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# Catalytic asymmetric synthesis of quaternary trifluoromethyl $\alpha$ - to $\varepsilon$ -amino acid derivatives via umpolung allylation/2-aza-Cope rearrangement†

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In this study, we developed an efficient Ir-catalyzed cascade umpolung allylation/2-aza-Cope rearrangement of tertiary  $\alpha$ -trifluoromethyl  $\alpha$ -amino acid derivatives for the preparation of a variety of quaternary  $\alpha$ -trifluoromethyl  $\alpha$ -amino acids in high yields with excellent enantioselectivities. The umpolung reactivity empowered by the activation of the key isatin-ketoimine moiety obviates the intractable enantioselectivity control in Pd-catalyzed asymmetric linear  $\alpha$ -allylation. In combination with quasi parallel kinetic resolution or kinetic resolution, the generality of this method is further demonstrated by the first preparation of enantioenriched quaternary trifluoromethyl  $\beta$ -,  $\gamma$ -,  $\delta$ - and  $\varepsilon$ -amino acid derivatives.

## Introduction

Enantioenriched fluorinated amino acids (AAs) and their biopolymers have received great attention in the past decades due to their potential in preparing bioactive molecules with unique characteristics.<sup>1</sup> The introduction of the trifluoromethyl group into amino acids often exerts increased environmental and metabolic stability with enhanced biological activity,<sup>2</sup> thus the products have found widespread bio-organic and medical applications as, for example, biological tracers, mechanistic probes, and enzyme inhibitors.<sup>3</sup> Accordingly, the development of innovative synthetic protocols to construct chiral trifluoromethylated amino acids with yet unknown chemical and biological attributes is in extremely high demand. Although some achievement has been made in this field, the progress in developing reliable synthetic methodologies to synthesize diverse quaternary trifluoromethyl amino acids is far from being fully explored. For example, the catalytic asymmetric synthesis of trifluoromethylated  $\alpha$ -amino acids has been well established with many addition methods, such as catalytic asymmetric Strecker-type reaction, nucleophilic addition and amination.<sup>4,5</sup> In sharp contrast, the asymmetric construction of enantioenriched trifluoromethylated AAs other than  $\alpha$ -amino

acids, such as  $\beta$ -,  $\gamma$ -,  $\delta$ - and  $\varepsilon$ -AAs, has been scarcely reported and in most of the methods developed so far chiral auxiliaries or enzymes were employed.<sup>6</sup> In addition, the asymmetric construction of quaternary trifluoromethyl amino acids, which are particularly useful in the design of peptides and proteins with enhanced properties,<sup>7</sup> represents another synthetic challenge in this area because of the disfavored steric hindrance.<sup>4c</sup>

In our continuous interest in the asymmetric synthesis of unnatural amino acids,<sup>8</sup> we recently disclosed an Ir-catalyzed asymmetric  $\alpha$ -allylation of an  $\alpha$ -CF<sub>3</sub> aldimino ester (Scheme 1a,  $n = 0$ ).<sup>9</sup> Quasi-kinetic resolution of the formed diastereomeric allylation intermediates would produce enantioenriched quaternary  $\alpha$ -trifluoromethyl  $\alpha$ -amino acids ( $\alpha$ -Tfm  $\alpha$ -AAs) and homoallylic amines simultaneously. However, further attempts to extend this protocol for the preparation of more challenging quaternary trifluoromethyl  $\beta$ -,  $\gamma$ -,  $\delta$ - and  $\varepsilon$ -amino acids through elongating the length of the ester carbon chain all failed due to the reduced nucleophilicity of the carbon connected to CF<sub>3</sub> in the corresponding aldimino ester. Inspired by previous investigation on the 2-azaallyl anion,<sup>10,11</sup> we surmised that an appropriate imino activating group connected to the N-terminus of a tertiary trifluoromethylated amino ester should be capable of regulating the reactivity of the *in situ*-formed 2-azaallyl carbanion and allowing an Ir-catalyzed asymmetric branched-selective allylation<sup>12</sup> exclusively at the  $\alpha'$ -position in an umpolung manner. The generated allylation intermediate containing two adjacent multi-substituted stereogenic centers would readily undergo subsequent 2-aza-Cope rearrangement<sup>11a,b,13</sup> to release the steric congestion and produce linear allyl substituted  $\alpha$ -Tfm  $\alpha$ -AAs in high enantioselectivity control. Most importantly, the umpolung strategy not only obviates the intractable Pd-catalyzed linear  $\alpha$ -allylation but

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Scheme 1 Catalytic asymmetric synthesis of quaternary trifluoromethyl α-AAs (previous work) and α- to ε-AAs (this work).

might tolerate broader α-ester carbon chains, and therefore enable precise construction of diverse types of quaternary trifluoromethylated amino acids. Only one report of palladium-catalyzed linear allylation of an α-CF<sub>3</sub> aldmino ester has been disclosed so far with a single example of enantioenriched quaternary α-Tfm α-AAs with 50% ee (Scheme 1b, left side).<sup>14</sup> To realize this design, several challenging issues need to be considered: (1) regioselectivity: the competitive nucleophilicity of the α and α' positions of the 2-azaallyl anion in the first allylation step; (2) stereoselectivity: it is a formidable task to achieve high diastereo-/enantioselectivity control in the allylation/2-aza-Cope rearrangement with the bulky CF<sub>3</sub>-containing 2-azaallyl anion as a prochiral nucleophile; (3) chemoselectivity: it is well-known that a CF<sub>3</sub> group attached to a carbon atom bearing a hydrogen atom easily undergoes β-fluorine elimination.<sup>15</sup> Herein, we report the development, stereochemical modulation, substrate generality and synthetic applications of Ir-catalyzed umpolung allylation/2-aza-Cope rearrangement for the preparation of chiral quaternary trifluoromethyl α-, β-, γ-, δ- and ε-amino acid derivatives that are not readily accessed by other methodologies.

## Results and discussion

Our initial trials were conducted between methyl cinnamyl carbonate **2a** and different potential 2-azaallyl anion precursors **1a–1c** using [Ir(cod)Cl]<sub>2</sub>/(*S,S,S*)-L1 (ref. 16 and 17) as the catalyst and Cs<sub>2</sub>CO<sub>3</sub> as the base in 1,2-dichloroethane (DCE) at room temperature. No reaction occurred with ketoimine esters derived from benzophenone or fluorenone (Table 1, entries 1 and 2). To our delight, with isatin-activated ketoimine ester **1c**,

the desired quaternary trifluoromethyl α-amino acid derivative **3a** was isolated in 99% yield with 96% ee. Considering the significant effect of the isatin-derived imino moiety on the reactivity and the predicted pK<sub>a</sub> values (in DMSO: 17.38 (**1a**), 12.66 (**1b**), 12.44 (**1c**)),<sup>18,19</sup> we believed that both the steric effect and the electronic effect affect the reactivity of the tested ketoimine esters. Encouraged by these promising results, further screening of other parameters was performed. No desired product was observed in the absence of a base or using a weak organic base Et<sub>3</sub>N, indicating that an appropriate base with sufficient basicity is essential for the formation of 2-azaallyl carbanion (entries 4 and 5). When DBU was employed, **3a** was obtained in 80% yield along with a small amount of β-fluorine elimination byproduct (entry 6). Performing the reaction in other solvents including dichloromethane, benzene, tetrahydrofuran, and toluene all led to decreased yield although the enantioselectivities remain excellent (entries 7–10).

With optimized reaction conditions in hand, we set out to evaluate the generality of this cascade reaction. Firstly, a variety of substituted allyl carbonates were investigated. As summarized in Table 2, *para*-, *meta*-substituted and 3,4-disubstituted cinnamyl carbonates reacted smoothly with **1a**, giving α-Tfm α-AAs **3b–3i** in 87–99% yield with 90–96% ee (Table 2, entries 2–9). The current transformation shows good

Table 1 Optimizations on Ir-catalyzed umpolung allylation/2-aza-Cope rearrangement for the synthesis of quaternary CF<sub>3</sub> α-amino acids<sup>a</sup>



Entry	1	Base	Solvent	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	<b>1a</b>	Cs <sub>2</sub> CO <sub>3</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	NR	—
2	<b>1b</b>	Cs <sub>2</sub> CO <sub>3</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	NR	—
3	<b>1c</b>	Cs <sub>2</sub> CO <sub>3</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	99	96
4	<b>1c</b>	—	(CH <sub>2</sub> Cl) <sub>2</sub>	NR	—
5	<b>1c</b>	NEt <sub>3</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	NR	—
6	<b>1c</b>	DBU	(CH <sub>2</sub> Cl) <sub>2</sub>	80	95
7	<b>1c</b>	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	90	94
8	<b>1c</b>	Cs <sub>2</sub> CO <sub>3</sub>	Benzene	85	95
9	<b>1c</b>	Cs <sub>2</sub> CO <sub>3</sub>	THF	37	96
10	<b>1c</b>	Cs <sub>2</sub> CO <sub>3</sub>	Toluene	80	93

<sup>a</sup> All reactions were carried out with 0.2 mmol **1**, 0.22 mmol **2a** and 0.2 mmol base in 2 mL of solvent. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC analysis.



tolerance towards the electronic effect of the substituents; both electron-withdrawing and electron-donating groups were well-tolerated. In line with previous Ir-catalyzed asymmetric allylation with Feringa-type ligands, *ortho*-methyl substituted cinnamyl carbonate **2j** was not a viable  $\pi$ -allyl precursor in this catalytic system. Fortunately, the corresponding product **3j** could be obtained in 82% yield with 64% ee when using You's ligand (*R,R*<sub>a</sub>)-**L2** (ref. 20) (entry 10). Fused 2-naphthyl, hetero-aromatic 2-thienyl and 2-furyl substituted carbonates **2k–m** worked well, affording the corresponding **3k–m** in good yields with high to excellent enantioselectivities (entries 11–13). In addition, crotyl carbonate **2n** was also proven to be a suitable reaction partner, delivering the desired quaternary CF<sub>3</sub>-containing  $\alpha$ -amino acids **3n** in 95% yield with 86% ee (entry 14).

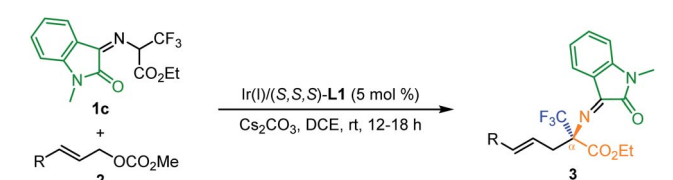
Having established the asymmetric construction of quaternary trifluoromethyl  $\alpha$ -amino acids, we then extended the current methodology for the preparation of more challenging trifluoromethyl-containing  $\beta$ -amino acids using isatin-activated ketoimine ester **1d** as the 2-azaallyl carbanion precursor. The reaction between **1d** and **2a** under identical conditions except that DBU was used as the base instead of Cs<sub>2</sub>CO<sub>3</sub> affords quaternary  $\beta$ -CF<sub>3</sub>  $\beta$ -amino acid ( $\beta$ -Tfm  $\beta$ -AA) **4a** in 37% yield along with 54% yield of isomerized allylation product **5a** with excellent enantioselectivities (Table 3, entry 1). It is believed that a quasi-parallel kinetic resolution (PKR) process occurred with the two diastereomeric branched allylation intermediates formed. Although no better improvement in the ratio of the two products could be achieved *via* further reaction optimization,



Fig. 1 X-ray of (*R*)-**3k'** and (*S,S*)-**5a**.<sup>21</sup>

compounds **4a** and **5a** could be readily separated through silica gel column purification due to the distinct polar difference, which is ascribed to the intramolecular hydrogen bond interaction existing in the isomerized allylation product **5a** (Fig. 1). The isolated compound **5a** (98% ee) could be further converted to *ent*-**4a** with 64% ee (opposite configuration) upon heating in dichloroethane or toluene (see the ESI<sup>†</sup> for more details). In view of the fact that both enantioenriched  $\beta$ -Tfm  $\beta$ -AAs and 3-amino oxindole derivatives<sup>22</sup> are useful building blocks in organic synthesis, developing a general method to prepare the two chiral compounds in one-pot is of particular interest. Thus, the generality of this transformation was then evaluated using **1d** as the 2-azaallyl anion precursor. As shown in Table 3, *meta*- and *para*-substituted cinnamyl carbonates are all compatible

Table 2 Substrate scope for the synthesis of quaternary CF<sub>3</sub>  $\alpha$ -amino acids<sup>a</sup>



Entry	R	3	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	Ph ( <b>2a</b> )	<b>3a</b>	99	96
2	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )	<b>3b</b>	91	94
3	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )	<b>3c</b>	89	96
4	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> ( <b>2d</b> )	<b>3d</b>	99	94
5	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> ( <b>2e</b> )	<b>3e</b>	87	94
6	3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> ( <b>2f</b> )	<b>3f</b>	99	90
7	<i>m</i> -MeOC <sub>6</sub> H <sub>4</sub> ( <b>2g</b> )	<b>3g</b>	99	94
8 <sup>e</sup>	<i>m</i> -MeC <sub>6</sub> H <sub>4</sub> ( <b>2h</b> )	<b>3h</b>	92	94
9	Piperonyl ( <b>2i</b> )	<b>3i</b>	98	94
10 <sup>d</sup>	<i>o</i> -MeC <sub>6</sub> H <sub>4</sub> ( <b>2j</b> )	<b>3j</b>	82	63
11 <sup>e</sup>	2-Naphthyl ( <b>2k</b> )	<b>3k</b>	86	94
12	2-Thienyl ( <b>2l</b> )	<b>3l</b>	90	94
13	2-Furyl ( <b>2m</b> )	<b>3m</b>	92	86
14	Me ( <b>2n</b> )	<b>3n</b>	95	86

<sup>a</sup> All reactions were carried out with 0.2 mmol **1c**, 0.22 mmol **2**, Cs<sub>2</sub>CO<sub>3</sub> (0.2 mmol) in 2 mL of DCE. <sup>b</sup> Isolated yield. <sup>c</sup> Ee determined by HPLC analysis. <sup>d</sup> (*R,R*<sub>a</sub>)-**L2** was used. <sup>e</sup> X-ray structure of hydrolyzed (*R*)-**3k'** was obtained (Fig. 1).

Table 3 Substrate scope for the synthesis of quaternary CF<sub>3</sub>  $\beta$ -amino acids<sup>a</sup>



Entry	R	4	5
1	Ph ( <b>2a</b> )	<b>4a</b> , 37(91)	<b>5a</b> , 54(98) <sup>d</sup>
2	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )	<b>4b</b> , 35(90)	<b>5b</b> , 45(98)
3	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )	<b>4c</b> , 34(85)	<b>5c</b> , 57(96)
4	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> ( <b>2d</b> )	<b>4d</b> , 38(90)	<b>5d</b> , 52(98)
5	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> ( <b>2e</b> )	<b>4e</b> , 35(90)	<b>5e</b> , 55(97)
6	3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> ( <b>2f</b> )	<b>4f</b> , 34(92)	<b>5f</b> , 48(87)
7	<i>m</i> -MeOC <sub>6</sub> H <sub>4</sub> ( <b>2g</b> )	<b>4g</b> , 32(89)	<b>5g</b> , 47(91)
8	<i>m</i> -MeC <sub>6</sub> H <sub>4</sub> ( <b>2h</b> )	<b>4h</b> , 39(94)	<b>5h</b> , 57(97)
9	Piperonyl ( <b>2i</b> )	<b>4i</b> , 41(85)	<b>5i</b> , 53(95)
10	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub> ( <b>2j</b> )	<b>4j</b> , 43(93)	<b>5j</b> , 56(97)
11	2-Naphthyl ( <b>2k</b> )	<b>4k</b> , 35(90)	<b>5k</b> , 45(97)
12	2-Thienyl ( <b>2l</b> )	<b>4l</b> , 90(94)	<b>5l</b> , trace
13	2-Furyl ( <b>2m</b> )	<b>4m</b> , 81(85)	<b>5m</b> , trace
14	Me ( <b>2n</b> )	—	<b>5n</b> , 88(89) <sup>e</sup>

<sup>a</sup> All reactions were carried out with 0.40 mmol **1d**, 0.44 mmol **2**, base (0.4 mmol) in 2 mL of DCE. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC analysis. <sup>d</sup> X-ray structure of (*S,S*)-**5a** was obtained. <sup>e</sup> 89% ee (major) and 81% ee (minor).



reaction partners, giving the desired **4b–j** and **5b–j** in high overall yields with excellent enantioselectivities (Table 3, entries 2–10). No reaction occurred with *ortho*-substituted cinnamyl carbonate due to the disfavored steric hindrance at the nucleophilic 2-azaallyl anion and electronic Ir- $\pi$ -allyl intermediate. 2-Naphthyl substituted **2k** reacted smoothly with **1d**, producing **4k** and **5k** in 35% and 45% yield, respectively, with excellent enantioselectivities (entry 11). To our surprise, when using 2-furyl and 2-thienyl allyl carbonates as the  $\pi$ -allyl precursors,  $\beta$ -Tfm  $\beta$ -AA derivatives **4l** and **4m** were observed as the major products in high yields and good enantioselectivity along with a trace amount of **5** (entries 12 and 13). The varying ratios of products **4** and **5** were attributed to the different diastereoselectivities in the first allylation step. Furthermore, when crotyl carbonate **2n** was tested in this reaction, only allylation product **5n** was isolated in 2 : 1 dr without further rearrangement (entry 14).

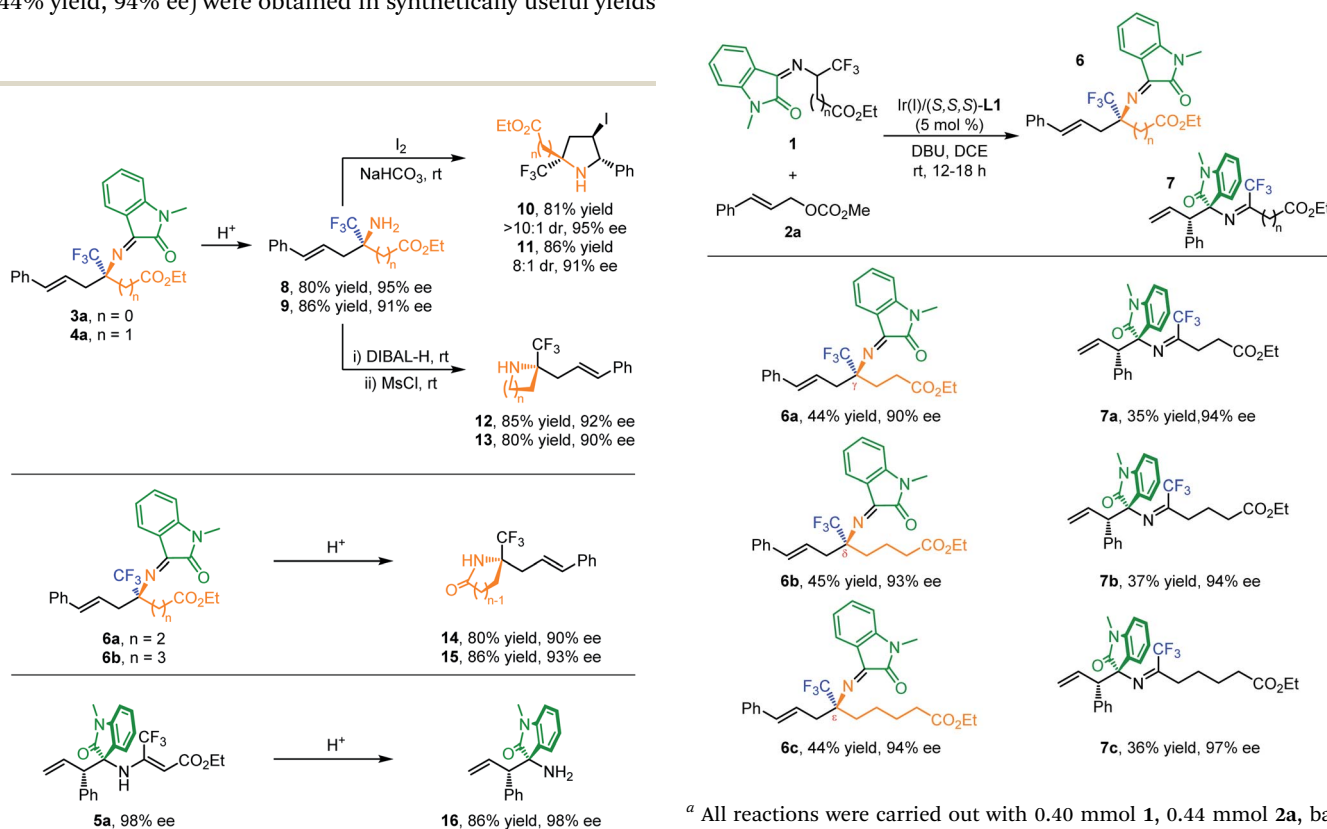
Remarkably, the current method is also capable of constructing quaternary trifluoromethyl  $\gamma$ -,  $\delta$ - and  $\epsilon$ -amino acids through further elongating the length of the ester carbon chain. As shown in Table 4, the reaction between isatin-activated  $\gamma$ -CF<sub>3</sub>  $\gamma$ -amino ester **1e** and **2a** undergoes an umpolung Ir-catalyzed allylation followed by quasi-kinetic resolution *via* 2-aza-Cope rearrangement, delivering the desired product **6a** (44% yield, 90% ee) and less reactive allylation product **7a** (35% yield, 94% ee). Similarly, using isatin-activated  $\delta$ -CF<sub>3</sub>  $\delta$ -amino ester derived **1f** and  $\epsilon$ -CF<sub>3</sub>  $\epsilon$ -amino ester derived **1g** as the 2-azaallyl anion precursors, the corresponding quaternary  $\delta$ -CF<sub>3</sub>  $\delta$ -amino acid **6b** (45% yield, 93% ee) and  $\epsilon$ -CF<sub>3</sub>  $\epsilon$ -amino acid derivative **6c** (44% yield, 94% ee) were obtained in synthetically useful yields

and excellent enantioselectivities along with the allylation products **7b** (37% yield, 94% ee) and **7c** (36% yield, 97% ee).

To further showcase the utility of this method, several synthetic transformations were conducted as shown in Scheme 2. Acidic hydrolysis of **3a** and **4a** afforded trifluoromethylated amino esters **8** and **9** in high yields with maintained enantioselectivities. I<sub>2</sub>-promoted intramolecular cyclization of compounds **8** and **9** provides a straightforward entry to highly functionalized pyrrolidines **10** and **11** in high yield with high diastereoselectivity control. Reduction of **8** and **9** with DIBAL-H followed by one-pot mesylation/intramolecular nucleophilic substitution produced enantioenriched aziridine **12** and azetidine **13** bearing a CF<sub>3</sub>-containing N-quaternary stereogenic center in good yields without loss of enantioselectivity (Scheme 2a). On the other hand, quaternary  $\gamma$ -CF<sub>3</sub>  $\gamma$ -amino ester **6a** and  $\delta$ -CF<sub>3</sub>  $\delta$ -amino ester **6b** could be directly transformed to  $\gamma$ -butyrolactam **14** and  $\delta$ -valerolactam **15** *via* acidic hydrolysis/lactamization. Furthermore, both branched allylation products **5a** and **7a** could be readily hydrolyzed under mild conditions, giving compound **16** in good yield with maintained stereoselectivity.

Based on the experimental results and previous literature reports,<sup>11,13</sup> a plausible mechanism was proposed to explain the stereochemistry outcome and the different reaction pathways (Scheme 3). The reaction between isatin-activated ketoimine

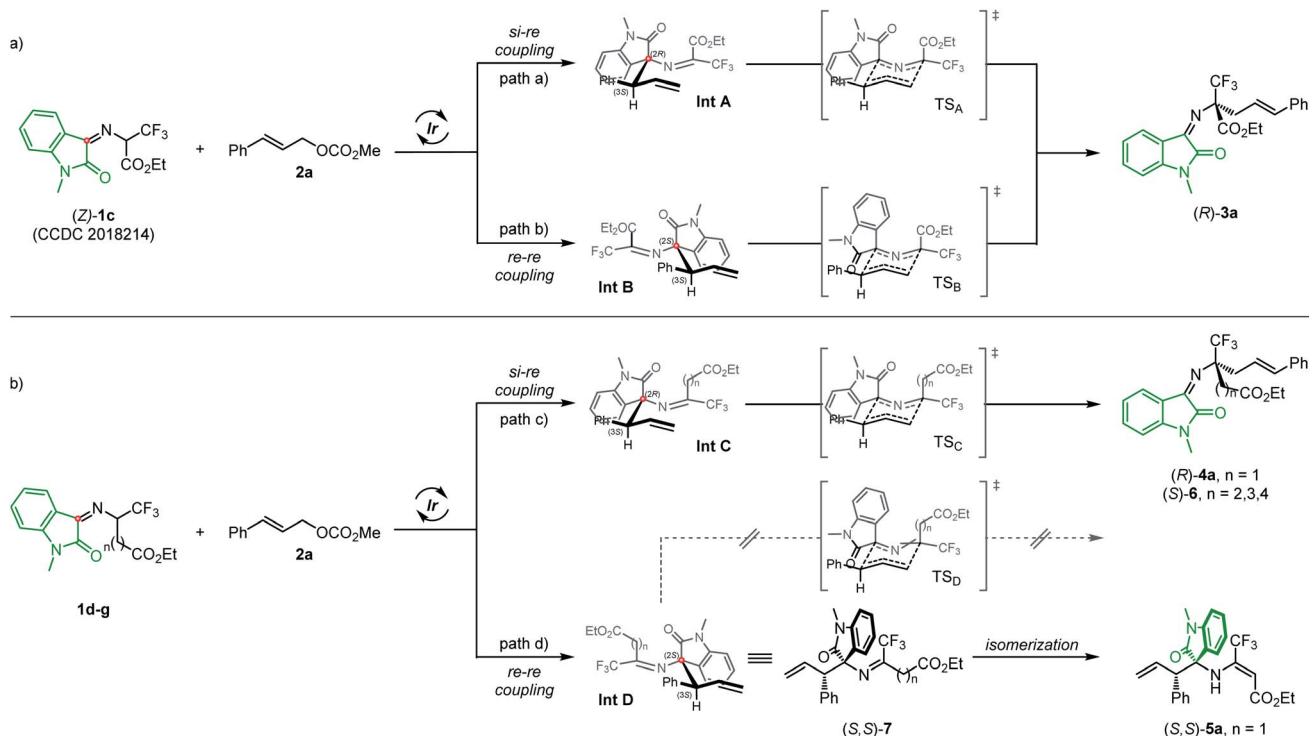
Table 4 Asymmetric synthesis of quaternary  $\gamma$ ,  $\delta$ ,  $\epsilon$ -amino acids<sup>a</sup>



Scheme 2 Synthetic transformation.

<sup>a</sup> All reactions were carried out with 0.40 mmol **1**, 0.44 mmol **2a**, base (0.4 mmol) in 2 mL of DCE. Isolated yield. The ee value was determined by HPLC analysis.





Scheme 3 Proposed mechanism for Ir-catalyzed umpolung allylation/2-aza-Cope rearrangement of isatin-ketoimino esters **1c-g**.

ester (*Z*)-**1c**<sup>21</sup> and **2a** starts with the nucleophilic attack of either the *Re*- or *Si*-face of the 2-azaallyl carbanion *via* exclusive *a'*-regioselectivity of the azadienolate to the *Re*-face of the *in situ* formed  $\pi$ -allyl-iridium species,<sup>23</sup> delivering diastereoisomeric branched allylation intermediates **Int A** and **Int B**. Driven by the steric congestion around the two adjacent stereogenic centers, **Int A** and **Int B** undergo a stereospecific aza-Cope rearrangement *via* highly ordered six-membered chair-like transition states  $TS_A$  and  $TS_B$ ,<sup>24</sup> respectively, in both of which the bulky  $CF_3$  group resides in the equatorial position, affording (*R*)-**3a** in good yield and excellent enantioselectivity. Similarly, the diastereomeric **Int C** and **Int D** are formed in the umpolung Ir-catalyzed allylation of **1d-g**; however, the carbon atoms in the imine moiety of **Int C/Int D** are less electron-deficient compared with those in **Int A/Int B**, which would decelerate the subsequent 2-aza-Cope rearrangement. **Int C** could undergo further rearrangement to afford the corresponding amino acid derivatives **4a** and **6a-c** *via* the energy-favored  $TS_C$ , in which the bulky  $CF_3$  group resides in the equatorial position, while in  $TS_D$  the bulky substituent (Ph) of the oxindole ring residing in the axial position would lead to an increasing steric congestion (with a larger *A* value)<sup>25</sup> in comparison with  $TS_C$ , no matter whether the  $CF_3$  or ester carbon chain resides in the axial position. Thus, **Int D** is incapable of undergoing further rearrangement at room temperature since the corresponding  $TS_D$  is energetically and electronically disfavored. When isatin-activated  $\beta$ - $CF_3$   $\beta$ -amino ester derived **1d** was employed as the reaction partner, the allylation intermediate **Int D** would readily convert into thermodynamically stable (*S,S*)-**5a** through imine/enamine isomerization.

## Conclusions

In conclusion, we have developed a highly efficient Ir-catalyzed cascade allylation/2-aza-Cope rearrangement for the synthesis of quaternary trifluoromethylated  $\alpha$ -amino acid derivatives in high yields with excellent enantioselectivities. The umpolung reactivity empowered by the activation of the isatin-ketoimine moiety is the key to success and obviates the intractable enantioselectivity control in previous Pd-catalyzed asymmetric linear  $\alpha$ -allylation. In combination with quasi-parallel kinetic resolution or kinetic resolution, the generality of the method is further demonstrated by the first preparation of enantioenriched quaternary trifluoromethyl  $\beta$ -,  $\gamma$ -,  $\delta$ - and  $\epsilon$ -amino acids along with 3-amino oxindole in one-pot. Synthetic transformation of the obtained amino acid derivatives afforded a variety of biologically important compounds including trifluoromethyl-containing N-heterocycles and lactams. Further investigations on the mechanistic insights and synthetic applications of the current methodology are on-going in our laboratory.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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