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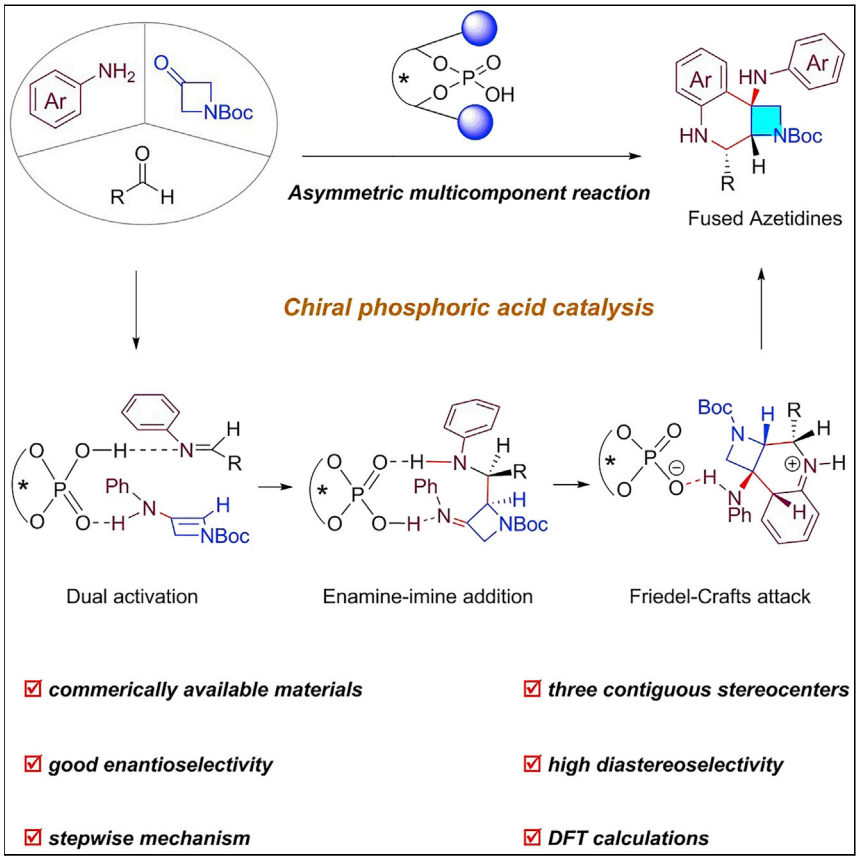
# CPA-catalyzed multicomponent reaction of anilines, aldehydes, and azetidinones: Rapid access to enantiopure-fused azetidines




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. Qian et al. develop a chiral phosphoric acid (CPA)-catalyzed multicomponent reaction of anilines, aldehydes, and azetidinones to access tetrahydroquinoline-fused azetidines with three contiguous stereocenters.

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## Highlights

Assembly of enantiopure-fused azetidines via chiral phosphoric acid catalysis

Asymmetric multicomponent reaction of anilines and aldehydes with azetidinones

One-step construction of three contiguous stereocenters

DFT calculations to elucidate the stepwise mechanism

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

Lei-Lei Qian,[1,2] Yan-Cheng Hu,[1,2,*] Xiang-Ting Min,[1,2] Sa-Na Yang,[1,2] Bing-Xue Shen,[1,2] Boshun Wan,[1,2] and Qing-An Chen[1,2,3,*]

## 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

## THE BIGGER PICTURE

Enantiopure-fused azetidines are widespread in natural products and medically relevant molecules. Therefore, exploration of efficient catalytic systems for rapid assembly of such important frameworks is in great demand. Compared with significant advances achieved in transition-metal catalysis, organocatalytic strategies lag far behind. Here, this is accomplished with chiral phosphoric acid (CPA) catalysis using commercially available anilines, benzaldehydes, and azetidinones as starting materials. This protocol enables one-step construction of three contiguous stereocenters with high diastereo- and enantioselectivities. DFT calculations imply that a stepwise mechanism consisting of enamine-imine addition and Friedel-Crafts attack is likely involved. This work not only provides an efficient alternative to access chiral fused azetidines but also opens up an avenue to design other asymmetric multicomponent reactions.

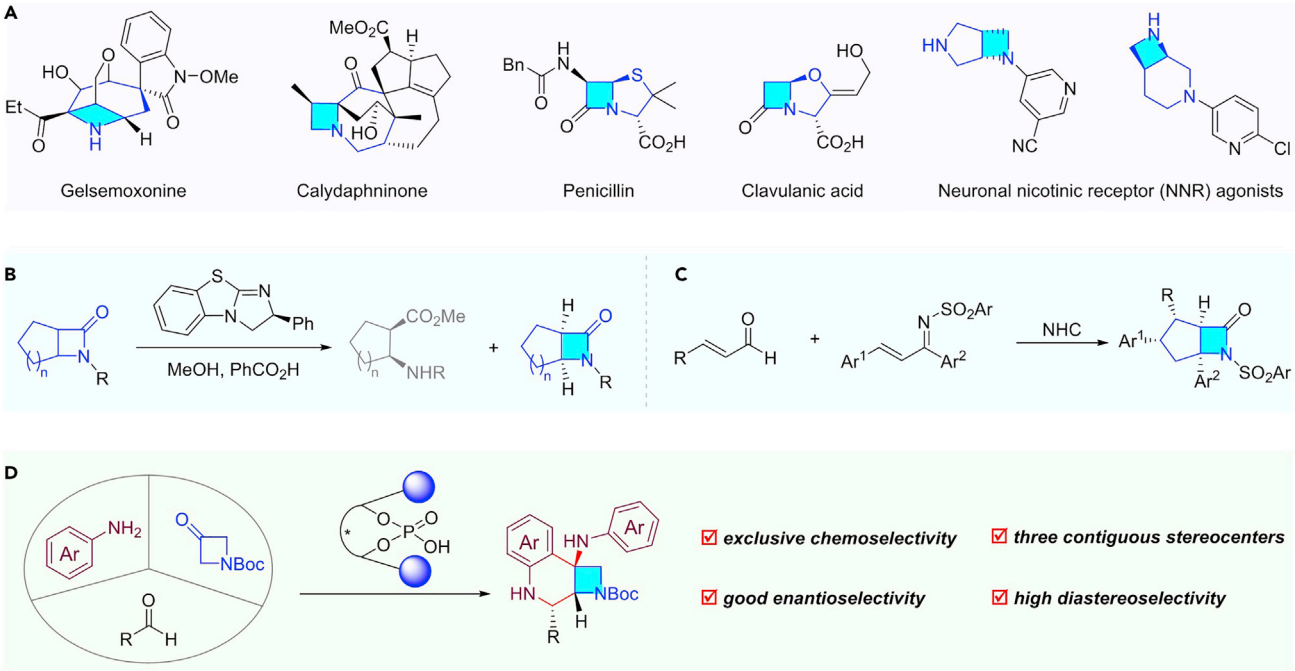


**Figure 1. Synthesis of enantiopure-fused azetidines via asymmetric organocatalysis**

(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.

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**.[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

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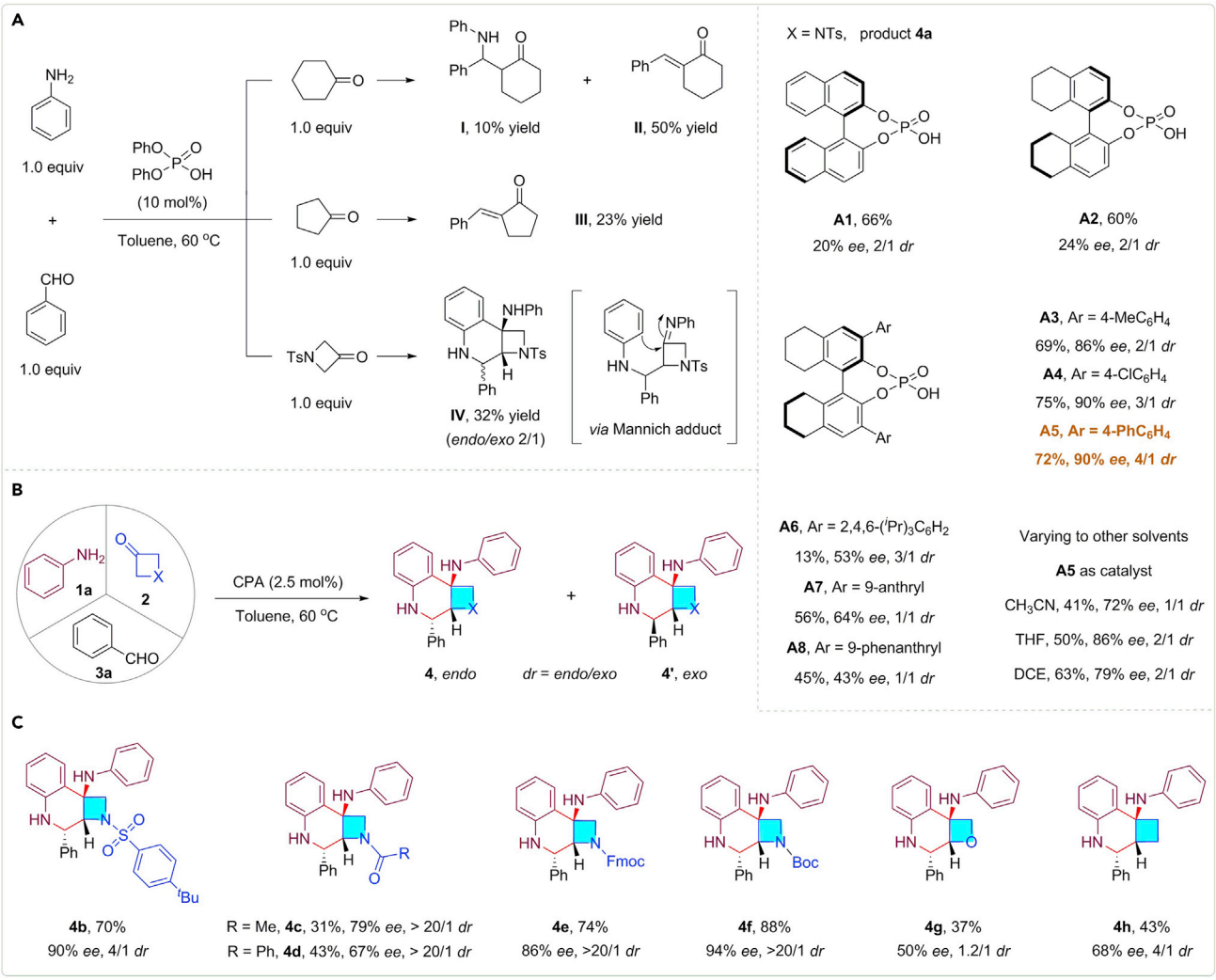


**Figure 2. Catalytic MCR of anilines, aldehydes, and azetidinones**

(A) Serendipitous selectivity induced by ring size. Isolated yields were given.

(B) Control of enantio- and diastereoselectivity under CPA catalysis. NMR yields were given.

(C) The effect of the four-membered ring on enantio- and diastereoselectivity. Isolated yields were given. Reaction conditions: **1a** (0.40 mmol), **2** (0.20 mmol), **3a** (0.20 mmol), CPA (2.5 mol %), toluene (1.0 mL), 60°C for 16 h. *dr* (diastereoselectivity) and *ee* (enantioselectivity) were determined by $^{1}$H NMR and chiral HPLC analysis, respectively.

Ts, *p*-toluenesulfonyl; Fmoc, 9-fluorenylmethoxycarbonyl; THF, tetrahydrofuran; DCE, 1,2-dichloroethane.

(**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 $CH_3CN$, 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-$^{t}$Bu 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**),

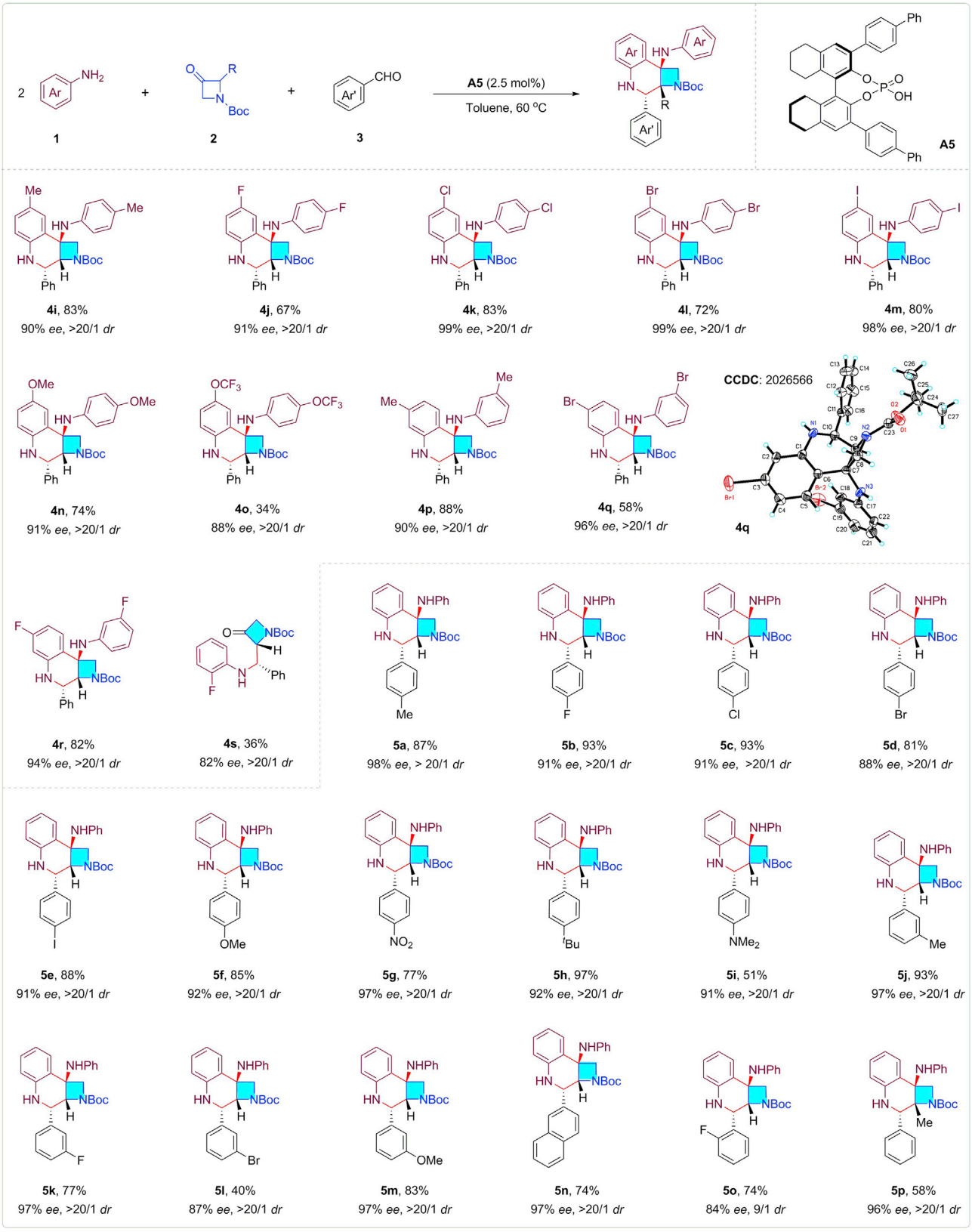
2
Ar
NH2
1
R
O
N
Boc
2
Ar'
CHO
3
A5 (2.5 mol%)
Toluene, 60 °C
Ar
HN
HN
NBoc
R
Ar'
Ph
O
P
O
O
OH
Ph
A5
Me
Me
4i, 83%
90% ee, >20/1 dr
F
F
4j, 67%
91% ee, >20/1 dr
Cl
Cl
4k, 83%
99% ee, >20/1 dr
Br
Br
4l, 72%
99% ee, >20/1 dr
I
I
4m, 80%
98% ee, >20/1 dr
OMe
OMe
4n, 74%
91% ee, >20/1 dr
OCF3
OCF3
4o, 34%
88% ee, >20/1 dr
Me
Me
4p, 88%
90% ee, >20/1 dr
Br
Br
4q, 58%
96% ee, >20/1 dr
CCDC: 2026566
4q
F
F
4r, 82%
94% ee, >20/1 dr
O
NBoc
H
Ph
F
4s, 36%
82% ee, >20/1 dr
NHPh
Me
5a, 87%
98% ee, > 20/1 dr
F
5b, 93%
91% ee, >20/1 dr
Cl
5c, 93%
91% ee, >20/1 dr
Br
5d, 81%
88% ee, >20/1 dr
I
5e, 88%
91% ee, >20/1 dr
OMe
5f, 85%
92% ee, >20/1 dr
NO2
5g, 77%
97% ee, >20/1 dr
tBu
5h, 97%
92% ee, >20/1 dr
NMe2
5i, 51%
91% ee, >20/1 dr
Me
5j, 93%
97% ee, >20/1 dr
F
5k, 77%
97% ee, >20/1 dr
Br
5l, 40%
87% ee, >20/1 dr
OMe
5m, 83%
97% ee, >20/1 dr
5n, 74%
97% ee, >20/1 dr
F
5o, 74%
84% ee, 9/1 dr
Me
5p, 58%
96% ee, >20/1 dr

**Figure 3. Substrate scope of CPA-catalyzed MCR of anilines, aldehydes, and azetidinones**

Reaction conditions: **1** (0.40 mmol), **2** (0.20 mmol), **3** (0.20 mmol), **A5** (2.5 mol %), toluene (1.0 mL), 60°C, 16 h. Isolated yields were given. *dr* and *ee* were determined by $^{1}$H NMR and chiral HPLC analysis, respectively.

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-$^{t}$Bu benzaldehyde and 2-formylnaphthalene 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-Methyl-substituted 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%

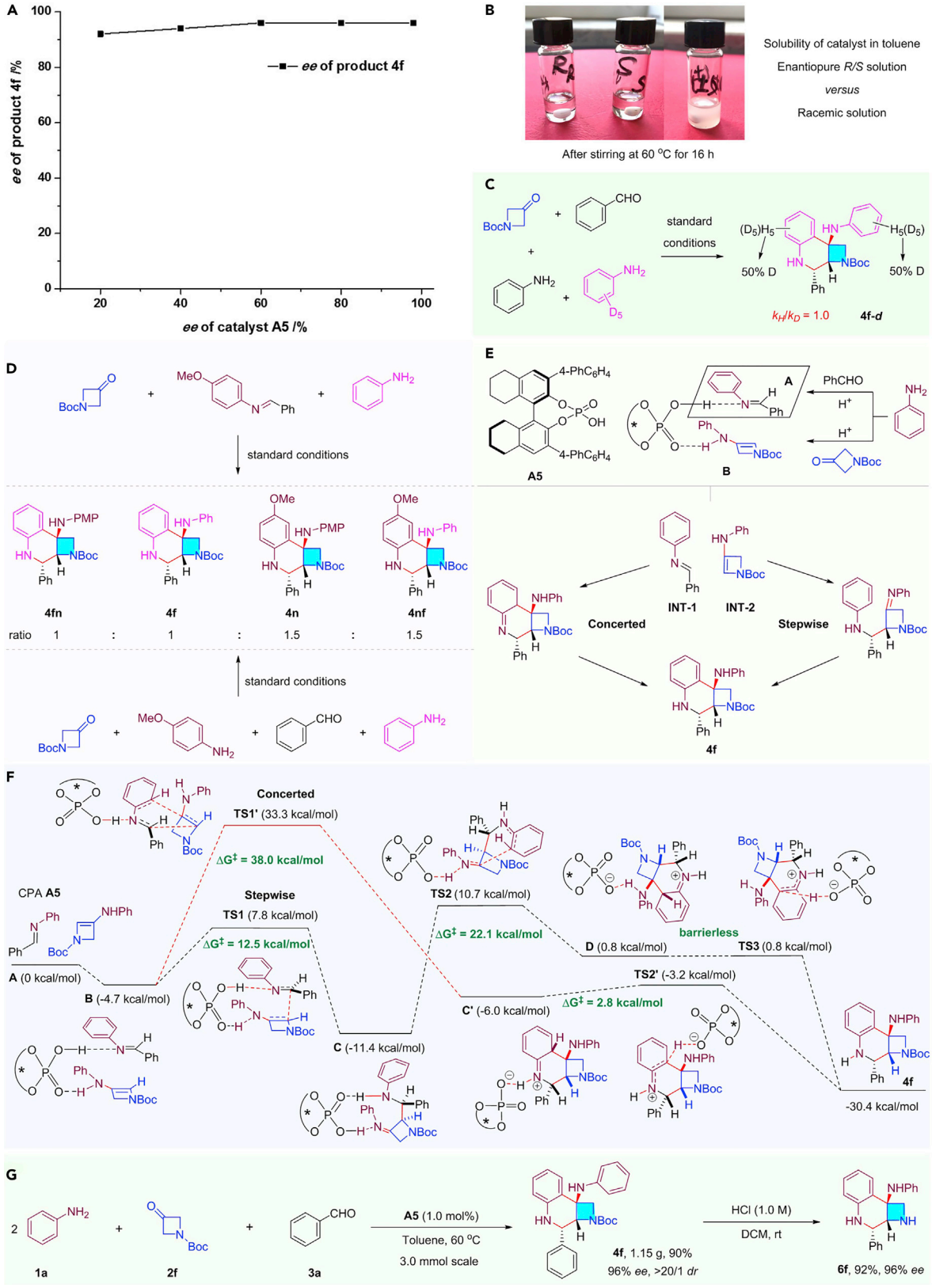
A
ee of product 4f /%
ee of catalyst A5 /%
ee of product 4f
B
Solubility of catalyst in toluene
Enantiopure R/S solution
versus
Racemic solution
After stirring at 60 °C for 16 h
C
standard conditions
50% D
50% D
kH/kD = 1.0
4f-d
D
standard conditions
4fn
4f
4n
4nf
ratio 1 : 1 : 1.5 : 1.5
standard conditions
E
A5
B
PhCHO
Concerted
Stepwise
INT-1
INT-2
4f
F
Concerted
TS1' (33.3 kcal/mol)
ΔG‡ = 38.0 kcal/mol
CPA A5
Stepwise
TS1 (7.8 kcal/mol)
ΔG‡ = 12.5 kcal/mol
A (0 kcal/mol)
B (-4.7 kcal/mol)
C (-11.4 kcal/mol)
TS2 (10.7 kcal/mol)
ΔG‡ = 22.1 kcal/mol
C' (-6.0 kcal/mol)
ΔG‡ = 2.8 kcal/mol
TS2' (-3.2 kcal/mol)
D (0.8 kcal/mol)
barrierless
TS3 (0.8 kcal/mol)
4f
-30.4 kcal/mol
G
A5 (1.0 mol%)
Toluene, 60 °C
3.0 mmol scale
4f, 1.15 g, 90%
96% ee, >20/1 dr
HCl (1.0 M)
DCM, rt
6f, 92%, 96% ee
1a
2f
3a

**Figure 4. Mechanistic investigations and further de-protection**

(A) Non-linear effects.

(B) Photograph of enantiopure and racemic catalysts in toluene after stirring at 60°C for 16 h.

(C) Kinetic isotope effect.

(D) Crossover experiments. The ratio of the four products was determined by $^{1}$H NMR of the crude mixture.

(E) Proposed mechanism.

(F) DFT calculations (see also Figure S3).

(G) Gram-scale reaction and de-protection.

PMP, *p*-methoxyphenyl.

*ee* of catalyst **A5**, the desired product **4f** was afforded with high entantioselectivity (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 1:1:1.5:1.5 (**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.

## ACKNOWLEDGMENTS

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## AUTHOR CONTRIBUTIONS

Y.-C.H. and L.-L.Q. performed the experiments. X.-T.M., S.-N.Y., B.-X.S., and B.W. provided useful advice. Y.-C.H., L.-L.Q., and Q.-A.C. wrote the manuscript.

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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