

Cite this: *Chem. Sci.*, 2023, 14, 5665

All publication charges for this article have been paid for by the Royal Society of Chemistry

# Chiral aldehyde catalysis enables direct asymmetric $\alpha$ -substitution reaction of N-unprotected amino acids with halohydrocarbons†

Hao-Ran Shen,<sup>‡</sup> Chao-Xing Li,<sup>‡</sup> Xin Jiang, Yao Lin, Jian-Hua Liu, Fang Zhu, Zhu-Lian Wu,<sup>‡</sup> Tian Cai,<sup>‡</sup> Wei Wen,<sup>‡</sup> Rong-Xing He<sup>‡</sup> and Qi-Xiang Guo<sup>‡</sup>\*

The direct catalytic  $\alpha$ -hydrocarbylation of readily available amino acids with halohydrocarbons is one of the most straightforward methods leading to  $\alpha,\alpha$ -disubstituted non-proteinogenic  $\alpha$ -amino acid compounds. However, all the reported methodologies depend on N-protected amino acids as starting materials. Herein, we report on three highly efficient aldehyde-catalyzed direct  $\alpha$ -hydrocarbylations of N-unprotected amino acid esters with aryl-, allyl-, and benzyl halides. By promoting a simple chiral BINOL-aldehyde catalyst or combining catalysts of a chiral aldehyde and Lewis acid ZnCl<sub>2</sub>, the asymmetric  $\alpha$ -arylation,  $\alpha$ -allylation, and  $\alpha$ -benzylation of amino acid esters with the corresponding halohydrocarbons proceed smoothly, producing  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acids in moderate-to-high yields and good-to-excellent enantioselectivities. The asymmetric  $\alpha$ -arylation reaction can be applied in the formal synthesis of the clinical candidate compound (+)-AG-041R. Based on the results given by control experiments, three reaction models are proposed to illustrate the stereoselective-control outcomes.

Received 10th March 2023

Accepted 2nd May 2023

DOI: 10.1039/d3sc01294h

rsc.li/chemical-science

## Introduction

The halohydrocarbon-involved substitution reaction is one of the most classic transformations in organic chemistry for the formation of carbon-carbon and carbon-heteroatom bonds.<sup>1</sup> With the utilization of halohydrocarbons such as aryl, alkenyl, and alkyl halides as reactants, a large number of optically active molecules have been constructed *via* S<sub>N</sub>Ar,<sup>2</sup> S<sub>N</sub>1, or S<sub>N</sub>2 substitutions,<sup>3</sup> or *via* couplings.<sup>4</sup> Among these reactions, the catalytic asymmetric  $\alpha$ -substitution reactions of readily available amino acid derivatives with halohydrocarbons provide a highly efficient pathway for the preparation of optically active unnatural  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acids. Especially, chiral phase-transfer catalysis has enabled important advances, benefiting from highly efficient catalytic ability, broad application scope and lack of chemoselectivity issues. Conversely, protection and deprotection steps are unavoidable (Fig. 1, path a).<sup>5</sup> In contrast, an ideal catalytic strategy leading to such products could directly promote the  $\alpha$ -hydrocarbylation of N-unprotected amino acid esters with high efficiency (Fig. 1, path b); however, such a valuable methodology has not been disclosed

until now. As an alternative strategy, the chiral aldehyde/transition-metal dual catalysis allows for the one-step synthesis of NH<sub>2</sub>-unprotected  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acids by utilizing electrophiles generated *in situ*. (path c).<sup>6</sup>

A unique property of chiral aldehyde catalysis,<sup>6</sup> directly promoting the asymmetric  $\alpha$ -functionalization of N-unprotected amino acid esters by increasing the acidity through catalytic formation of a chiral imine, has been demonstrated in alkylation,<sup>7</sup> Michael addition,<sup>8</sup> Mannich,<sup>9</sup> aldol,<sup>10</sup> allylation,<sup>11</sup> benzylation,<sup>12</sup> and propargylation<sup>13</sup> reactions. We envisioned that this strategy may be promising for the direct asymmetric  $\alpha$ -hydrocarbylation of amino acid esters with halohydrocarbons. However, it was challenging to control the chemoselectivity of C/N-functionalization in this transformation. In the previously reported reactions employing

Key Laboratory of Applied Chemistry of Chongqing Municipality, Chongqing Key Laboratory of Soft-Matter Material Chemistry and Function Manufacturing, School of Chemistry and Chemical Engineering, Southwest University, Chongqing, 400715, China. E-mail: wenwei1989@swu.edu.cn; qxguo@swu.edu.cn

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d3sc01294h>

‡ These authors contributed equally to this work.

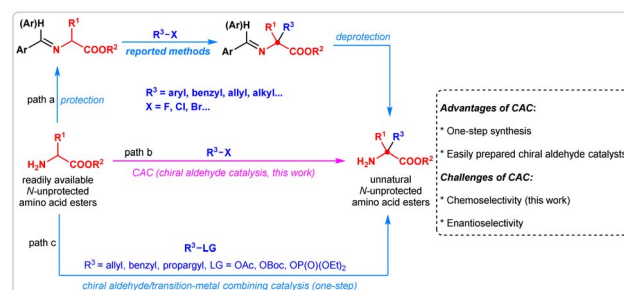


Fig. 1 Catalytic asymmetric  $\alpha$ -hydrocarbylation reaction of amino acid esters.



chiral aldehyde catalysis, either the electrophiles were gradually generated *in situ* during the reaction process (for alkylation, allylation, benzylation, and propargylation reactions), or the N-functionalization side products were unstable and reversely decomposed to starting material (for Michael, Mannich, and aldol reactions). Therefore, the side reaction of N-functionalization in those reactions was efficiently suppressed. In our proposed reaction, chiral aldehyde-catalyzed  $\alpha$ -hydrocarbylation of N-unprotected amino acid esters with halohydrocarbons, the equivalent amounts of halohydrocarbon electrophiles and the possible formation of stable N-hydrocarbylation byproducts made chemoselectivity more difficult to control. Thus, it was necessary to develop an aldehyde-catalyzed direct  $\alpha$ -hydrocarbylation reaction of amino acid esters with improved chemoselectivity and enantioselectivity. Here, we report three chiral aldehyde-catalyzed asymmetric  $\alpha$ -substitution reactions of N-unprotected amino acid esters with aryl halides,<sup>14</sup> allyl chlorides, and benzyl chlorides.<sup>15</sup> Although the N-functionalization byproducts are not suppressed completely, the desired C-functionalization products can be generated in moderate-to-high yields with good-to-excellent enantioselectivities for all three transformations. Furthermore, the  $\alpha$ -arylation product is used for the formal total synthesis of the clinical candidate compound (+)-AG-041R, and three reaction models are proposed based on the results of control experiments.

## Results and discussion

### Initial studies

We initially investigated the possibility of our proposal in the asymmetric reactions of amino acid ester **1a** with 2-nitro fluorobenzene **2a**, allyl chloride **5a**, and benzyl chloride **8a**. The simple chiral aldehyde **CA-1** was chosen as a catalyst, and the base  $\text{Cs}_2\text{CO}_3$ , or tetramethylguanidine (TMG), was added to accelerate the deprotonation process. We found that the arylation reaction of *tert*-butyl alaninate **1a** and 2-nitro fluorobenzene **2a** took place smoothly, providing the desired product **3a** in 25% yield with >99% enantioselective excess (ee), although the side product **4a** was obtained in 16% yield (Fig. 2a). For the allylation reaction of **1a** with cinnamyl chloride

**5a**, the desired product **7a** was obtained in 23% yield with 8% ee. However, no product **9a** was observed in the benzylation of **1a** with **8a**. To suppress the N-functionalization side reaction, the Lewis acid  $\text{ZnCl}_2$  was added. As expected, the yield of the allylation product **6a** was enhanced to 89%, and the benzylation product **9a** was obtained in 15% yield (Fig. 2b and c).

### Asymmetric $\alpha$ -arylation reaction

Encouraged by the initial results, we systematically studied the chiral aldehyde-catalyzed arylation reaction. Because of the excellent enantioselectivity of **3a** obtained in Fig. 2a, chiral aldehyde **CA-1** was chosen for optimization of the reaction conditions. Base screening indicated that inorganic bases were suitable for this reaction, and  $\text{K}_3\text{PO}_4$  provided the greatest yield of **3a** (Fig. 3a). The choice of solvent also affected the yield of **3a**. When this reaction was conducted in  $\text{Et}_2\text{O}$ , product **3a** was obtained in 86% yield with >99% ee (Fig. 3b). Then, the base equivalent and the reaction concentration were tuned. The results indicated that using 5 equivalents of  $\text{K}_3\text{PO}_4$  and 0.2 M **2a** ( $y = 1$ ) produced the best yield (Fig. 3c and d).

After determining the optimal reaction conditions, we examined the substrate scopes for this reaction. First, various substituted amino acid esters were employed as reaction partners with 2-nitro fluorobenzene **2a** (Fig. 4a). The variation of the alkoxyl group on reactant **1** affected the yields but had little influence on the enantioselectivity (Fig. 4a, **3a–3e**). Generally, the benzyl and methyl alaninate produced corresponding products **3c** and **3e** in moderate yields. The decrease in yields may be caused by the amine-ester exchange reaction of amino acid esters containing less bulky alkoxyl groups. Amino acid esters bearing saturated linear alkyls were effective reaction partners for **2a**, producing **3f–3i** in good-to-high yields with excellent enantioselectivities. Similar results were observed when the saturated branched alkyl- or unsaturated linear alkyl-substituted amino acid esters participated in this reaction (Fig. 4a, **3j–3m**). Other functional groups, such as ester,

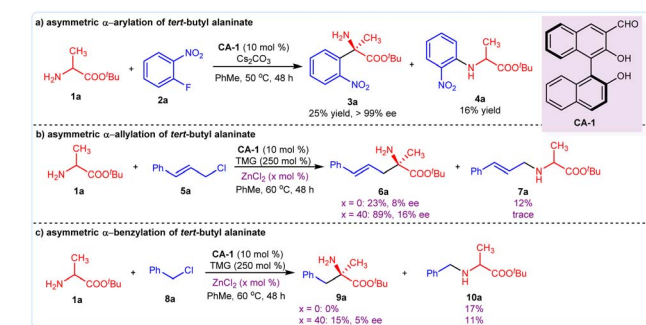


Fig. 2 Initial investigation of the catalytic asymmetric  $\alpha$ -hydrocarbylation of amino acid esters. (a) Asymmetric arylation; (b) asymmetric allylation; (c) asymmetric benzylation.

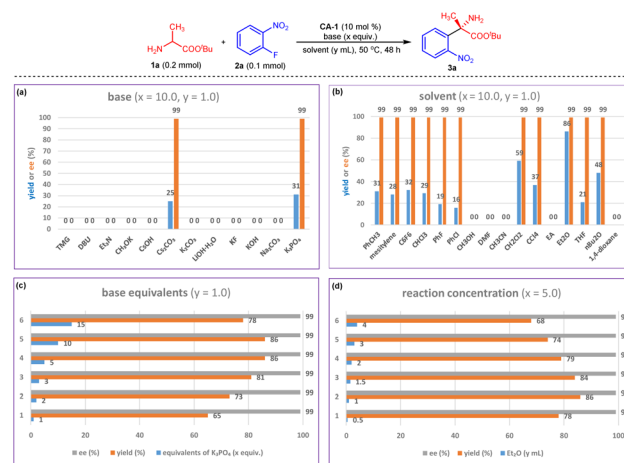


Fig. 3 Reaction condition optimization for arylation of **1a** with **2a**. (a) Bases screening; (b) solvents screening; (c) base equivalents screening; (d) reaction concentration optimization.



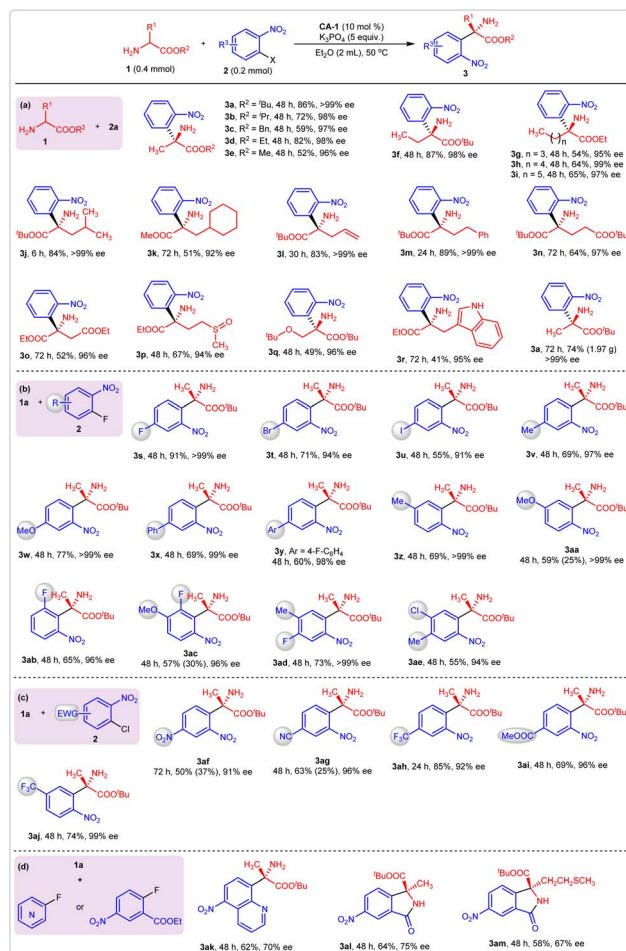


Fig. 4 Substrate scopes of the asymmetric arylation reaction. (a) For amino acid esters; (b) for substituted 2-nitro fluorobenzenes; (c) for substituted 2-nitro chlorobenzenes; (d) for other substituted fluorobenzenes.

sulfoxide, and indolyl, that are contained in the amino acid esters were well tolerated under the optimal reaction conditions; products **3n–3q** were obtained in moderate-to-good yields with excellent enantioselectivities. The model reaction was readily expanded to the gram scale. With 10 mmol of 2-nitro fluorobenzene, compound **3a** was produced in 74% yield (1.97 g) with >99% ee.

Then, various substituted 2-nitro fluorobenzenes **2** were examined (Fig. 4b). The introduction of a third substituent did not affect the enantioselectivity, but the yield was affected by its electronic effects. For example, the 1,4-difluoro-2-nitrobenzene gave product **3s** in 91% yield with >99% ee. When a third substituent with less electronegativity than the fluoro moiety was installed at the *para*-position of the benzene ring, the yields slightly decreased (Fig. 4b, **3t–3y** vs. **3s**). Besides the *para*-substituted 2-nitro fluorobenzenes, the *meta*- and *ortho*-substituted ones also gave the desired products in good yields with excellent enantioselectivities (Fig. 4b, **3z–3ab**). When two substituents were introduced simultaneously on the benzene ring, the combination of an electron-donating and electron-withdrawing group was necessary to obtain satisfactory yields

(Fig. 4b, **3ac–3ae**) because the increase of strong electron-withdrawing groups accelerated the generation of N-arylation side products. Particularly, when 2,4-dinitro fluorobenzene was introduced as an arylation reagent, only the N-arylation byproduct was observed. For most substrates, the generation of N-functionalization side products was unavoidable. For example, accompanying the formation of C-functionalization products **3aa** and **3ac**, corresponding N-arylation side products were obtained in 25% and 30% yield, respectively.

To overcome the drawback that only N-arylation byproducts were generated in reactions using a strong electron-withdrawing group-substituted 2-nitro fluorobenzene, corresponding 2-nitro chlorobenzenes were employed as reactants. As expected, the desired C-arylation became dominant, and only a small amount of N-arylation was observed. For example, nitro, cyano, trifluoromethyl, and ester-substituted 2-nitro chlorobenzenes gave products **3af–3aj** in good-to-high yields with excellent enantioselectivities (Fig. 4c). 8-Fluoro-5-nitroquinoline was also a suitable reaction partner with amino acid ester **1a**, which gave products **3ak** in 62% yield with 70% ee. Furthermore, when ethyl 2-fluoro-5-nitrobenzoate was used as an arylation reagent, optically active chiral isoindolinones were produced *via* a tandem arylation/cyclization process (Fig. 4d, **3al–3am**). The absolute configuration of product **3a** was assigned as *S* by comparing its optical rotation value with the literature data (see ESI<sup>†</sup>), and the stereochemistries of the other products in Fig. 4 were assigned accordingly.

### Asymmetric $\alpha$ -allylation and benzylation reactions

Allyl and benzyl chlorides are two other types of commonly used alkylation reagents for carbon–carbon and carbon-heteroatom bonds formations. However, the N-functionalization byproducts can form spontaneously because of their high reactivity. Thus, the chemoselectivity of the chiral aldehyde-catalyzed  $\alpha$ -functionalization of N-unprotected amino acid esters with allyl or benzyl chlorides becomes extremely difficult to control. Nevertheless, our initial experimental results revealing that the target  $\alpha$ -allylation product could be obtained in 89% yield with 16% ee under the promotion of a chiral aldehyde-ZnCl<sub>2</sub> system encouraged us to pursue high efficiency using allyl or benzyl chlorides. Therefore, we systematically investigated the reaction conditions of the catalytic asymmetric allylation of *tert*-butyl alaninate **1a** with cinnamyl chloride **5a**. Chiral aldehyde catalyst screening indicated that most of the 3-formyl BINOL aldehydes could produce **6a** in good-to-excellent yields; however, the enantioselectivities were not satisfactory. The 2-formyl BINOL-aldehyde CA-15 gave excellent enantioselectivity (94% ee), but the yield was moderate (61%) (Fig. 5a, i). We chose CA-15 as the chiral aldehyde catalyst for further condition optimization. Various solvents were evaluated, and mesitylene was optimal in terms of yield and enantioselectivity (Fig. 5a, ii). When this reaction was conducted at 50 °C, product **6a** was obtained in 65% yield with 94% ee (Fig. 5a, iii). We found that the reaction concentration affected the yield to some degree: the usage of 0.4 mL mesitylene at 0.2 mmol scales of reactant **1a** could produce compound **6a** in 73% yield with 94% ee (Fig. 5a, iv).



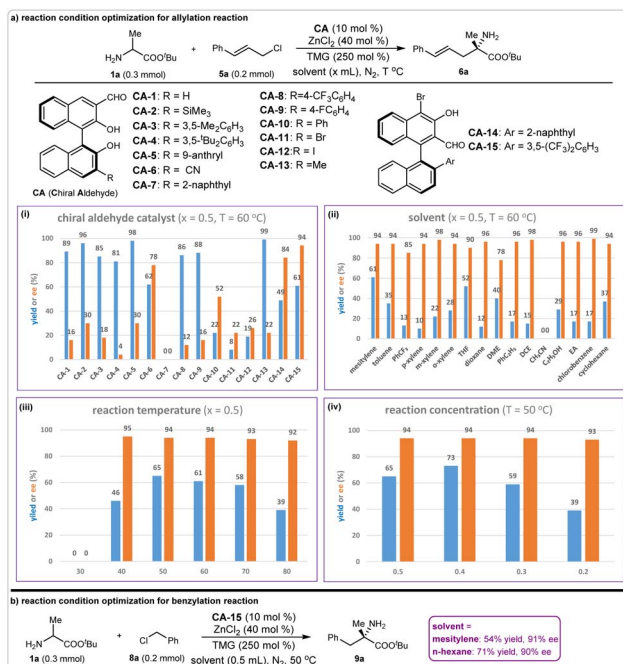


Fig. 5 Condition optimizations for asymmetric allylation and benzylation reactions. (a) Catalysts screening; (b) solvents screening; (c) reaction temperature optimization; (d) reaction concentration optimization.

Based on these results, the optimal reaction conditions for the asymmetric  $\alpha$ -allylation reaction were determined.

Due to the similar reaction activities of benzyl chlorides with allyl chlorides, we directly applied the above optimal reaction conditions in the asymmetric  $\alpha$ -benzylation reaction. As expected, this reaction took place smoothly, giving the desired product **9a** in 54% yield with 90% ee. Then, optimization of the reaction conditions was performed, including the screening of chiral aldehyde catalysts, bases, solvents, and reaction temperature (see ESI†). Finally, we found that product **9a** could be obtained in 71% yield with 91% ee when *n*-hexane was used as the reaction solvent (Fig. 5b). Thus, the optimal reaction conditions for this asymmetric benzylation were determined.

Under the optimal reaction conditions, we examined the corresponding substrate scopes of these asymmetric allylation and benzylation reactions. First, various substituted cinnamyl chlorides were assessed. The results indicated that cinnamyl chlorides bearing single or double substituents on benzene ring were effective reaction partners with amino acid ester **1a**, providing compounds **6b–6k** in moderate-to-good yields with excellent enantioselectivities. The experimental outcomes were not affected by the steric and electronic properties of the substituent. Concerning the substrates of amino acid esters, the yields of corresponding products were affected by the steric influence of their  $\alpha$ -substituents. For all eight amino acid esters we employed in this reaction, products **6l–6s** were obtained in moderate yields with excellent enantioselectivities.

Similar results were observed in the asymmetric benzylation reaction. Various substituted benzyl chlorides exhibited good

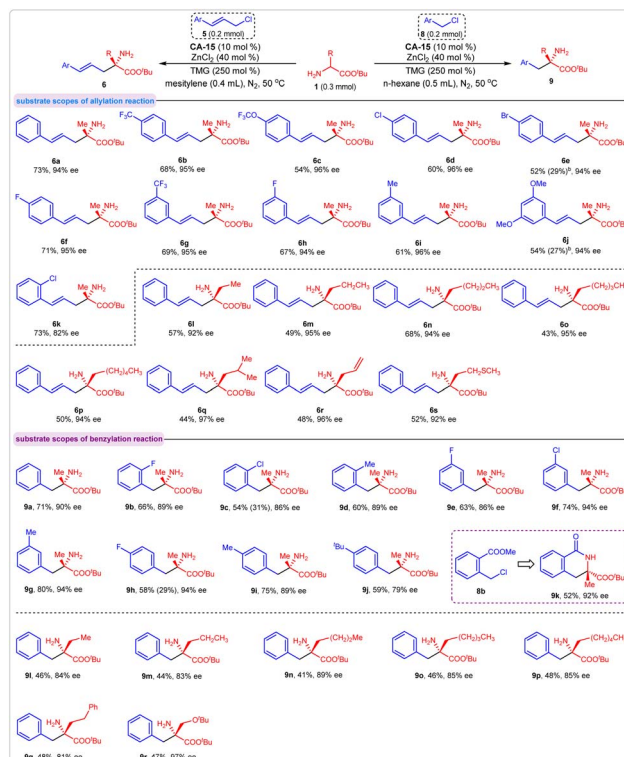


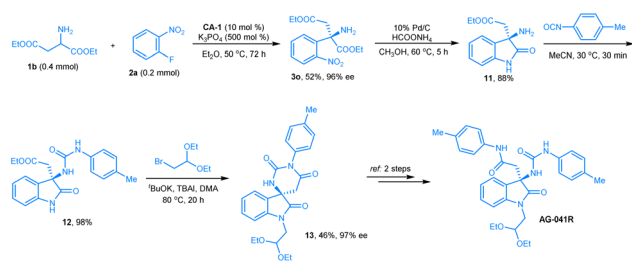
Fig. 6 Substrate scopes of the asymmetric allylation and benzylation reactions.

activities in this reaction and gave the corresponding products in moderate-to-high yields with good enantioselectivities (Fig. 6, **9b–9j**). When the methyl 2-(chloromethyl)benzoate **8b** was used as an acceptor, the product **9k** was obtained in 52% yield with 92% ee *via* a tandem benzylation/lactamization process. Because of the steric influence of their  $\alpha$ -substituents, amino acid esters other than **1a** gave products with moderate yields. In addition, all the enantioselectivities for these products were maintained at a high level (Fig. 6, **9l–9r**). The absolute configurations of products **6b** (*S*) and **9a** (*S*) were determined by comparing their optical rotation values with the literature data (see ESI†), and the stereochemistries of the other products in Fig. 6 were assigned accordingly.

### Synthetic application

The clinical candidate compound (+)-AG-041R is a gastrin/CCK-B receptor antagonist with an IC<sub>50</sub> of 1.1 nmol.<sup>16</sup> Few catalytic asymmetric methodologies have been developed for preparing this compound,<sup>17</sup> but we envisioned that its core oxindole unit can be constructed from our arylation product by a reduction of the nitro group and an *in situ* intramolecular amidation reaction, and a new catalytic asymmetric synthetic route for this clinical candidate was anticipated. As we discussed in the section on substrate scope, the diethyl aspartate **1b** reacted smoothly with 2-nitro fluorobenzene **2a** under the optimal reaction conditions, and product **3o** was obtained in 52% yield with >99% ee. Then, we reduced the nitro group of **3o** to an amine. An intramolecular amidation took place *in situ* to give 3-





Scheme 1 The formal synthesis of AG-041R.

amino oxindole, product **11**. Using the reported methods, urea moiety-contained oxindole **12** and Iwabuchi intermediate **13** (ref. 17a) were prepared, successively (Scheme 1). The spectra data and optical rotation of compound **13** agree with the literature (see ESI†). Thus, based on the chiral aldehyde-catalyzed arylation of amino acid esters, a new synthetic route for the formal synthesis of AG-041R was achieved.

### Reaction mechanism investigation

The possible reaction models for these three reactions were investigated. For the asymmetric arylation of amino acid ester **1a** with **2a**, once the reactant 2-nitro fluorobenzene **2a** was replaced by 3-nitro fluorobenzene or 4-nitro fluorobenzene, the reaction efficiency was greatly decreased. Protecting the 2' hydroxyl of the chiral aldehyde catalyst **CA-1** also prevented the formation of product **3a** with high efficiency (Fig. 7a). These results indicated that hydrogen bond interactions may have occurred between the 2' hydroxyl of **CA-1** and the nitro group of 2-nitro fluorobenzene **2a**. Thus, a possible transition state **I** (TS **I**) was proposed for the production of (*S*)-**3a** (Fig. 7c).

For the asymmetric allylation and benzylation reactions, all of the yields of the corresponding products decreased greatly in the absence of Lewis acid  $ZnCl_2$ , no matter whether the amino acid ester **1a** or the formed Schiff base **CA-15-1a** was employed as donor (Fig. 7b), indicating that the Lewis acid can accelerate the processes of Schiff base formation and deprotonation. Furthermore, the slight decreases in enantioselectivities showed that the Lewis acid can enhance the stereoselective-control ability of the corresponding transition states. It was reasonable to deduce that these reactions took place between the Zn-Schiff base complexes and halohydrocarbons. Therefore, two transition states, **TS II** and **TS III**, were proposed. Thus, products (*S*)-**6a** and (*S*)-**9a** were generated respectively (Fig. 7c).

## Conclusions

In conclusion, we demonstrated highly efficient chiral aldehyde-catalyzed  $\alpha$ -substitution reactions of  $\alpha$ -amino acid esters with aryl, allyl, and benzyl halides. In the promotion of the simple chiral aldehyde **CA-1**, the  $\alpha$ -arylation reaction of *N*-unprotected amino acid esters with aryl halides takes place smoothly, giving  $\alpha$ -aryl  $\alpha,\alpha$ -disubstituted amino acid derivatives in moderate-to-high yields with good-to-excellent enantioselectivities. The combinational catalytic system comprising chiral aldehyde **CA-15** and Lewis acid  $ZnCl_2$  efficiently promotes the reactions of asymmetric allylation and benzylation, giving  $\alpha$ -allyl and  $\alpha$ -benzyl  $\alpha,\alpha$ -disubstituted amino acid derivatives in moderate-to-good yields with good-to-excellent enantioselectivities. The  $\alpha$ -arylation product **3o** is used for the formal total synthesis of AG-041R, and three transition states are proposed to illustrate the stereoselective-control results.

## Data availability

All data supporting the findings of this study are available within the article and its ESI† file.

## Author contributions

W. W. and G. Q. X. conceived this project. S. H. R., L. C. X., J. X., L. Y., L. J. H. and Z. F. carried out the experiments. W. Z. L. and C. T. performed the HRMS analysis. H. R. X. and J. X. discussed the transition states. G. Q. X. wrote the manuscript. All authors discussed the results.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We are grateful for financial support from NSFC (22071199, 22201235), the Innovation Research 2035 Pilot Plan of Southwest University (SWU-XDZD20211), and the Chongqing Science Technology Commission (cstcxljrc201701, cstc2018jcyjAX0548).

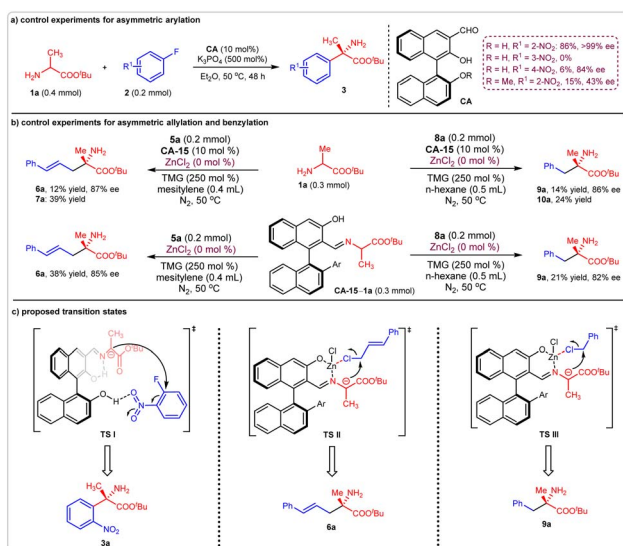


Fig. 7 Control experiments and possible transition states. (a) Control experiments for asymmetric arylation reaction; (b) control experiments for asymmetric allylation and benzylation reactions; (c) proposed transition states.



## Notes and references

- 1 (a) J. McMurry, *Organic Chemistry*, 9th edn; Cengage Learning, 2015; (b) F. Carey and R. Giuliano, *Organic Chemistry*, 8th edn; McGraw-Hill, 2021; (c) L. G. Wade, *Organic Chemistry*, 8th edn; Pearson Education India, 2012; (d) J. Clayden, N. Greeves, S. Warren and P. Wothers, *Organic Chemistry*, 2nd edn; Oxford University Press, Oxford, 2012.
- 2 O. F. Terrier, *Modern Nucleophilic Aromatic Substitution*, Wiley-VCH, Weinheim, Germany, 2013.
- 3 (a) S. R. Hartshorn, *Aliphatic Nucleophilic Substitution*, Cambridge University Press, London, 1973; (b) E. V. Anslyn and D. A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books, Sausalito, 2006.
- 4 (a) J. Choi and G. C. Fu, *Science*, 2017, **356**, eaaf7230; (b) A. de Meijere, S. Bräse and M. Oestreich, *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley-VCH, Weinheim, 2014; (c) T. J. Colacot, *New Trends in Cross-Coupling: Theory and Applications*, Royal Society of Chemistry, Cambridge, 2015; (d) Y.-J. Hao, X.-S. Hu, Y. Zhou, J. Zhou and J.-S. Yu, *ACS Catal.*, 2020, **10**, 955–993; (e) G. C. Fu, *ACS Cent. Sci.*, 2017, **3**, 692–700; (f) M. Orlandi, M. Escudero-Casao and G. Licini, *Synthesis*, 2021, **53**, 4559–4566.
- 5 (a) C. Nájera and J. M. Sansano, *Chem. Rev.*, 2007, **107**, 4584–4671; (b) A. Perdih and M. S. Dolenc, *Curr. Org. Chem.*, 2007, **11**, 801–832; (c) C. Cativiela and M. D. Diaz-De-Villegas, *Tetrahedron: Asymmetry*, 2007, **18**, 569–623; (d) K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013–3028; (e) B. Lygo and B. I. Andrews, *Acc. Chem. Res.*, 2004, **37**, 518–525; (f) M. J. O'Donnell, *Acc. Chem. Res.*, 2004, **37**, 506–517; (g) M. J. O'Donnell, *Aldrichimica Acta*, 2001, **34**, 3–15.
- 6 (a) W. Wen and Q.-X. Guo, *Synthesis*, 2023, **55**, 719–732; (b) K.-J. Lin, A. Shi, C.-H. Shi, J.-B. Lin and H.-G. Lin, *Front. Chem.*, 2021, **9**, 687–817; (c) Z.-Q. Yuan, J. Liao, H. Jiang, P. Cao and Y. Li, *RSC Adv.*, 2020, **10**, 35433–35448; (d) Q. Wang, Q. Gu and S.-L. You, *Angew. Chem., Int. Ed.*, 2019, **58**, 6818–6825.
- 7 B. Xu, L.-L. Shi, Y.-Z. Zhang, Z.-J. Wu, L.-N. Fu, C.-Q. Luo, L.-X. Zhang, Y.-G. Peng and Q.-X. Guo, *Chem. Sci.*, 2014, **5**, 1988–1991.
- 8 (a) W. Wen, L. Chen, M.-J. Luo, Y. Zhang, Y.-C. Chen, Q. Ouyang and Q.-X. Guo, *J. Am. Chem. Soc.*, 2018, **140**, 9774–9780; (b) W.-Z. Wang, H.-R. Shen, J. Liao, W. Wen and Q.-X. Guo, *Org. Chem. Front.*, 2022, **9**, 1422–1426; (c) J.-G. Ma, Q.-H. Zhou, G.-S. Song, Y.-C. Song, G.-Q. Zhao, K.-L. Ding and B.-G. Zhao, *Angew. Chem., Int. Ed.*, 2021, **60**, 10588–10592.
- 9 (a) J.-F. Chen, X. Gong, J.-Y. Li, Y.-K. Li, J.-G. Ma, C.-K. Hou, G.-Q. Zhao, W.-C. Yuan and B.-G. Zhao, *Science*, 2018, **360**, 1438–1442; (b) W. Wen, M.-J. Luo, Y. Yuan, J.-H. Liu, Z.-L. Wu, T. Cai, Z.-W. Wu, Q. Ouyang and Q.-X. Guo, *Nat. Commun.*, 2020, **11**, 5372.
- 10 (a) A. Cheng, L. Zhang, Q. Zhou, T. Liu, J. Cao, G. Zhao, K. Zhang, G. Song and B. Zhao, *Angew. Chem., Int. Ed.*, 2021, **60**, 20166–20172; (b) P. Ji, X. Liu, J. Xu, X. Zhang, J. Guo, W.-W. Chen and B. Zhao, *Angew. Chem., Int. Ed.*, 2022, **61**, e202206111; (c) C. Hou, B. Peng, S. Ye, Z. Yin, J. Cao, X. Xiao and B. Zhao, *Nat. Catal.*, 2022, **5**, 1061–1068.
- 11 (a) L. Chen, M.-J. Luo, F. Zhu, W. Wen and Q.-X. Guo, *J. Am. Chem. Soc.*, 2019, **141**, 5159–5163; (b) F. Zhu, Q.-W. Shen, W.-Z. Wang, Z.-L. Wu, T. Cai, W. Wen and Q.-X. Guo, *Org. Lett.*, 2021, **23**, 1463–1467; (c) J. Ma, B. Gao, G. Song, R. Zhang, Q. Wang, Z. Ye, W.-W. Chen and B. Zhao, *Angew. Chem., Int. Ed.*, 2022, **61**, e202200850.
- 12 J.-H. Liu, W. Wen, J. Liao, Q.-W. Shen, Y. Lin, Z.-L. Wu, T. Cai and Q.-X. Guo, *Nat. Commun.*, 2022, **13**, 2509.
- 13 F. Zhu, C.-X. Li, Z.-L. Wu, T. Cai, W. Wen and Q.-X. Guo, *Nat. Commun.*, 2022, **13**, 7290.
- 14 (a) M. Chaari, A. Jenhi, J. P. Lavergne and P. Viallefont, *Tetrahedron*, 1991, **47**, 4619–4630; (b) S. Shirakawa, K. Yamamoto and K. Maruoka, *Angew. Chem., Int. Ed.*, 2015, **54**, 838–840; (c) S. Shirakawa, K. Yamamoto, T. Tokuda and K. Maruoka, *Asian J. Org. Chem.*, 2014, **3**, 433–436; (d) K. Tomohara, T. Yoshimura, R. Hyakutake, P. Yang and T. Kawabata, *J. Am. Chem. Soc.*, 2013, **135**, 13294–13297; (e) Y. Li, H. Pan, W.-Y. Li, X. Feng and X. Liu, *Synlett*, 2021, **32**, 587–592; (f) F. Foschi, A. Tagliabue, V. Mihali, T. Pilati, I. Pecnikaj and M. Penso, *Org. Lett.*, 2013, **15**, 3686–3689.
- 15 (a) J.-S. Yang, K. Lu, C.-X. Li, Z.-H. Zhao, X.-M. Zhang, F.-M. Zhang and Y.-Q. Tu, *Angew. Chem., Int. Ed.*, 2022, **61**, e202114129; (b) Y. Kubota, S. Shirakawa, T. Inoue and K. Maruoka, *Tetrahedron Lett.*, 2012, **53**, 3739–3741; (c) Y. P. Park, S. Kang, Y. J. Lee, T. S. Kim, B. S. Jeong, H. Park and S. Jew, *Org. Lett.*, 2009, **11**, 3738–3741; (d) T. S. Kim, Y. J. Lee, K. Lee, B. S. Jeong, H. Park and S. Jew, *Synlett*, 2009, **4**, 671–674; (e) S. Jew, B. S. Jeong, J. H. Lee, M. S. Yoo, Y. J. Lee, B. Park, M. G. Kim and H. Park, *J. Org. Chem.*, 2003, **68**, 4514–4516; (f) S. Woo, Y. G. Kim, B. Lim, J. Ho, Y. Lee, H. Gwon and K. Nahm, *RSC Adv.*, 2018, **8**, 2157–2160; (g) T. Ooi, T. Miki and K. Maruoka, *Org. Lett.*, 2005, **7**, 191–193; (h) M. Kitamura, S. Shirakawa and K. Maruoka, *Angew. Chem., Int. Ed.*, 2005, **44**, 1549–1551; (i) T. Achard, Y. N. Belokon, J. A. Fuentes, M. North and T. Parsons, *Tetrahedron*, 2004, **60**, 5919–5930; (j) Y. N. Belokon, D. Bhave, D. D'Addario, E. Groaz, M. North and V. Tagliuzucca, *Tetrahedron*, 2004, **60**, 1849–1861; (k) B. Lygo, J. Crosby and J. A. Peterson, *Tetrahedron Lett.*, 1999, **40**, 8671–8674; (l) T. Ooi, M. Takeuchi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 2000, **122**, 5228–5229; (m) M. J. O'Donnell and S. Wu, *Tetrahedron: Asymmetry*, 1992, **3**, 591–594; (n) U.-H. Dolling, P. Davis and E. J. J. Grabowski, *J. Am. Chem. Soc.*, 1984, **106**, 446–447; (o) M. J. O'Donnell, W. D. Bennett and S. Wu, *J. Am. Chem. Soc.*, 1989, **111**, 2353–2355.
- 16 (a) T. Chiba, Y. Kinoshita, M. Sawada, K. Kishi, A. Baba and E. Hoshino, *Yale J. Biol. Med.*, 1998, **71**, 247–255; (b) E. Lindstrom, M. Björkqvist and R. Hakanson, *Br. J. Pharmacol.*, 1999, **127**, 530–536; (c) X.-Q. Ding, E. Lindstrom and R. Hakanson, *Clin. Pharmacol.*, 1997, **81**, 232–237; (d) M. Ochi, K. Kawasaki, H. Kataoka, Y. Uchio and H. Nishi, *Biochem. Biophys. Res. Commun.*, 2001, **283**,



- 1118–1123; (e) H. Kitamura and M. Okazaki, *Osteoarthr. Cartilage*, 2005, **13**, 287–296; (f) W.-H. Sun, F. Zhu, G.-S. Chen, H. Su, C. Luo, Q.-S. Zhao, Y. Zhang, J. Shao, S.-M. Sun, G.-X. Zhou, Y.-L. Ding and Y.-L. Cheng, *Cancer Lett.*, 2008, **263**, 302–311.
- 17 (a) T. Emura, T. Esaki, K. Tachibana and M. Shimizu, *J. Org. Chem.*, 2006, **71**, 8559–8564; (b) S. Sato, M. Shibuya, N. Kanoh and Y. Iwabuchi, *J. Org. Chem.*, 2009, **74**, 7522–7524; (c) S. Sato, M. Shibuya, N. Kanoh and Y. Iwabuchi, *Chem. Commun.*, 2009, **41**, 6264–6266; (d) S. Hajra, S. Laskar and B. Jana, *Chem.–Eur. J.*, 2019, **25**, 14688–14693; (e) X.-J. Xia, Q.-Q. Zhu, J. Wang, J. Chen, W.-G. Cao, B. Zhu and X.-Y. Wu, *J. Org. Chem.*, 2018, **83**, 14617–14625; (f) M. Sawa, S. Miyazaki, R. Yonesaki, H. Morimoto and T. Ohshima, *Org. Lett.*, 2018, **20**, 5393–5397; (g) J. Dai, D. Xiong, T.-R. Yuan, J. Liu, T. Chen and Z.-H. Shao, *Angew. Chem., Int. Ed.*, 2017, **56**, 12697–12701; (h) O. D. Engl, S. P. Fritz and H. Wennemers, *Angew. Chem., Int. Ed.*, 2015, **54**, 8193–8197; (i) J. Wang, Q.-X. Zhang, B.-Y. Zhou, C. Yang, X. Li and J.-P. Cheng, *Science*, 2019, **16**, 511–533; (j) K. Zhao, T. Shu, J.-Q. Jia, G. Raabe and D. Enders, *Chem.–Eur. J.*, 2015, **21**, 3933–3936; (k) N. Hara, S. Nakamura, M. Sano, R. Tamura, Y. Funahashi and N. Shibata, *Chem.–Eur. J.*, 2012, **18**, 9276–9280.

