well in the protocol, giving the desired products with good yields and diastereo- and enantioselectivities (4i and 4n). In contrast, strong electron-deficient 4-(trifluoromethyl)aniline was not compatible with the process because of its low reactivity for the Friedel-Crafts addition step. For similar reason, 4-(trifluoromethoxy)aniline was converted to product 4o with a decreased yield but good dr and ee. With these results, we surmised that the reaction of electron-rich N-PMP (para-methoxyphenyl) imine, azetidinone, and electron-deficient 4-(trifluoromethyl)aniline might provide a crossover product. However, this attempt failed, and only the homo product 4n was afforded, possibly because the imine can be rapidly converted to the initial starting materials 4-methoxyaniline and benzaldehyde under the reaction conditions. A set of halogens, including -F, -Cl, -Br, and -I, at the para position of aniline was well tolerated, and the expected products were delivered with 67%–83% yields with excellent enantiocontrol (91%–99% ee, 4j–4m). Notably, meta-substituted anilines were also applicable to the process, and no regioselectivity issue was observed (4p–4r). The absolute configuration of the enantiopure-fused azetidine was determined by X-ray crystallography analysis of product 4q (Cambridge Crystallographic Data Center [CCDC]: 2026566). Treatment with 2-fluoroaniline under standard conditions furnished Mannich adduct 4s as a main product, likely because the second Friedel-Crafts step was hampered by the ortho substituent.

The substrate scope with respect to benzaldehydes was further investigated (Figure 3). A wide range of 3- and 4-substituted benzaldehydes was suitable with the protocol, regardless of the electronic and steric factors of the substituents. For instance, electron-rich benzaldehydes participated well in this transformation, giving rise to the desired fused azetidines in 91%–98% ee (5a, 5f, 5i, 5j, and 5m). Strong electron-deficient 4-nitrobenzaldehyde was readily transformed into 5g with 77% yield and 97% ee. This process could be successfully extended to diverse halogen-derived substrates, and the target products were afforded with good yield and selectivity (5b–5e, 5k, and 5l). Bulky 4-tBu benzaldehyde and 2-formyl naphthalene proved to be viable substrates as well, furnishing the corresponding adducts 5h and 5n in 92% and 97% ee, respectively. The desired azetidine 5o could also be obtained in the coupling of ortho-substituted (2-F) benzaldehyde. Aliphatic aldehydes, cyclohexanecarboxaldehyde for instance, were not compatible with the process. 2-Methylsubstituted azetidinone also worked well in this transformation, providing the expected adduct 5p with 58% yield and 96% ee.

**Mechanistic studies**

To gain deeper insights into the reaction pathway, additional control experiments were carried out. An investigation of non-linear effects revealed that even with 20%
ee of catalyst A5, the desired product 4f was afforded with high enantioselectivity (92% ee; Figure 4A). This unexpected chirality amplification prompted us to examine the solubility of the catalyst. When the solution of racemic catalyst in toluene was stirred at 60°C for 16 h, obvious precipitation was observed, whereas the system of enantiopure catalyst remained homogeneous constantly (Figure 4B). For racemic phosphoric acid, it is easier to form less soluble heteroaggregates in toluene, resulting in precipitation of the racemate and enhancing the ee of catalyst in solution.37,38 A kinetic isotope effect (KIE) experiment was performed, with a competitive reaction between aniline and deuterated aniline (Figure 4C). The low KIE value ($k_H/k_D = 1.0$) might suggest that the final deprotonation (or re-aromatization) step is not rate determining (Figures S1 and S2).

As illustrated in Figure 4D, coupling of N-PMP aldimine, aniline, and N-Boc-3-azetidinone resulted in two homo products (4f and 4n) and two crossover products (4fn and 4nf) with a molar ratio of 1:1:5:1.5 (4fn:4f:4n:4nf). A competitive reaction between 4-methoxyaniline and aniline under standard conditions gave the same result. These observations indicate that formation of aldimine is a reversible process and that electron-rich aniline is beneficial to the reaction efficiency. Products 4f and 4fn were obtained in equal molar amounts, and so were products 4n and 4nf. This shows that the enamine intermediates, generated from anilines and 3-azetidinone, have minimal influence on the outcome.

On the basis of these preliminary results and precedents on CPA catalysis,39–46 a plausible mechanism was proposed to explain the absolute stereochemistry of chiral fused azetidines as exemplified by formation of product 4f (Figure 4E). Initially, in the presence of acid, benzaldehyde and azetidione easily react with aniline to yield aldimine INT-1 and enamine INT-2, respectively. These two intermediates can be simultaneously activated by CPA A5 via hydrogen-bonding interactions. A subsequent nucleophilic attack of enamine to imine from Si-face via a concerted or stepwise pathway results in formation of enantiopure-fused azetidine 4f.

During exploration of the substrate scope, we found that subjecting 2-fluoroaniline to standard conditions mainly gave rise to the Mannich adduct 4s (Figure 3). This result demonstrates that a stepwise mechanism consisting of the Mannich and Friedel-Crafts cascade is presumably involved. To validate the presence of this mechanism, a computational study was conducted (Figures 4F, S3, and S4). Starting from dual activation of aldimine and enamine with CPA A5, the concerted [4 + 2] pathway is predicted to have a free energy cost of 38.0 kcal/mol (TS1), whereas the energy barriers for enamine-imine addition (TS1, 12.5 kcal/mol) and Friedel-Crafts attack (TS2, 22.1 kcal/mol) are much lower. As a result, our protocol favorably proceeds through a stepwise pathway rather than a concerted one. Friedel-Crafts attack is likely to be a rate-determining step because its activation energy is higher than that of the first enamine-imine addition step.
Scale-up synthesis and transformations
To demonstrate the practicability of this methodology, a gram-scale reaction was performed. As shown in Figure 4G, even with as low as 1.0 mol % of catalyst A5, the multicomponent coupling of aniline, benzaldehyde, and N-Boc-3-azetidinone still could be successfully scaled up to 3.0 mmol, delivering the expected adduct 4f (1.15 g) with 90% yield and 96% ee with greater than 20:1 dr. The Boc-protecting group of 4f was removed with high efficiency by a simple treatment with diluted HCl, and no significant erosion of enantioselectivity was observed (6f).

We have developed an efficient CPA-catalyzed MCR of anilines, aldehydes, and azetidinones for facile synthesis of tetrahydroquinoline-fused azetidines with three contiguous stereocenters. In most cases, high chemo-, diastereo-, and enantioselectivities were obtained. The protocol also features mild reaction conditions, good compatibility with diverse functional groups, easy operation, and scalability. A good outcome relies on dual activation of imine and enamine intermediates with CPA. Application of this strategy in synthesis of biologically active molecules is currently underway in our lab.

EXPERIMENTAL PROCEDURES
Resource availability
Lead contact
Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Q.-A.C. (qachen@dicp.ac.cn).

Materials availability
Unique and stable reagents generated in this study will be made available upon request, but we might require a payment and/or a completed materials transfer agreement if there is potential for commercial application.

Data and code availability
Crystallographic data for the structure of 4q have been deposited at the CCDC (CCDC: 2026566). Copies of the data can be obtained free of charge from https://www.ccdc.cam.ac.uk/structures/. Details about experimental procedures, mechanistic studies, computational methods, characterization data of products, NMR (nuclear magnetic resonance) (Figures S5–S91) and HPLC (high performance liquid chromatography) spectra (Figures S92–S167) are available in the supplemental information. Table S1 shows B3LYP (Becke-3-parameter-Lee-Yang-Parr) geometries for all optimized compounds and transition states. Additional data are available from the lead contact upon reasonable request.

SUPPLEMENTAL INFORMATION
Supplemental information can be found online at https://doi.org/10.1016/j.checat.2022.05.023.

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AUTHOR CONTRIBUTIONS
Q.-A.C. conceived and supervised the project. All authors discussed the results and commented on the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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