# Highly Enantioselective Catalytic Allylboration of Ketiminoesters: Practical and Scalable Synthesis of α-Fully-Substituted Amino Esters

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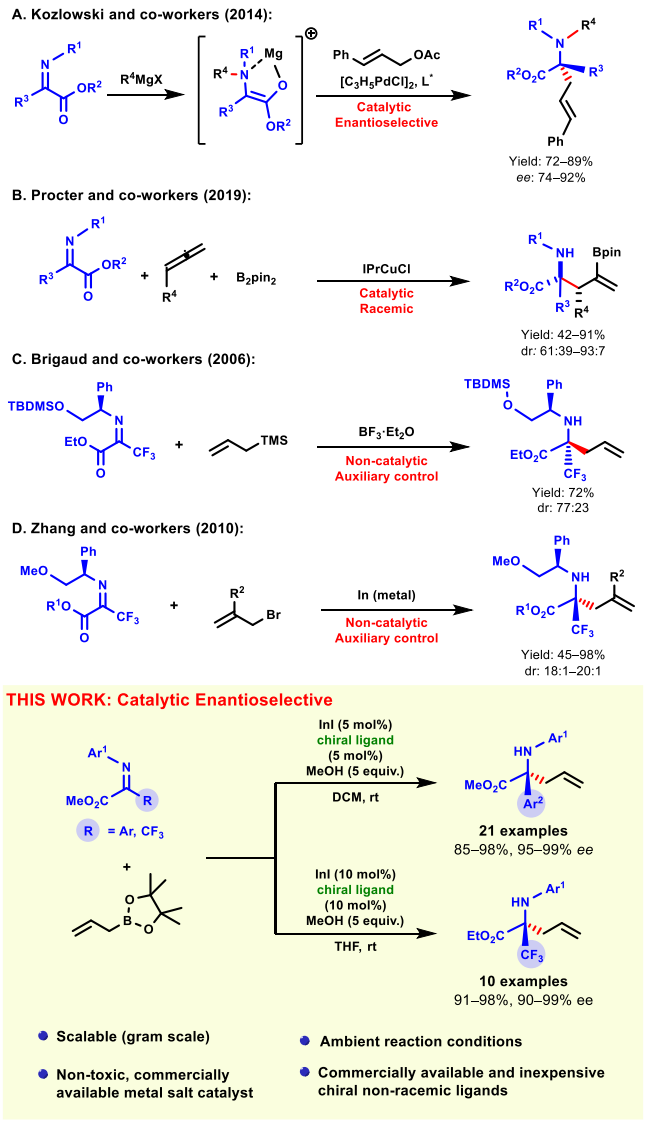
*Supporting Information Placeholder*

**ABSTRACT:** We report the first catalytic enantioselective allylboration of α-ketiminoesters to afford chiral α-allyl-α-aryl and α-allyl-α-trifluoromethyl amino esters in excellent isolated yields and with high optical purity. This operationally simple allylation proceeds under ambient conditions with indium(I)-iodide/BOX-type ligand (5–10 mol%) and can be performed on a gram scale. A proposed qualitative model for the high stereoselectivity indicates that the origin of selectivity is likely due to attractive interactions between the substrate and the BOX ligand. Using a different BOX-type ligand reverses the reaction's absolute sense of enantioselectivity. The allylated products are easily converted to enantiomerically enriched α-substituted proline derivatives.

Enantioenriched α,α-di-substituted amino acids (e.g., α-allyl-α-aryl and α-allyl-α-trifluoromethyl) are important synthetic building blocks as they are readily diversified to densely functionalized structures prevalent in various natural products and pharmaceuticals.[1,2] In particular, α-allyl-α-trifluoromethyl amino acid derivatives can be used to incorporate $CF_3$ groups into active pharmaceutical ingredients (APIs) for desirable chemical, biological and physical properties.[3] Another key feature of homoallylic α-amino esters is their fully substituted stereogenic carbon center, which translates to increased stability under various physiological conditions. When incorporated into peptidomimetics, their resistance toward enzymatic degradation is significantly enhanced.[4, 5]

Enantioenriched homoallylic α-amino esters are prepared with asymmetric allylation of ketiminoesters. However, unlike well-studied aldiminoesters,[6] there are only a few examples of asymmetric allylation of ketiminoesters in the literature.[7] Ketiminoesters, compared to aldiminoesters, are more challenging substrates as they are less reactive and their enantiofacial distinction at the prochiral C=N site is lower.[8] In 2014, Kozlowski and co-workers reported a Pd-catalyzed asymmetric tandem alkylation/α-allylation of α-aryl α-iminoesters (**Scheme 1A**); yields and enantioselectivities ranged from moderate to very good.[7] Recently, the Procter group developed a copper-catalyzed allylboration of α-aryl α-iminoesters utilizing an *in situ*-generated allylboronate reagent; the racemic products were obtained with moderate to high diastereoselectivities (**Scheme 1B**).[9]

**Scheme 1: Allylation of Ketiminoesters:**



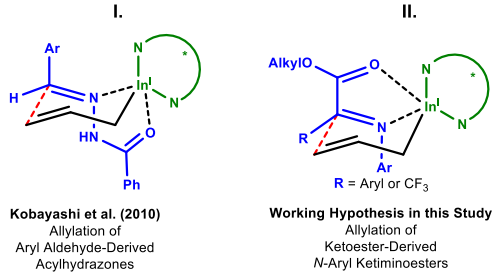
A diastereoselective, chiral auxiliary controlled allylsilylation of a enantioenriched α-trifluoromethyl α-iminoesters was reported by Brigaud *et al.* (**Scheme 1C**),[10] while Zhang and co-workers disclosed a related diastereoselective allylindium addition using a similar auxiliary (**Scheme 1D**).[11] There have also been reports (e.g., by Leighton[12] and Juaristi[13]) on the asymmetric allylsilylation of ketoester hydrazones using stoichiometric enantiopure allylating reagents, albeit with narrow substrate scopes.

To the best of our knowledge, a general and direct catalytic asymmetric allylation of α-aryl and α-trifluoromethyl ketiminoesters is currently unknown. Herein, we demonstrate the use of chiral indium(I) catalysts featuring BOX-type ligands for the practical and scalable catalytic asymmetric allylboration of both α-aryl- and α-trifluoromethyl ketiminoesters. At the outset of our study, we applied a number of previously reported catalytic asymmetric allylation methods (e.g., Yamamoto,[14] Shibasaki[15] and Schaus[16] who used AgF, CuF and a BINOL-derivative as catalysts, respectively) to a model ketiminoester **1a**. These methods were specifically developed for the allylation of aldimine and ketimine substrates with either allylsilanes or allylboronates. However, all of these conditions led to racemic product **3a** when applied to substrate **1a** (see SI p. 10).

Thus, we concluded that a mechanistically different allylation was needed. This could be achieved by employing main group metal salts, such as indium(I)iodide, as catalysts *in lieu* of transition metal complexes, as demonstrated by Kobayashi and co-workers for the catalytic allylboration of aldehyde acyl hydrazones.[17] Indium compounds are also non-toxic and relatively cheap, further justifying this choice.[17,18, 19]

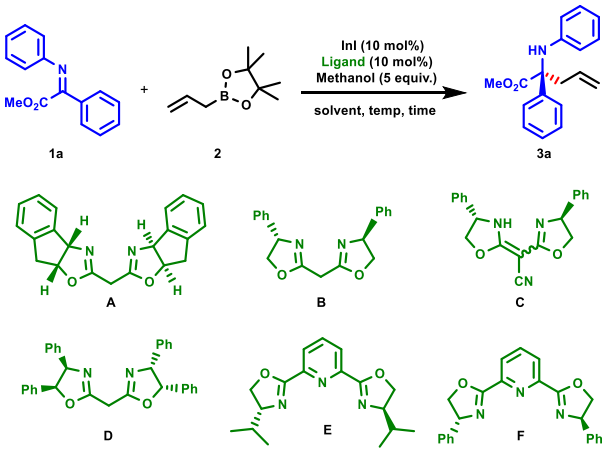
In the Kobayashi-type allylation, a chiral allylic indium(I) complex is formed *in situ* via transmetallation of AllBpin. In the proposed transition state, both the acyl hydrazone and the BOX ligand[20] bind to indium(I) in a bidentate mode, leading to a closed, six-membered Zimmerman–Traxler type transition state (**I**, Figure 1). We envisioned our ketiminoester substrate (**1a**) could also function as a bidentate ligand, leading to a similar transition state (**II**, Figure 1) and result in a high level of enantioinduction.

**Figure 1: Initial Working Model for Allyl-Transfer**




A thorough optimization of the reaction conditions was carried out (**Table 1;** See SI p. 11). These results confirmed that using a main group metal complex was indeed the right choice. Semicorrin (**C**) (entries **14**–**18**) emerged to be the best ligand partner. A 5 mol% loading of InI with 5 mol% ligand **C** in DCM with methanol as the key additive was the best combination for the asymmetric allylation of **1a** (entry **18**, 94% yield and 99% *ee*). The methanol additive was required for the reaction to proceed; ethanol was found to be nearly equally good as an additive, however, in the presence of trifluoroethanol the allylation does not proceed. The screening also revealed that ligand **D** could reverse the stereoselectivity, so that the opposite enantiomer of the product (**ent-3a**) could be obtained in excellent yield and enantioselectivity (entry **19**, 94% yield and –99% *ee*).

**Table 1: Screening the Conditions for Catalytic Asymmetric Allylation of Ketiminoester:**

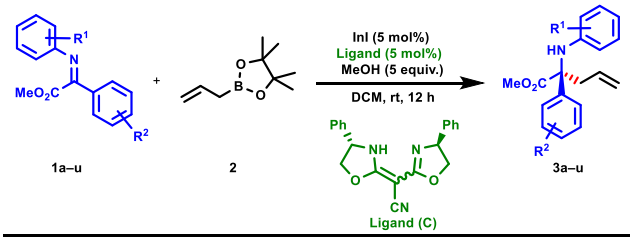


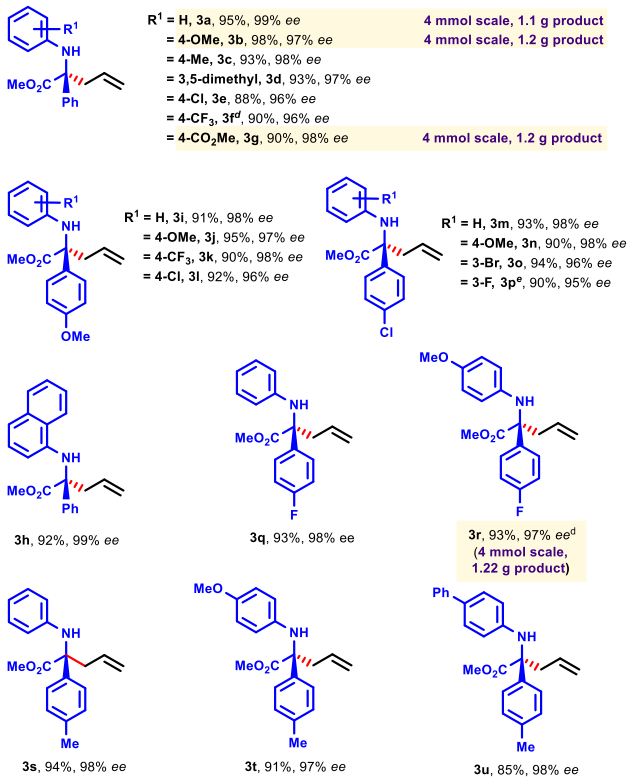

| Entry | Ligand[a] | Solvent[b] | Temp (Time) | Yield (%) | *ee* (%) |
|---|---|---|---|---|---|
| 1 | (*R*)-BINAP | THF | rt (24 h) | 77 | *rac* |
| 2 | (*R*)-SEGPHOS | THF | rt (24 h) | 67 | *rac* |
| 3 | (*R*)-DIFLUOPHOS | THF | rt (24 h) | 75 | *rac* |
| 4 | **A** | Toluene | rt (24 h) | – | – |
| 5 | **A** | THF | rt (24 h) | 85 | 64 |
| 6 | **A** | DCM | rt (26 h) | 86 | 67 |
| 7 | **A** | $Et_2O$ | rt (36 h) | 86 | 58 |
| 8 | **A** | THF | –5 °C (80 h) | 82 | 65 |
| 9 | **A** | DCM | –5 °C (80 h) | 82 | 71 |
| 10 | **B** | THF | rt (11 h) | 88 | 95 |
| 11 | **B** | DCM | rt (19 h) | 90 | 97 |
| 12 | **B** | $Et_2O$ | rt (24 h) | – | – |
| 13 | **B** | DME | rt (24 h) | – | – |
| 14 | **C** | THF | rt (12 h) | 90 | 96 |
| 15 | **C** | DCM | rt (12 h) | 93 | 99 |
| 16 | **C** | DCM[c] | rt (12 h) | 90 | 99 |
| 17 | **C** | DCM[d] | rt (12 h) | 88 | 99 |
| **18** | **C**[e] | **DCM**[b] | **rt (12 h)** | **94** | **99** |
| 19 | **D**[e] | DCM[b] | rt (9 h) | 95 | –99 |
| 20 | **E**[e] | DCM[b] | rt (26 h) | 82 | *rac* |
| 21 | **F**[e] | DCM[b] | rt (27 h) | 79 | *rac* |

Conditions: Unless otherwise stated, 0.5 mmol of **1a**, the ligand (10 mol%) and InI (10 mol%) were added in 1.5 mL solvent (0.33 M). Next, 0.75 mmol of **2** was added to the reaction mixture along with MeOH (2.5 mmol). The progress of the reaction was monitored by TLC. All yields are isolated yields. The enantiomeric excesses were determined by HPLC on chiral stationary phase. [a]10 mol% of ligand with 10 mol% of InI; [b]0.33 M; [c]0.16 M; [d]0.66 M; [e]5 mol% of ligand with 5 mol% of InI.

With the optimized conditions in hand, we explored the scope of substrates. Twenty α-aryl α-ketiminoesters (**1b**-**1u**), featuring both electron-withdrawing and donating-substitutents were evaluated (**Table 2**). In all the cases, excellent isolated yields (85–98%) and enantiomeric excesses (96–98%) were obtained. We performed several of these reactions on multi-mmol scale in order to assess the scalability and overall robustness of the method. All four substrates studied (**3a**, **3b**, **3g** and **3r**, **Table 2**) yielded the desired products in nearly identical yields on the gram scale.

**Table 2: Catalytic Asymmetric Allylboration of α-Aryl α-Iminoesters:**[a, b, c]




[a]Conditions: Ketiminoester (**1a**–**1u**, 0.5–4.0 mmol), AllylBpin (**2**, 0.75–6.0 mmol), InI (0.025–0.2 mmol), Ligand (0.025–0.2 mmol), MeOH (2.5–20.0 mmol) in 1.5–12.0 mL of DCM at rt. [b]All the reported yields are isolated yields. [c]All the *ee*-s are determined by HPLC or SFC analysis on chiral stationary phase. [d]The *ee* for compound **3f** was determined by HPLC analysis of the corresponding amino alcohol obtained *via* hydroboration and oxidation of the olefin. [e]Reaction took 78 hours to complete; in THF 12 h (90%, 93% *ee*).

Next, we optimized the method for catalytic asymmetric allylboration of α-trifluoromethyl α-iminoesters (see SI p. 14). Slightly higher In(I)I and ligand (**C**) loadings (10 mol%) were needed and THF was identified as the best solvent. Using the optimized conditions, ten α-trifluoromethyl α-iminoesters (**Table 3**; **4a to 4i**) were allylated in excellent yields (91–99%) and enantioselectivities (90–99%). In particular, imine **4e** stood out as it furnished the corresponding homoallylic aminoester product (**5e**) in 98% yield and with over 99% *ee*. Reactions in this series could be readily scaled-up to furnish homoallylic amines **5a**, **5e** and **5h** in multi-mmol quantities (**Table 3**).

We propose a preliminary mechanistic model that accounts for the observed high *S* stereoselectivity. To construct this model, we assume the following: (1) the allyl group is transferred to indium to give an indium(I) allyl species; (2) the α-ketiminoester substrate coordinates as a bidentate ligand and (3) the reaction takes place via a chair-type transition-state around a square pyramidal indium(I) metal center. The commonly invoked steric model has the α-ketiminoester bound to the open face of the chiral indium(I) complex, and the smaller allyl group to the sterically more congested site (Figure 2).[21] This steric model incorrectly predicts the absolute configuration of the major allylation product to be *R* instead of the experimentally observed *S* (See SI p. 19, 46). In comparison, an alternative stereochemical model, which invokes attractive interactions, correctly predicts *S* as the major product. In the attractive model the α-ketiminoester group resides on the sterically more hindered site next to a phenyl group of the BOX ligand. This phenyl group can be envisioned to develop attractive interactions to the substrate ketiminoester π system.[22] These attractive interactions potentially lock the substrate in place for the highly selective allyl delivery.

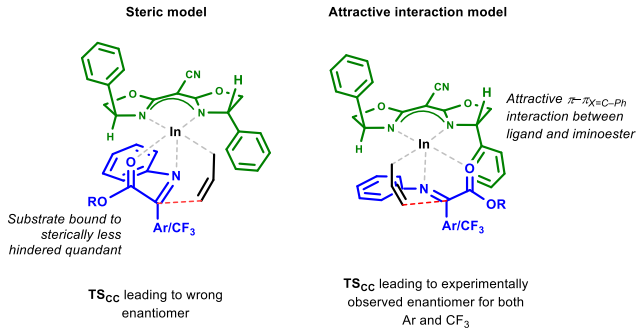
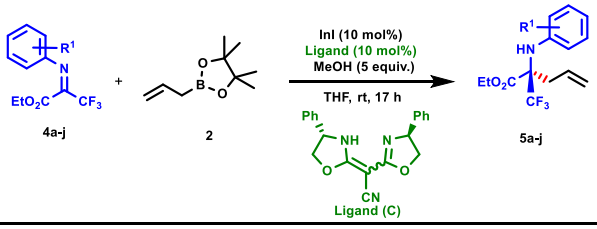
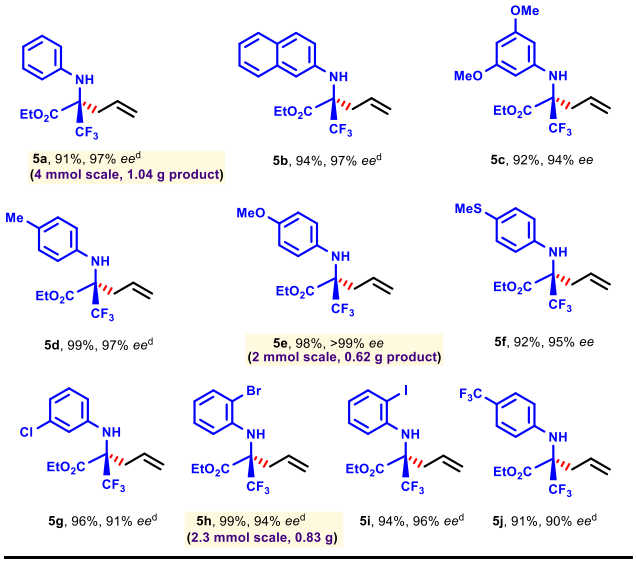



**Figure 2.** Preliminary stereoselectivity model involves attractive interactions between α-ketiminoester and BOX ligand.

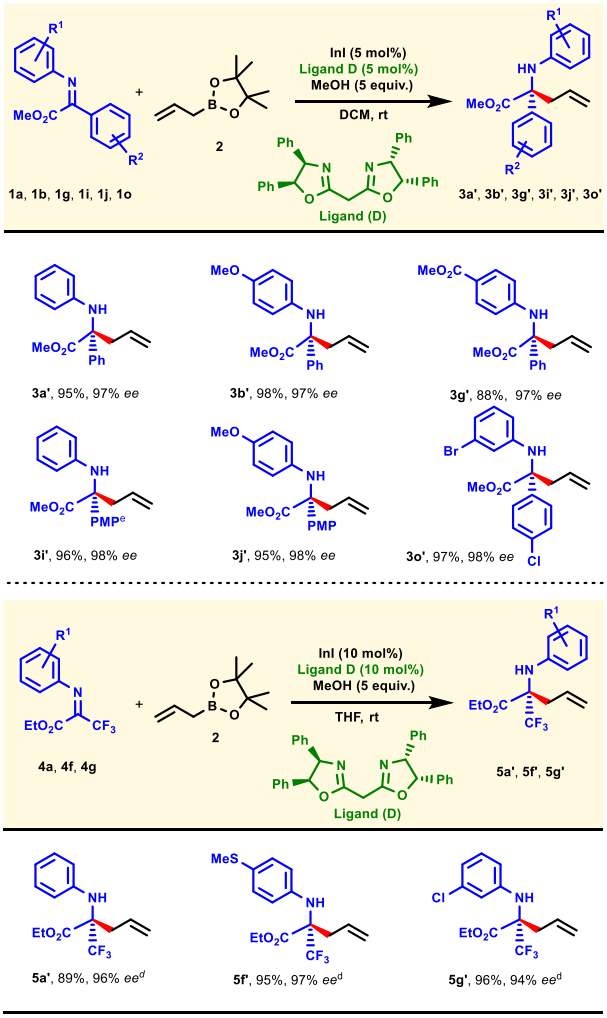
**Table 3: Catalytic Asymmetric Allylboration of α-Trifluoromethyl α-Iminoesters:**[a, b, c]




[a]Conditions: Trifluoroiminoester (**4a**–**4j**, 0.5–4.0 mmol), AllylBpin (**2**, 0.75–6.0 mmol), InI (0.05–0.4 mmol), Ligand (0.05–0.4 mmol), MeOH (2.5–20.0 mmol) in 1.5–12.0 mL of THF at rt for the indicated time. [b]All reported yields are isolated yields. [c]All the *ee*-s are determined by HPLC or SFC analysis on chiral stationary phase. [d]The enantiomeric excesses for these compounds were determined by HPLC or SFC analysis of the corresponding amino alcohol.

**Table 4: Change of Ligand Leads to Enantiomeric products:[a, b, c]**

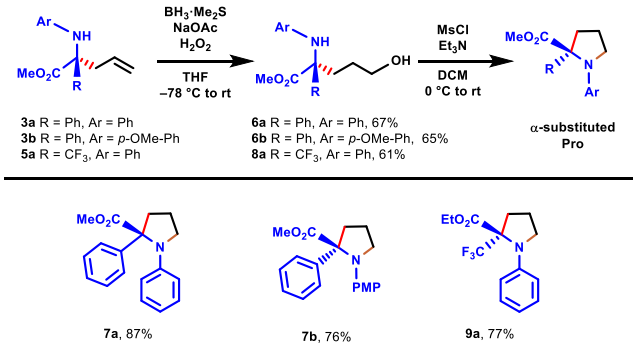



[a]Conditions: Iminoester (0.5 mmol), AllylBpin (**2**, 0.75 mmol), InI (0.025 or 0.05 mmol), Ligand (0.025 or 0.05 mmol), MeOH (2.5 mmol) in 1.5 mL of DCM or THF at rt. [b]All the reported yields are isolated yields. [c]All the *ee*-s are determined by HPLC or SFC analysis on chiral stationary phase. [d]The enantiomeric excesses for these compounds were determined by HPLC or SFC analysis on chiral stationary phase of the corresponding amino alcohol. [e]*p*-Methoxyphenyl.

Ligand *ent*-**C**, that would be required for the preparation of the opposite product enantiomer, is not commercially available. Fortuitously, in the initial screening the structurally related BOX-ligand **D** performed comparably to ligand **C** but reversed the sense of enantio-induction. Using thr commercially available and cheap ligand **D**,[23] six different α-aryl (**1a**, **1b**, **1g**, **1i**, **1j**, **1o**) and three α-trifluoromethyl α-iminoesters (**4a**, **4f**, **4j**) were subjected to the allylation conditions (**Table 1**, entry **19**). In all cases, the opposite enantiomers of the desired homoallylic α-aminoester products were isolated in very good to excellent yields and with excellent enantioselectivities (**Table 4**).

Finally, to demonstrate the method's broader synthetic utility, we used the allylated products to prepare three α-substituted *N*-substituted proline ester derivatives **7a**, **7b** and **9a** *via* sequential hydroboration-oxidation–cyclization (Scheme 2). This short sequence provides convenient access to a range of important α-substituted prolines, especially biologically and biochemically important α-trifluoromethylproline.[24] Similar densely functionalized pyrrolidine moieties are also ubiquitous substructures in many natural products,[25] drugs,[26] and organocatalysts.[27]

**Scheme 2: Transformations of the Chiral Homoallylic Amine Products into α-substituted Proline esters:**




In summary, we have developed a direct catalytic asymmetric allylboration of α-aryl and α-trifluoromethyl ketiminoesters using chiral In(I) complexes. The structurally diverse allylated products are highly enantioenriched, and the sense of absolute stereochemistry can be selected by simply switching between two commercially available BOX-type ligands. This work demonstrates how a catalytic enantioselective method can be conveniently rendered enantiodivergent by employing two structurally-related catalysts instead of having to use the enantiomers of a single catalyst. The optimized allylation reactions are operationally simple and both can be carried out on gram-scale without the need to extensively exclude air and moisture. Furthermore, we have also demonstrated the broader synthetic utility of the allylated products as chiral building blocks for the construction of α-substituted proline derivatives. We expect these allylated products to be versatile starting materials for the synthesis of various other heterocycles. In-depth computational and experimental studies to better understand the stereoselectivity controlling factors of the reaction are ongoing in our laboratories.

## ASSOCIATED CONTENT

Complete experimental procedures and characterization data including $^{1}H$ and $^{13}C$ NMR spectra and chromatograms. This material is available free of charge via the Internet at **http://pubs.acs.org**.

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### Notes

The authors declare no competing financial interest.

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## HIGHLY ENANTIOSELECTIVE CATALYTIC ALLYLBORATION OF α-KETIMINOESTERS