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Iridium-catalyzed regiospecific and stereospecific allylic amination for the syntheses of α,β-unsaturated γ-amino esters and the bifurcation of the reaction pathway leading to the formation of oxazolidin-2-ones†‡

Jun Hee Lee and Sang-gi Lee*

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A pair of iridium-catalyzed regiospecific and stereospecific reactions of the carbonates of γ-hydroxy α,β-unsaturated esters were developed. The reaction pathways are strongly affected by the choice of amines employed. A diverse range of γ-substituted α,β-unsaturated γ-amino esters were prepared in excellent yields with various amine nucleophiles such as benzylamine, diallylamine, morpholine, aniline and *N*-methylaniline. Substitution at the γ-position was well tolerated, encompassing alkyl, aryl and heteroaryl substituents. Enantioenriched (*E*)-α,β-unsaturated γ-amino esters could also be synthesized from the corresponding enantioenriched allylic carbonates with complete chirality transfer. In sharp contrast, a series of 3,4-disubstituted oxazolidin-2-ones were obtained by using allylamine as a nucleophile.

Introduction

The synthesis of highly functionalized molecules in an efficient and straightforward manner represents an ongoing challenge in organic chemistry. Due to not only their polyfunctionality for further manipulations, but also their abundance in bioactive natural and non-natural products, α,β-unsaturated γ-amino acid derivatives have attracted significant interest from the synthetic community.[1] α,β-Unsaturated γ-amino esters are generally prepared through the classical Wittig-type olefination of the corresponding *N*-protected α-amino aldehydes.[2] However, such substrates are highly sensitive to base-induced epimerization and can usually be accessed from the amino acids only through a tedious synthetic sequence. Direct catalytic methods for their selective construction have also been developed, including the Ru-catalyzed co-dimerization of *N*-acetyl α-arylamines with acrylates,[3a] the Pd-catalyzed insertion of α-diazoesters into vinyl halides and subsequent trapping with amines,[3b] Lewis acid-catalyzed N–H insertions of methyl styryldiazoacetate with aniline,[3c] Rh- and Pd-catalyzed ring-opening of vinyl epoxides with azides and amines,[3d,e] the Pd-catalyzed rearrangement of α-sulfonimidoyl β,γ-unsaturated esters[3f] and stereoconvergent synthesis using a combination of an asymmetric Horner–Wadsworth–Emmons reaction and a stereoselective Pd-catalyzed allylic amination.[3g] Despite these advances, there still exists a need for new catalytic methods with broad substrate scope to gain access to α,β-unsaturated γ-amino esters.

Over the past decade, allylic substitution reactions catalyzed by metallacyclic iridium phosphoramidite complexes have emerged as an excellent method for the controlled formation of carbon–carbon and carbon–heteroatom bonds.[4] In general, transition-metal-catalyzed allylic amination reactions have been limited to the synthesis of terminal allylic amines.[5] To the best of our knowledge, Ir-catalyzed allylic aminations of substrates bearing different substituents at the two allylic termini remain thus far unexplored.[6] Furthermore, examples of the Ir-catalyzed allylic amination reaction of enantioenriched allylic electrophiles that occur with high stereospecificity are rare.[7] In the context of our research program directed toward the extensions of transition-metal-catalyzed reactions for the preparation of synthetically useful structural motifs,[8] we envisioned that the allylic amination of electronically biased allylic electrophiles of the type **1** possessing an alkyl, aryl, or heteroaryl substituent at C1 and an electron withdrawing group, such as an ester functionality at C3 would provide ready access to α,β-unsaturated γ-amino esters. During the course of the investigation, to our surprise, it was also found that the reaction pathways are strongly dependent on the amine nucleophiles employed, and bifurcated to allow the selective synthesis of either γ-aminated α,β-unsaturated esters **2** or 3,4-disubstituted oxazolidin-2-ones **3** using an iridium catalyst (Fig. 1).

Department of Chemistry and Nano Science (BK 21), Ewha Womans University, Seoul 120-750, Korea. E-mail: sanggi@ewha.ac.kr; Fax: +82 2 3277 3419; Tel: +82 2 3277 4505

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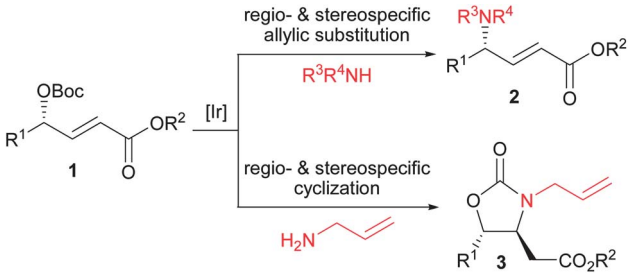


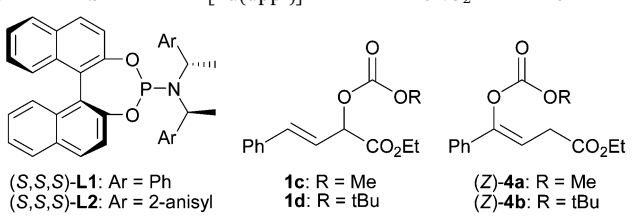
Fig. 1 Bifurcation of the catalytic reaction pathways.

Results and discussion

Our investigations started with a well-defined iridium catalytic system composed of $[Ir(cod)Cl]_2$ and racemic Feringa's phosphoramidite **L1** as a standard catalyst.[9] In the presence of a metallacyclic iridium phosphoramidite catalyst, generated *in situ* by heating a mixture of 2 mol% $[Ir(cod)Cl]_2$ and 4 mol% *rac*-**L1** with propylamine at 50 °C for 20 min, as described previously,[10] the reaction of methyl carbonate **1a** with benzylamine (1.2 equiv.) in THF at room temperature for 13 h gave the desired amination product **2a** as a single regio- and stereoisomer, albeit in a moderate yield of 54% (Table 1, entry 1).[11] Similar or inferior results in terms of the isolated yield were obtained in other solvents such as 1,4-dioxane, 1,2-dimethoxyethane (DME), acetonitrile and dichloromethane (entries 2–5). While a diminished yield of 41% was obtained from the reaction catalyzed by an iridacyclic complex generated from the Alexakis' phosphoramidite ligand **L2** (entry 7),[12] a slightly improved yield of 62% was attained when the reaction was carried out in nitromethane using the standard catalytic system (entry 6). In these reactions, substantial amounts of a γ-keto ester (ethyl 4-oxo-4-phenylbutanoate) and methyl benzylcarbamate were isolated as by-products, presumably derived from olefin isomerization of **1a** followed by aminolysis of the isomerized carbonate (*e.g.* **4a**) with benzylamine. We were pleased to find that switching the substrate from methyl carbonate **1a** to the corresponding *tert*-butyl carbonate **1b** resulted in a significant improvement in isolated yield. Thus, the desired α,β-unsaturated γ-amino ester **2a** was isolated in 88% yield from the reaction of **1b** with benzylamine in nitromethane (entry 8). Under these conditions, the olefin isomerization side reaction was completely suppressed, whereas a certain amount of isomerized by-product (*e.g.* (*Z*)-**4b**)[13] was observed when the reactions were performed in other solvents. Furthermore, the position of the leaving group strongly affected the outcome of the reactions. In particular, efforts using substrates bearing the carbonate leaving group at the α-position proved fruitless under the standard conditions (entries 9 and 11). However, both **1c** and **1d** showed some reactivity when exposed to a palladium catalyst,[14] generated *in situ* from the pre-complexation of $Pd_2(dba)_3$ with dppf, to afford the γ-amination product **2a** in 38% and 31% yields, respectively (entries 10 and 12). Finally, the reaction of **1b** using the palladium catalyst indicates the superiority of the iridium catalyst system for this γ-amination reaction (Table 1, entry 8 *versus* entry 13).

Table 1 Optimization study[a]

Entry	Substrate	Catalytic system	Solvent	Yield (%)[b]
1	**1a**	[Ir(*rac*-**L1**)][c]	THF	54
2	**1a**	[Ir(*rac*-**L1**)][c]	1,4-dioxane	55
3	**1a**	[Ir(*rac*-**L1**)][c]	DME	55
4	**1a**	[Ir(*rac*-**L1**)][c]	MeCN	40
5	**1a**	[Ir(*rac*-**L1**)][c]	CH_2Cl_2	31
6	**1a**	[Ir(*rac*-**L1**)][c]	$MeNO_2$	62
7	**1a**	[Ir((*S*,*S*,*S*)-**L2**)][c]	$MeNO_2$	41
8	**1b**	[Ir(*rac*-**L1**)][c]	$MeNO_2$	88
9	**1c**	[Ir(*rac*-**L1**)][c]	$MeNO_2$	0
10	**1c**	[Pd(dppf)][d]	$MeNO_2$	38
11	**1d**	[Ir(*rac*-**L1**)][c]	$MeNO_2$	0
12	**1d**	[Pd(dppf)][d]	$MeNO_2$	31
13	**1b**	[Pd(dppf)][d]	$MeNO_2$	62

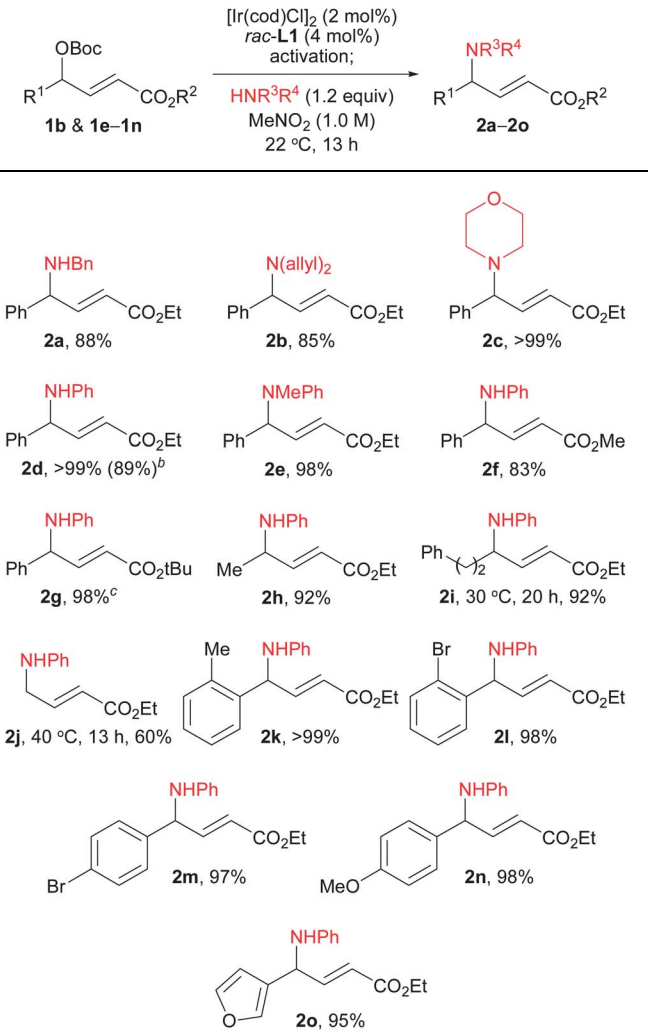


[a] *Reactions conditions*: precatalyst (4.0 mol%), **1** (0.50 mmol) and benzylamine (0.60 mmol) in different solvents (1.0 M) at room temperature for 13 h. [b] Yield of isolated **2a**. [c] $[Ir(cod)Cl]_2$ (2.0 mol%) and a phosphoramidite ligand **L** (4.0 mol%). [d] $Pd_2(dba)_3$ (2.0 mol%) and dppf (4.0 mol%).

With the optimized reaction conditions in hand (Table 1, entry 8), we next explored the scope and limitations of this γ-amination reaction. As shown in Table 2, the reaction of the standard substrate **1b** allowed for the regiospecific and stereospecific synthesis of (*E*)-α,β-unsaturated γ-amino esters **2** in excellent yields with a broad range of amine nucleophiles such as linear primary and secondary alkyl amines (entries 1 and 2), a cyclic secondary amine (entry 3), a primary arylamine (entry 4), and a secondary alkyl arylamine (entry 5). In stark contrast, replacing the amine nucleophile with allylamine generated unexpected oxazolidin-2-ones **3** without any competitive formation of **2** (see discussion below and Scheme 1). Notably, the Ir-catalyzed reaction can be easily scaled up, even with a lower catalyst loading of 2 mol%, to furnish the amination product **2d** in a gram quantity, albeit at the expense of a slightly decreased yield. Steric variation in the ester group of the substrates **1** was also well tolerated, as both the sterically less demanding methyl ester **1e** and the more hindered *tert*-butyl ester **1f** gave the desired products **2f** and **2g** in high yields with aniline.

We next examined the optimized conditions with substrates bearing different substituents at the γ-position, while using

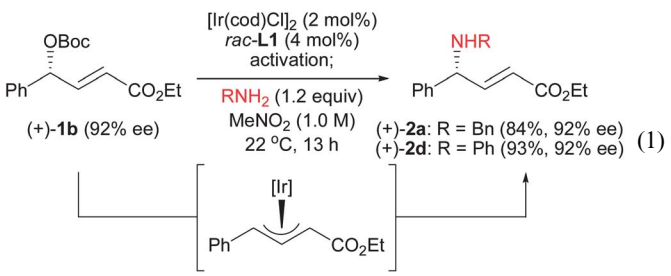
Table 2 Ir-Catalyzed synthesis of α,β-unsaturated γ-amino esters[a]



[a] *Reaction conditions*: precatalyst (4.0 mol%), **1** (0.50 mmol) and amine (0.60 mmol) in $MeNO_2$ (1.0 M) at room temperature for 13 h and then isolated yield was obtained. [b] Precatalyst (2.0 mol%) and **1b** (4.00 mmol). [c] Reaction in a 1 : 1 mixture of THF/$MeNO_2$ (v/v, 0.5 M).

aniline as a nucleophile. The amination proceeded smoothly with γ-alkylated substrates **1g** and **1h** to yield the desired products in excellent yields (**2h** and **2i**), although slightly elevated reaction temperatures were required in some cases. For example, the reaction of **1h** bearing a phenethyl group at the γ-position proceeded cleanly at 30 °C to afford the desired amination product **2i** in an excellent yield of 97%, whereas the same reaction at room temperature (*ca.* 22 °C) gave a somewhat decreased product yield of 77%. Though an even higher reaction temperature (40 °C) was necessary, the γ-unsubstituted substrate **1i** (R^1 = H) similarly participated in the reaction with aniline to afford the corresponding product **2j** in a moderate yield of 60%. We also examined the γ-arylated substrates having different substituents on the aryl moiety. Both electron-donating and electron-withdrawing substituents at either the *ortho* or *para* positions of the aryl moiety exerted little influence in these aminations and were well tolerated, providing potential synthetic handles for further transformations (**2k**, **2l**, **2m** and **2n**). Additionally, the iridium-catalyzed reaction was successfully employed in the synthesis of the (*E*)-α,β-unsaturated γ-amino ester **2o** which bears a 3-furyl substituent. It should be emphasized that only a single γ-regio- and (*E*)-stereoisomer was detected in the crude reaction mixture in all cases.

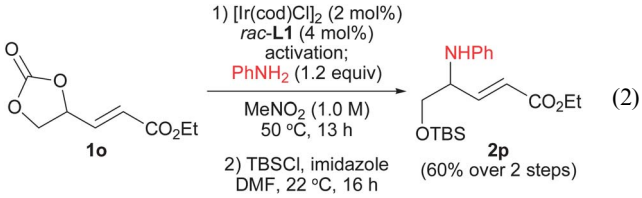
To gain a better understanding of the reaction mechanism, we examined the iridium-catalyzed allylic amination of enantioenriched substrate (+)-**1b** with 92% ee, which was synthesized from a commercially available chiral phenyl vinyl alcohol.[13] Most importantly, the reaction of (+)-**1b** with either an arylamine or an alkylamine as a nucleophile under the standard conditions proceeded smoothly with complete chirality transfer, affording (+)-**2a** and (+)-**2d** in 84% yield with 92% ee and in 93% yield with 92% ee, respectively (eqn (1)). The absolute stereochemistry of the substrate (+)-**1b** was retained during the overall process to afford both amines **2a** and **2d** with (*R*)-configuration at the γ-position.[13,15] This indicates that both the oxidative addition of the iridium(I) precatalyst to (+)-**1b** and subsequent nucleophilic attack of the amine nucleophile occur stereospecifically with inversion of configuration at the reacting γ-position.[5a,16] Furthermore, the excellent degree of chirality transfer obtained above can be rationalized by an explanation wherein the intermediary enantioenriched π-allyliridium(III) species does not undergo an allyl exchange reaction with the low-valent iridium(I) complex present in the reaction mixture, which could result in an inversion of configuration of allyl group containing two different substituents at each allyl terminus and concurrent erosion of the optical purity of the product **2**.[17,18] It is worth noting that the present protocol could be a general route to access chiral γ-substituted α,β-unsaturated γ-amino esters[19] because a diverse range of alkyl-, aryl, and heteroaryl substituted homochiral allylic alcohols as well as their derivatives can easily be prepared[20] and their olefin CM reactions are also well documented.[21,22]



(1)

Inspired by the recent success of iridium-catalyzed decarboxylative allylic amidation and with a desire to further evaluate the potential application of our new reaction,[23] we turned our attention to examining a cyclic carbonate **1o** under the standard reaction conditions (eqn (2)). However, cyclic carbonate **1o** did not show any reactivity at room temperature. To our delight, *ca.* 70% conversion into the desired product was observed when the reaction was carried out at 50 °C for 13 h. The reaction mixture was then treated with *tert*-butyldimethylsilyl chloride

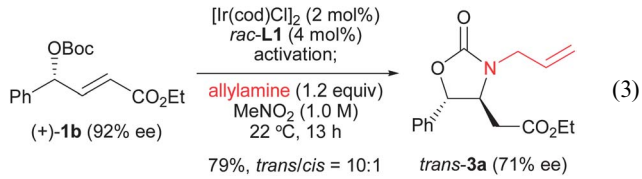
(TBSCl) in the presence of imidazole in DMF to furnish synthetically valuable *O*-protected α,β-unsaturated γ-amino-δ-hydroxy ester **2p** in 60% yield over two steps. To the best of our knowledge, this represents the first example of the iridium-catalyzed intermolecular decarboxylative allylic amination of a cyclic carbonate.[24]



(2)

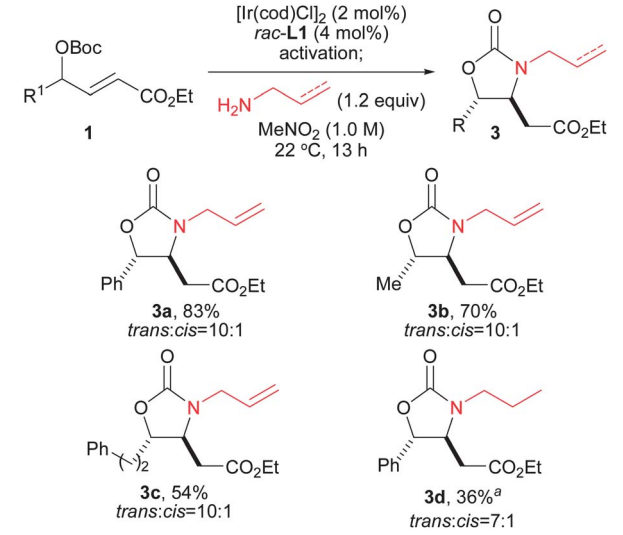
Next, we turned our attention to the unexpected finding of the nucleophile-dependent bifurcation of reaction pathways (Scheme 1). When the standard substrate **1b** was allowed to react with allylamine as a nucleophile, a 10 : 1 diastereomeric mixture of inseparable *trans*- and *cis*-oxazolidin-2-one **3a** was obtained in a combined yield of 83% under otherwise identical conditions. Furthermore, the reactions of carbonates **1g** and **1h** bearing an alkyl group at the γ-position furnished the corresponding oxazolidin-2-ones (**3b** and **3c**) with comparable diastereoselectivities and somewhat diminished yields. The relative configurations of the major *trans*-isomers were assigned on the basis of the vicinal coupling constants between the C-4 and C-5 protons, whose values are consistent with the ones reported for similar oxazolidin-2-ones,[25] and further confirmed through NOESY experiments.[13] At present it is difficult to know whether this unusual oxazolidin-2-one formation with allylamine is mainly due to its smaller steric demands or if a subtle electronic difference affects the nature of the nucleophilic addition event. Intriguingly, switching the nucleophile from allylamine to propylamine afforded a separable 1 : 1 mixture consisting of (*E*)-ethyl 4-(propylamino)-4-phenylbut-2-enoate (**2q**, 36%) and a 3-propyl-substututed oxazolidin-2-one **3d** (36%); the latter was isolated as a 7 : 1 mixture of inseparable *trans*- and *cis*-isomers.

Because substituted oxazolidin-2-ones are important motifs in many pharmaceuticals[26] and "privileged" chiral auxiliaries,[27] the enantioenriched (+)-**1b** (92% ee) was examined in this reaction, and was found to afford a 10 : 1 mixture of the desired *trans*- and *cis*-oxazolidin-2-ones **3a** in 79% combined yield and with 71% ee for the major (*trans*) isomer (eqn (3)).

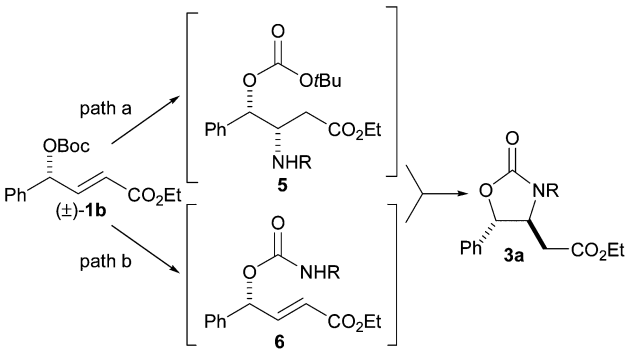


(3)

Although we cannot assert the mechanism of this unexpected reaction at this stage, two distinct mechanistic pathways are easily envisioned (Scheme 2): a *syn*-selective conjugate addition of allylamine with **1b** to give **5** followed by an intramolecular nucleophilic acyl substitution on the carbonate carbonyl group (path a) or a selective formation of a carbamate **6** through an intermolecular nucleophilic acyl substitution with allylamine and subsequent intramolecular conjugate addition (path b). Since the formation of **3a** is not observed in the absence of the iridium catalyst, we surmise that the metallacyclic complex can act as a Lewis acid catalyst for the conjugate additions. To distinguish between these potential pathways, iridium-catalyzed cyclization of the carbamate **6** was examined, which was separately prepared from the corresponding α,β-unsaturated γ-hydroxy ester.[13] Treatment of racemic **6** with 4 mol% of the racemic metallacyclic iridium phosphoramidite complex in nitromethane at 22 °C for 15 h did not furnish any oxazolidin-2-one **3a**. On the basis of this observation, along with the intrinsic difficulties in explaining the selective formation of the carbamate **6**, we rule out path b. Path a seems more likely to be a relevant mechanism for the oxazolidin-2-one formation. However, further mechanistic studies will be necessary to draw more definitive conclusions.



Scheme 1 Synthesis of oxazolidin-2-ones. [a] The corresponding (*E*)-α,β-unsaturated γ-amino ester (**2q**) was also isolated in 36% yield.



Scheme 2 Proposed reaction pathways (R = allyl).

Conclusions

In summary, we have demonstrated the first iridium-catalyzed regiospecific and stereospecific intermolecular amination of internal allylic carbonates possessing electronically differentiated substituents at each terminus with a wide range of amine nucleophiles. This process provides an expeditious synthetic method for the stereospecific synthesis of (*E*)-α,β-unsaturated γ-amino esters with various substitution patterns such as alkyl, aryl and heteroaryl at the γ-position in excellent yields. Optically active (*E*)-α,β-unsaturated γ-amino esters could also be synthesized from the corresponding chiral allylic carbonates with complete chirality transfer using alkylamine as well as aryl amine nucleophiles. In addition, by simply changing the nucleophile to allylamine, the reaction pathway was bifurcated to afford a series of 3,4-disubstituted oxazolidin-2-one derivatives as a 10 : 1 mixture of *trans*- and *cis*-isomers from the same carbonate substrates under otherwise identical conditions. The establishment of the salient features of the nucleophile-dependent bifurcation of the catalytic pathways will provide a new approach to chiral oxazolidinones.

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18 During the reviewing process of this manuscript, an insightful referee (that we thank) suggested the intermolecular allyl exchange mechanism.

19 During the preparation of our manuscript, Fu and co-workers reported an elegant organocatalytic asymmetric reaction for the preparation of γ-alkylated α,β-unsaturated γ-amino ester derivatives in enantioenriched forms, see: R. J. Lundgren, A. Wilsily, N. Marion, C. Ma, Y. K. Chung and G. C. Fu, *Angew. Chem., Int. Ed.*, 2013, **52**, 2525–2528.

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