Chiral Aldehyde Catalysis Enables Direct Asymmetric α–Substitution Reaction of *N*-Unprotected Amino Acids with Halohydrocarbons

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ABSTRACT: The direct catalytic α–hydrocarbylation of readily available amino acids with halohydrocarbons is one of the most straightforward methods leading to α,α–disubstituted non-proteinogenic α–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 α–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 $ZnCl_2$, the asymmetric α–arylation, α–allylation, and α–benzylation of amino acid esters with the corresponding halohydrocarbons proceed smoothly, producing α,α–disubstituted α–amino acids in moderate-to-high yields and good-to-excellent enantioselectivities. The asymmetric α–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.

1. 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.[1-4] 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_NAr,[5] S_N1, or S_N2 substitutions,[6-7] or via couplings.[8-13] Among these reactions, the catalytic asymmetric α–substitution reactions of readily available amino acid derivatives with halohydrocarbons provide a highly efficient pathway for the preparation of optically active unnatural α,α–disubstituted α–amino acids.[14-20] However, in those reported methodologies, protection and deprotection manipulations are always unavoidable (Figure 1, path a). Notably, an ideal catalytic strategy leading to such products could directly promote the α–hydrocarbylation of *N*-unprotected amino acid esters with high efficiency (Figure 1, path b); however, such a valuable methodology has never been disclosed until now.

The unique property of chiral aldehyde catalysis,[21-24] directly promoting the asymmetric α–functionalization of *N*-unprotected amino acid esters, has been demonstrated in alkylation,[25] Michael addition,[26-28] Mannich,[29-30] aldol,[31-33] allylation,[34-36] benzylation,[37] and propargylation[38] reactions. We envisioned that this strategy may be promising for the direct asymmetric α–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 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 α–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 α–hydrocarbylation reaction of amino acid esters with improved chemoselectivity and enantioselectivity.

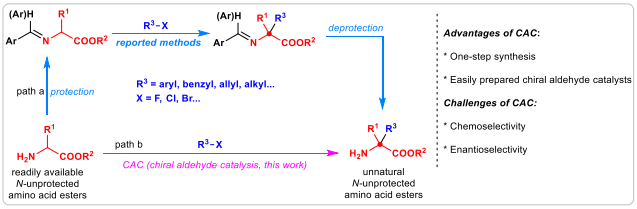


Figure 1. Catalytic asymmetric α–hydrocarbylation reaction of amino acid esters with halohydrocarbons.

In this work, we report on three chiral aldehyde-catalyzed asymmetric α–substitution reactions of *N*-unprotected amino acid esters with aryl halides,[39-44] allyl chlorides, and benzyl chlorides.[45-59] Although the *N*-functionalization byproducts are not suppressed completely, the de-

sired *C*-functionalization products can be generated in moderate-to-high yields with good-to-excellent enantioselectivities for all three transformations. Furthermore, the α–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 and density functional theory (DFT) calculations.

2. RESULTS AND DISCUSSION

2.1. 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 Cs_2CO_3, or tetramethylguanidine, 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 (Figure 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 $ZnCl_2$ 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 (Figure 2b–c).

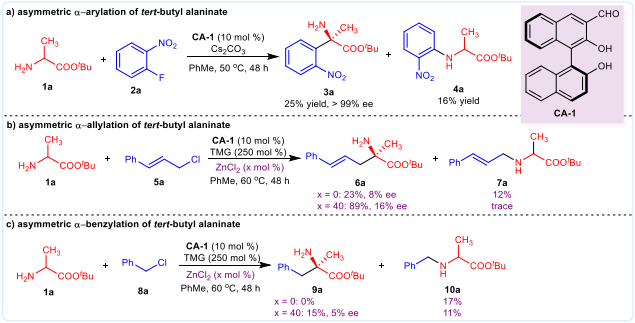


Figure 2. Initial investigation of the catalytic asymmetric α–hydrocarbylation of amino acid esters.

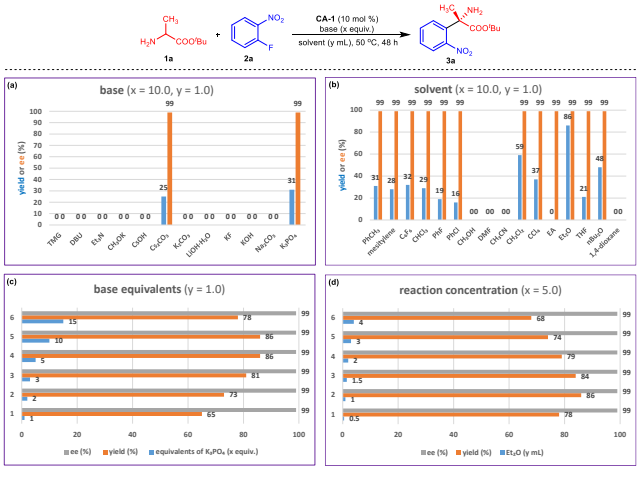


Figure 3. Reaction condition optimization for arylation of **1a** with **2a**.

2.2. Reaction Condition Optimization for The Asymmetric 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 Figure 1a, chiral aldehyde **CA-1** was chosen for optimization of the reaction conditions. Base screening indicated that inorganic bases were suitable for this reaction, and K_3PO_4 provided the greatest yield of **3a** (Figure 3a). The choice of solvent also affected the yield of **3a**. When this reaction was conducted in Et_2O, product **3a** was obtained in 86% yield with > 99% ee (Figure 3b). Then, the base equivalent and the reaction concentration were tuned. The results indicated that using 5 equivalents of K_3PO_4 and 0.2 M **2a** (y = 1) produced the greatest yield (Figure 3c–d).

2.3. Substrate Scopes of The Asymmetric Arylation Reaction. 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** (Figure 4a). The variation of the alkoxyl group on reactant **1** affected the yields but had little influence on the enantioselectivity (Figure 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 (Figure 4a, **3j**-**3m**). Other functional groups, such as ester, 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 (Figure 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 (Figure 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 (Figure 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 (Figure 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 (Figure 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 (Figure 4d, **3al**–**3am**). The absolute configuration of product **3a** was assigned as *S* by comparing its optical rotation value with the literature data (see Supplementary Information), and the stereochemistries of the other products in Figure 4 were assigned accordingly.

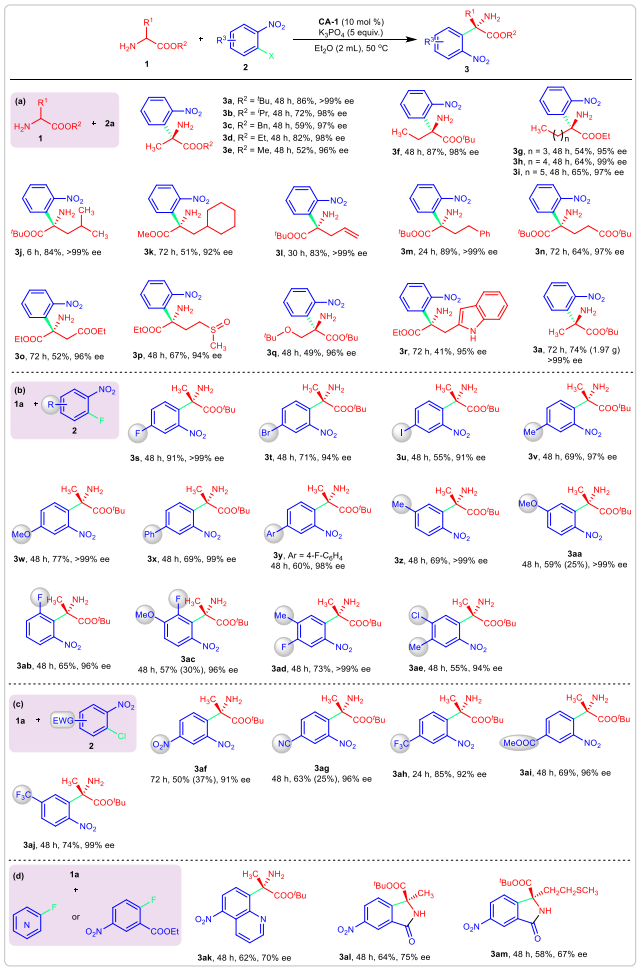


Figure 4. Substrate scopes of the asymmetric arylation reaction.

2.4. Reaction Condition Optimizations for The Asymmetric 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 α–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 α–allylation product could be obtained in 89% yield with 16% ee under the promotion of a chiral aldehyde-$ZnCl_2$ 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%) (Figure 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 (Figure 5a, ii). When this reaction was conducted at 50 °C, product **6a** was obtained in 65% yield with 94% ee (Figure 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 (Figure 5a, iv). Based on these results, the optimal reaction conditions for the asymmetric α–allylation reaction were determined.

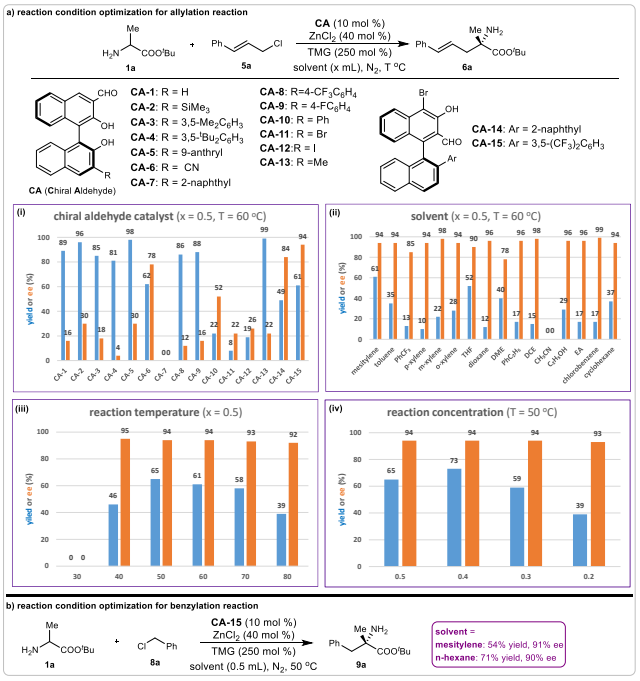


Figure 5. Condition optimizations for asymmetric allylation and benzylation reactions.

Due to the similar reaction activities of benzyl chlorides with allyl chlorides, we directly applied the above optimal reaction conditions in the asymmetric α–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 Supporting Information, Tables S14–S18). Finally, we found that product **9a** could be obtained in 71% yield with 91% ee when n-hexane was used as the reaction solvent (Figure 5b). Thus, the optimal reaction conditions for this asymmetric benzylation were determined.

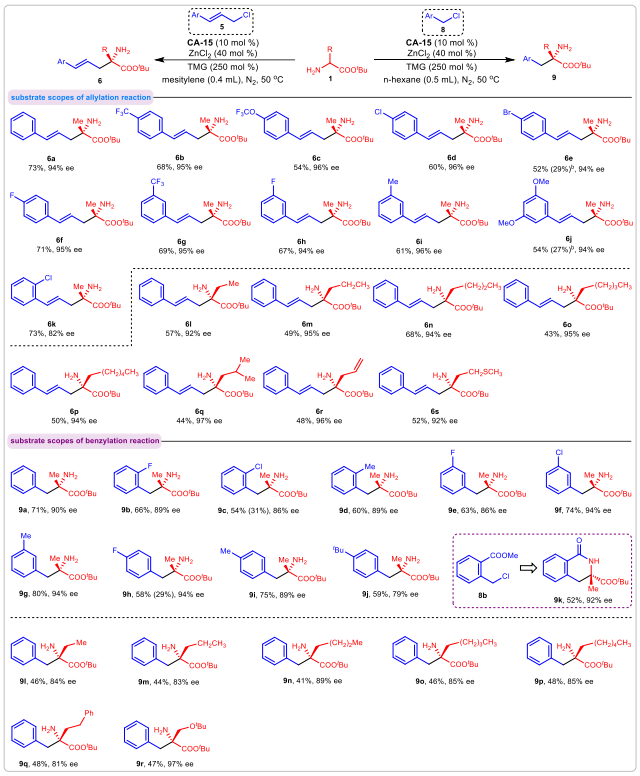
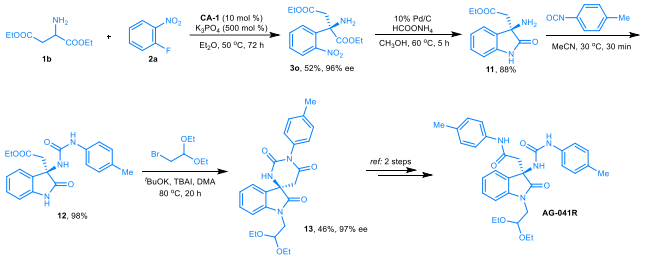


Figure 6. Substrate scopes of the asymmetric allylation and benzylation reactions.

2.5. Substrate Scopes of The Asymmetric Allylation and Benzylation Reactions. 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 α–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 activities in this reaction and gave the corresponding products in moderate-to-high yields with good-to-excellent enantioselectivities (Figure 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 α–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 (Figure 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 Supporting Information), and the stereochemistries of the other products in Figure 6 were assigned accordingly.

2.6. Synthetic Application. The clinical candidate compound (+)-AG-041R is a gastrin/CCK-B receptor antagonist with an IC50 of 1.1 nmol.[60-65] Few catalytic asymmetric methodologies have been developed for preparing this compound,[66-76] 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-amino oxindole, product **11**. Using the reported methods, urea moiety-contained oxindole **12** and Iwabuchi intermediate **13**[67] were prepared, successively (Scheme 1). The spectra data and optical rotation of compound **13** agree with the literature (see Supporting Information). 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.



Scheme 1. The formal synthesis of AG-041R.

2.7. 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 (Figure 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.

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 (Figure 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 **III** and TS **IV**, were proposed (Figure 7c). Thus, products (*S*)-**6a** and (*S*)-**9a** were generated respectively (Figure 7c).

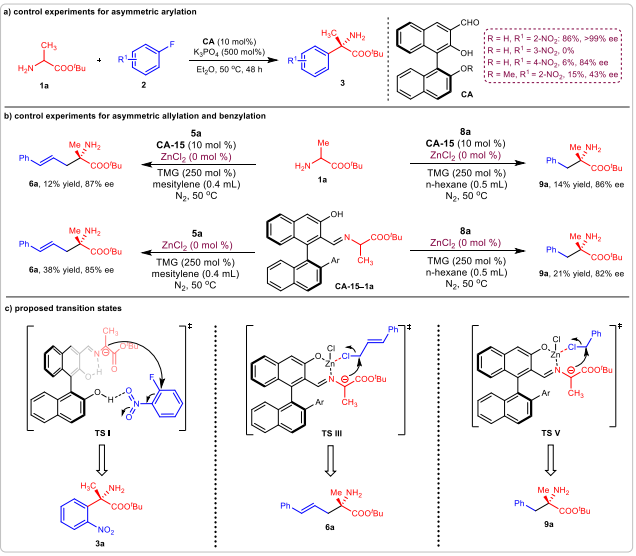


Figure 7. Control experiments and possible transition states.

3. CONCLUSION

In conclusion, we demonstrated highly efficient chiral aldehyde-catalyzed α–substitution reactions of *N*-amino acid esters with aryl, allyl, and benzyl halides. In the promotion of the simple chiral aldehyde **CA-1**, the α–arylation reaction of *N*-unprotected amino acid esters with aryl halides takes place smoothly, giving α–aryl α,α–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 α–allyl and α–benzyl α,α–disubstituted amino acid derivatives in moderate-to-good yields with good-to-excellent enantioselectivities. The α–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.

ASSOCIATED CONTENT

Supporting Information.

Complete experimental procedures, characterization of new products, NMR and HRMS spectra and HPLC chromatograms, and DFT calculation details (PDF)

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Notes

The authors declare no competing interests.

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