Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201801148

Link to VoR: http://dx.doi.org/10.1002/adsc.201801148

10.1002/adsc.201801148

UPDATE

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Enantioselective and Diastereodivergent Access to α-Substituted α-Amino Acids via Dual Iridium and Copper Catalysis

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. The work reported within this paper describes an example of the application of bimetallic catalysts system in allylic substitution reactions. The development of new nucleophiles and the control of enantio- and diastereoselectivity are the main research topics in this area. An improvement in the reactivity and diastereoselectivity has been realized for the dual Ir/Cu catalyzed allylic alkylation of inactive prochiral nucleophiles, under mild reaction conditions. Furthermore, the choice of the metallacyclic iridium complex and chiral Cu-Phox complex combination allows for access to all four stereoisomers from the same starting materials with excellent enantioselectivity and diastereoselectivity (up to >99% ee and >20:1 dr). Significantly, this method provides a stereodivergent access to 2-amino-3-methylpent-4-acid ester, an important fragment for the synthesis of Halipeptin A.

Keywords: Allylation; Asymmetric synthesis; Copper; Diastereodivergent; Iridium; Synergistic catalysis

α-Substituted α-amino acids (α-AAs) are not only important components of living organisms but they also participate in almost all life activities. Furthermore, α-AAs are frequently utilized as building blocks in biochemical and pharmacological research.[1] As such, the importance of α-AAs has attracted much attention among chemists and prompted the development of efficient synthetic methods towards their preparation.[2] Indeed, many efficient methodologies have been reported for the synthesis of different types of enantioenriched α-substituted α-AAs; both enantiomers of the α-AAs can be obtained by simply selecting between a pair of enantiomeric catalysts. However, the construction of α-AAs bearing vicinal stereocenters, with full control of the absolute and relative configuration, presents a considerable, ongoing synthetic challenge.[3,4] In consideration of the ubiquity of these structural motifs and the fact that their absolute and relative configurations are often crucial for the expression of their biological activities (Figure 1),[5] the development of reliable methodologies that lead to all possible stereoisomers of products is highly desired.

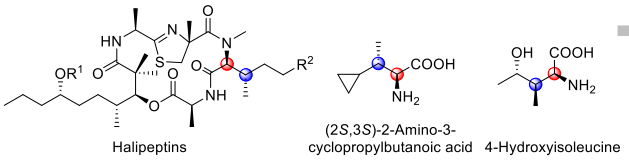

Figure 1. Representative Examples of Biologically Active Natural Products and Pharmaceuticals.

Much effort has been devoted to resolving this challenge. In 2001, Ohfune and co-workers provided a divergent access to α-substituted α-AAs necessitating the involvement of enantiopure allylic alcohols and the alteration of alkene geometry (*E* versus *Z*).[4a,4d] Subsequently, Takemoto and co workers succeeded in developing a diastereoselective asymmetric synthesis of glycine derivates by switching the base employed.[4b,4c] However, the development of a strategy to provide a unified and predictable route for the stereodivergent construction of α-substituted α-AAs bearing vicinal stereocenters, with selective access to all their stereoisomers from the same starting materials, remains an unmet challenge and is yet to be reported.

For this purpose, synergistic catalysis may provide an ideal strategy: dual catalysis consisting of two distinct chiral catalysts, whereby each catalyst allows

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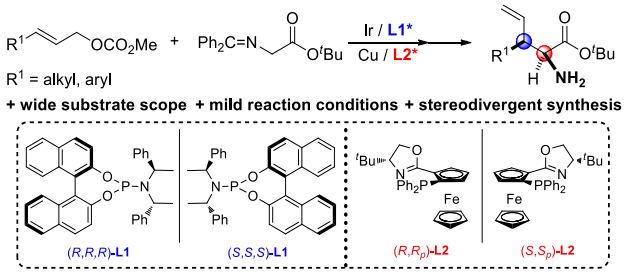
for full control over the configuration of each respective stereocenter, is expected to afford all possible stereoisomers of a desired product.[6] Recently, Carreira and co-workers successfully implemented this strategy for the stereodivergent allylation of aldehydes by combining iridium and enamine catalysis.[7] While the combination of transition metals and organocatalysts accommodates a range of functional groups,[8] synergistic catalysis using two metal catalysts may enable a much broader range of asymmetric transformations.[9] Indeed, several elegant bimetallic catalysts systems have been recently developed for stereodivergent synthesis by the groups of Zhang,[10] Wang,[11] and Hartwig.[12] In Wang's paper, a Ir(I)/Cu(I)-catalyzed allylation of aldimine esters with two examples of α-substituted α-AAs has been reported.[11]

Following our research on cooperative bimetallic catalysis and the asymmetric synthesis of unnatural α-AAs,[9h,9i,10c] we aim to provide a universal access to the stereodivergent construction of α-substituted α-AAs bearing two adjacent stereogenic centers with identical starting materials and reaction conditions, by using the predominant bimetalic catalysts system (Scheme 1). However, several problems must still be overcome to obtain highly enantiopure α-substituted α-AAs: (a) the internal contradictions of maintaining the high reactivity of the bimetallic catalysis and lowering the reactivity of the substrates to avoid the formation of disubstituted products, must be addressed; (b) the stereoselectivity of the prochiral nucleophile must be controlled; and (c) the potential enolization of α-substituted α-AAs in the presence of a Lewis acid or under basic conditions must be avoided.[13]

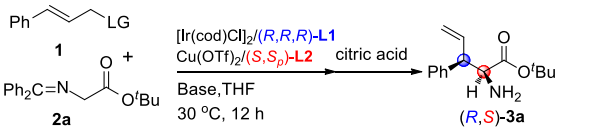


Scheme 1. Enantioselective and Diastereodivergent Allylation of the Glycine-based Ketimine Esters.

Herein, we report an efficient methodology for the stereodivergent allylation of achiral glycine ester derivatives from uniform starting materials with a dual Ir(I)/Cu(II) catalysts system. Compared with the base-controlled diastereoselective synthesis of glycine derivates, the dual Ir/Cu catalysis shows a noteworthy improvement in the reactivity and stereoselectivity of the reaction.

With the previously reported Ir-catalyzed allylic substitution reactions in mind,[14] we began our studies by examining the conditions: $[Ir(cod)Cl]_2$ (2 mol%), (*R*,*R*,*R*)-**L1** (4 mol%), $Cu(OTf)_2$ (5 mol%), (S,S_p)-**L2** in THF with cesium carbonate (Cs_2CO_3) as the additive. With the aldimine ester as the starting substrate, the desired product was obtained with moderate stereoselectivity (6:1 dr and 91% ee) in 84% yield with a trace amount (4%) of diallylated product (Table 1, Entry 1). Compared to aldimine derivates, the ketimine esters provided a balance between activation of the glycine-based α-AAs and suppression of the diallylation due to their steric hindrance and comparatively weaker ability to undergo enolization (pK_a = 18.7 and 22.8 for the ketimine and α-substituted ketimine respectively).[13]

Table 1. Optimization of the Reaction Conditions.[a]



Entry	LG[b]	Base	Yield[c] %	Ee[d] %	Dr[e]
1[f]	OCO_2Me	Cs_2CO_3	84	91	6:1
2	OAc	Cs_2CO_3	nr	--	--
3	OBoc	Cs_2CO_3	12	>99	8:1
4	OCO_2Me	Cs_2CO_3	93	>99	15:1
5[g]	OCO_2Me	Cs_2CO_3	80	99	6:1
6[h]	OCO_2Me	Cs_2CO_3	81	99	6:1
7	OCO_2Me	DBU	50	>99	2:1
8	OCO_2Me	DIPEA	22	>99	1.2:1
9	OCO_2Me	*t*BuOLi	99	97	5:1
10	OCO_2Me	*t*BuOK	trace	--	--
11[i]	OCO_2Me	Cs_2CO_3	74	>99	13:1
12[j]	OCO_2Me	Cs_2CO_3	nr	--	--
13[k]	OCO_2Me	Cs_2CO_3	nr	--	--
14[l]	OCO_2Me	Cs_2CO_3	nr	--	--
15[m]	OCO_2Me		nr	--	--
16[n]	OCO_2Me	Cs_2CO_3	74	99	15:1

[a] Reaction conditions: **1** (0.25 mmol, 1.0 equiv), **2a** (1.5 equiv), 2.0 mol% $[Ir(cod)Cl]_2$, 4.0 mol% (*R*,*R*,*R*)-**L1**, 5 mol% $Cu(OTf)_2$, 5 mol% (S,S_p)-**L2**, Cs_2CO_3 (1.2 equiv), THF (2 mL), 30 °C, 12 h.
[b] Leaving Group.
[c] Isolated yield. nr = no reaction.
[d] Determined by the HPLC using chiral column.
[e] Ratio of dr determined by ^{1}H NMR.
[f] Using the glycine aldimine ester instead of **2a**.
[g] Using the methyl ester instead of the *tert*-butyl ester **2a**.
[h] Using the ethyl ester instead of the *tert*-butyl ester **2a**.
[i] 10 ℃.
[j] Without Ir catalyst.
[k] Without Cu catalyst.
[l] Without (S,S_p)-**L2**.
[m] Without base.
[n] Prepared in one-pot protocol.

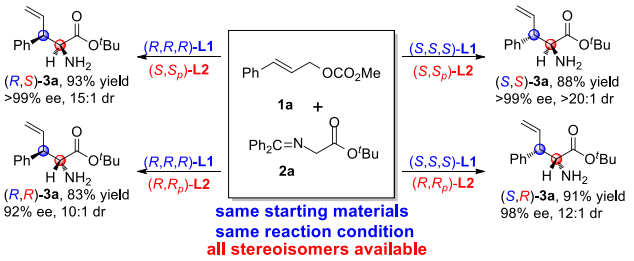
Therefore, the ketimine **2a** was initially used as a model substrate for the allylation reaction.

Additionally, a series of leaving groups (LG) of the π-allyl precursors were evaluated (Entries 2−4). No reaction occurred using a poor leaving group, such as acetate (OAc). The better leaving ability provided by *tert*-butyl carbonate (OBoc) gave the allylation product with promising stereoselectivity (>99% ee and 8:1 dr), albeit in only 12% yield. The methyl carbonate (OCO_2Me) leaving group provided superior results with almost quantitative conversion to the desidred product and excellent enantioselectivity (>99% ee) and diastereoselectivity (15:1 dr). According to the experiments, the basicity of the leaving groups and their decarboxylation products[12] appears to be critically important to the reactivity and diastereoselectivity of the reaction. Subsequently, the glycine methyl and ethyl esters have been used in the present reaction conditions. The desired products were obtained in 80% yield, 99% ee, 6:1 dr and 81% yield, 99% ee, 6:1 dr, respectively (Entries 5 and 6).

While aiming to maintain high levels of reactivity, we turned our attention towards improving diastereoselectivity. Setting Cs_2CO_3 as the baseline, we selected different kinds of additives based on their basicity. Employing relatively weak bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and diisoporpylethylamine (DIPEA), gave the desired product in low yields and with low dr values, revealing the difficulty of the deprotonation of the glycine-based substrates (Entries 7 and 8). In order to resolve this problem, a stronger base, lithium *tert*-butoxide (*t*BuOLi), was used but it did not provide high diastereoselsctivity (Entry 9). With potassium *tert*-butoxide (*t*BuOK) as base, the reaction delivered only trace amounts of products and generated a large excess of the hydrolyzed product, cinnamyl alcohol (Entry 10), showing that strongly basic conditions result in the hydrolyzation of the substrates. Futhermore, reduction of the reaction temperature resulted in substantially lower reactivity, and had a negligible effect on diastereoselectivity (13:1 versus 15:1) (Entry 11).

Subsequently, control experiments were conducted to confirm the synergistic effect of the bimetallic catalysis. Predictably, no desired product was detected in the absence of the Ir catalyst (Entry 12). Additionally, when the reaction was conducted with the Ir catalyst in the absence of the Cu catalyst or the ligand **L2** (Entries 13 and 14), no product was obtained. It was presumed that the low reactivity of ketimine could not be overcome by the participation of the activated Cu catalyst. Futhermore, no reaction occured in the absence of base (Entry 15). These data provided sufficient evidence to demonstrate that the bimetallic catalysts play a synergistic and indispensable role in improving the reactivity of the reaction. Furthermore, a one-pot experiment has been conducted. The desired product could be obtained in a slightly lower yield but with comparable stereoselectivity (Entry 16).

Considering that different stereoisomers of biomolecules can exhibit markedly different biological activities, we embarked upon the enantio- and diastereodivergent synthesis of the **3a**. Fortunately, from the same starting materials, **1a** and **2a**, and under almost identical conditions, the reactions proceeded smoothly, affording the full set of stereoisomers of **3a** in high yields (83-93% yield) with up to >99% ee and >20:1 dr by simply switching the configurations of the ligands (Scheme 2). The results suggested that the two distinct metal catalysts exert synergistic stereocontrol over the vicinal stereocenters. This methodology of enantio- and diastereodivergent synthesis of α-substituted α-AAs that provides four stereoisomers would not only provide a pathway to α-AAs with varied biological activities but also contribute to the exploration of structure−activity relationships, which is important in the drug discovery and development process.



Scheme 2. Construction of All Four Stereoisomers of **3a**.

With the optimized reaction conditions in hand, the scope of the allylic carbonates was explored in a stereodivergent manner (Tables 2 and 3). A range of allylated α-substituted α-AAs **3** were obtained, giving two diastereoisomers. Electron-donating (**1b** and **1c**) and electron-withdrawing (**1d**−**1f**) functional groups at the *para*-position of the cinnamyl aryl rings were

Table 2. The Substrate Scope of Allylic Carbonates.[a]

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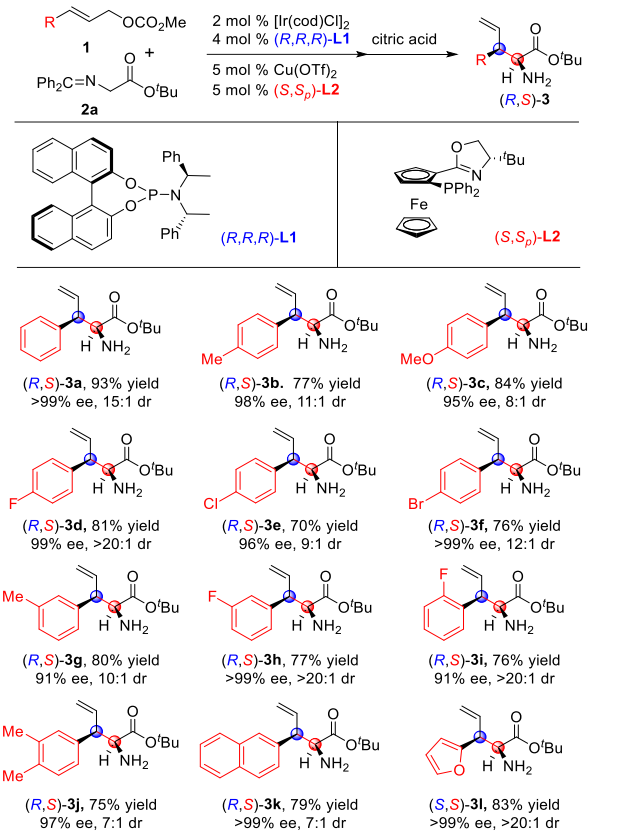
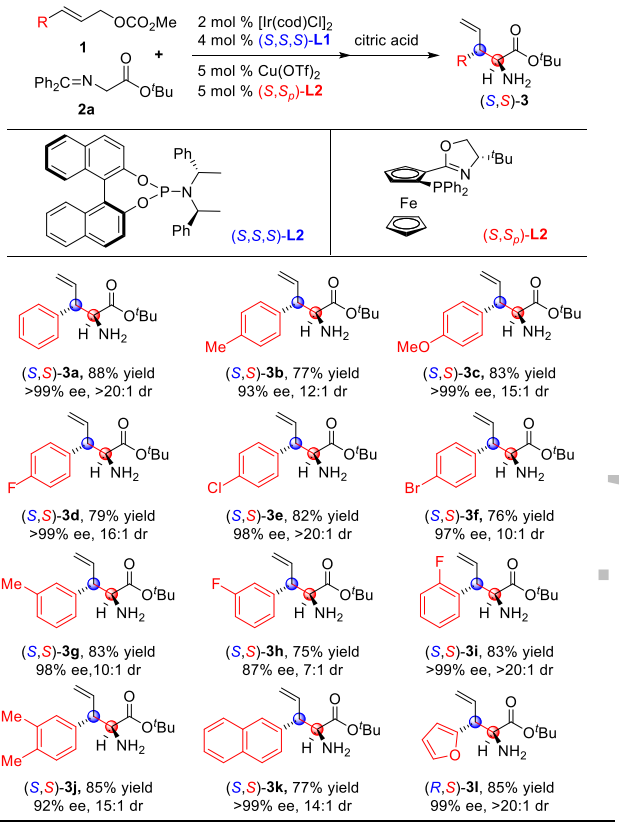


[a] Reaction conditions: **1** (0.25 mmol, 1.0 equiv), **2a** (1.5 equiv), 2.0 mol% $[Ir(cod)Cl]_2$, 4.0 mol% (*R*,*R*,*R*)-**L1**, 5 mol% $Cu(OTf)_2$, 5 mol% (*S*,S_p)-**L2**, Cs_2CO_3 (1.2 equiv), THF (2 mL), 30 °C, 12 h.



[a] Reaction conditions: **1** (0.25 mmol, 1.0 equiv), **2a** (1.5 equiv), 2.0 mol% $[Ir(cod)Cl]_2$, 4.0 mol% (*S*,*S*,*S*)-**L1**, 5 mol% $Cu(OTf)_2$, 5 mol% (*S*,S_p)-**L2**, Cs_2CO_3 (1.2 equiv), THF (2 mL), 30 °C, 12 h.

all tolerated under the allylation conditions. The corresponding products (**3b**−**3f**) were obtained with good enantio- and diastereoselectivities (93 to >99% ee and 8:1 to >20:1 dr). It was also found that cinnamyl carbonates bearing substituents at the *ortho*-, *meta*-, or *para*-position of the phenyl ring were all tolerated, This reaction also proceeded with cinnamyl carbonates that bear one or two substituents at the *ortho*-, *meta*-, or *para*-position of the phenyl ring, affording their respective products (**3b**, **3d**, **3g**−**3j**) in high yield with good stereoselectivity (up to >20:1 dr and >99% ee). Futhermore, a reation with the allylic carbonate containing a naphthyl group was successfully carried out to give its respective product (**3k**). Notably, an allylic cabonate that cotains a heteroaryl furyl (**1l**) substituent underwent allylation to give the product (**3l**) in more than 80% yield (isolated as a single diastereomer) with >20:1 dr and 99% ee.

Significiantly, the reaction provided 2-amino-3-methylpent-4-acid ester (**3m**), which is an important structural motif found in biologically active natural products and pharmaceuticals (e.g., halipeptins, (2*S*,3*S*)-2-amino-3-cyclopropylbutanoic acid and 4-hydroxyisoleucine).[15] In 2004, the Riccadis group[16] successfully prepared the amino acid derivatives with 1-(*tert*-butyldimethylsilyl)-2-butyn-1-ol as the starting material (6 steps, 44% overall yield) (Figure 2). Subsequently, the Ma group[17] used 2-butyn-1-ol as the starting material to obtain the analogue in 8 steps and in approximately 22% overall yield. Our new synthetic methodology based on our dual Ir/Cu catalyst system provided α-substituted α-AA (*S*,*S*)-**3m** in one step in 73% yield, and its diastereomer in 78% yield from the same starting materials, with high enantio- and diastereoselectivity (10:1 to 17:1 dr and >99% ee). The enantio- and diastereodivergent construction of α-substituted α-AAs can be applied to studies on the biological activities of the different stereoisomers of biomolecules and contribute to medicinal chemistry research.

Table 3. The Substrate Scope of Allylic Carbonates.[a]

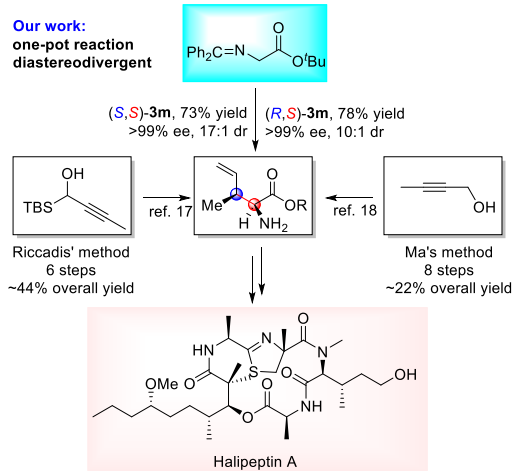


Figure 2. Methods for Synthesis of α-Substituted α-AA Fragment of the Halipeptin A.

In summary, we have documented a further application of synergistic bimetallic catalysts for the stereodivergent allylic substitution reaction. A range of α-subsutituted α-AAs bearing two vicinal stereocenters have been obtained in a diastereodivergent manner with good enantio- and diastereoselectivity under mild conditions. Furthermore, the reaction is able to provide two diastereomers of 2-amino-3-methylpent-4-acid esters (**3m**) in high yields and with high stereoselectivities, which are frequently utilized as building blocks in biochemical and pharmacological research. We are continuing our studies to further develop the bimetallic catalyst strategy, offering new opportunities for full stereodivergent access to difficult asymmetric transformations.

Experimental Section

General Procedure for Stereodivergent α-Allylation of α-Amino Acids via an Ir/Cu Dual Catalysis: **Preparation of the Ir catalyst**: A flame dried Schlenk tube was cooled to room temperature and filled with N_2. To this flask were added $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2 mol%), phosphoramidite ligand **L1** (5.4 mg, 0.010 mmol, 4 mol%), THF (0.5 mL) and *n*-propylamine (0.5 mL). The reaction mixture was heated at 50 °C for 30 min and then the volatile solvents were removed under vacuum to give a pale-yellow solid. Then the solid was dissolved in 1 mL THF under nitrogen atmosphere. **Preparation of the Cu catalyst**: A flame dried Schlenk tube was cooled to room temperature and filled with N_2. To this flask were added $Cu(OTf)_2$ (3.9 mg, 0.013mmol, 5.0 mol%), ferrocene ligand **L2** (6.8 mg, 0.013 mmol, 5.0 mol%), THF (1 mL). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 30 min.

A flame dried Schlenk tube was cooled to room temperature and filled with N_2. To this flask were added ketimine ester (0.30 mmol, 1.2 equiv) and Cs_2CO_3 (97.8 mg, 0.30 mmol). Ir catalyst (1 mL) and Cu catalyst (1 mL) were then added. Allylic carbonate (0.25 mmol, 1.0 equiv) was then added and the reaction mixture was stirred at 30 °C for 12 h. To the reaction mixture was added a 10% aqueous citric acid solution (4 mL) at room temperature and the mixture was stirred for 2 h. The mixture was neutralized with solid K_2CO_3 and extracted with EtOAc (5 mL x 3). The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was then purified by SiO_2 column chromatography (PE/EA = 3:1) to give the desired products. The ee value was determined by HPLC using a Daicel chiral column. The analytical data of the products are summarized below.

(2*S*,3*R*)-*tert*-Butyl 2-amino-3-phenylpent-4-enoate [(*R*,*S*)-3a]: ^{1}H NMR analysis of the crude mixture showed a dr of 15:1. Light yellow oil, 57.5 mg, 93% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.21 (m, 5H), 6.11 (ddd, *J* = 17.0, 10.2, 8.8 Hz, 1H), 5.23 (dd, *J* = 10.2, 1.6 Hz, 1H), 5.19 (ddd, *J* = 17.0, 1.6, 1.0 Hz, 1H), 3.65 (d, *J* = 7.6 Hz, 1H), 3.53 (dd, *J* = 8.8, 7.6 Hz, 1H), 1.65 (s, 2H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 140.8, 137.2, 128.5, 128.2, 126.8, 117.9, 81.1, 59.5, 55.6, 27.8. HRMS (Q–TOF Premier) calcd for $C_{15}H_{22}NO_2$ $(M+H)^+$: 248.1650; found: 248.1649. >99% ee [DAICEL CHIRALPAK OJ, hexane/*i*-PrOH = 95/5, 210 nm, 1.0 mL/min; t_{R1} = 7.1 min (major), t_{R2} = 7.8 min (minor)]. $[\alpha]_D^{20}$ = -21.3 (*c* 1.0, $CHCl_3$).

(2*R*,3*R*)-*tert*-Butyl 2-amino-3-phenylpent-4-enoate [(*R*,*R*)-3a]: ^{1}H NMR analysis of the crude mixture showed a dr of 10:1. Light yellow oil, 51.3 mg, 83% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.30 (m, 2H), 7.29 – 7.24 (m, 3H), 6.12 (ddd, *J* = 16.6, 10.8, 8.4 Hz, 1H), 5.17 (dd, *J* = 16.6, 1.2 Hz, 1H), 5.16 (dd, *J* = 10.8, 1.2 Hz, 1H), 3.67 (d, *J* = 7.6 Hz, 1H), 3.59 (dd, *J* = 8.4, 7.6 Hz, 1H), 1.54 (s, 2H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 140.1, 137.9, 128.6, 128.4, 127.0, 116.8, 81.5, 59.6, 55.2, 28.1. HRMS (Q–TOF Premier) calcd for $C_{15}H_{22}NO_2$ $(M+H)^+$: 248.1650; found: 248.1648. 92% ee [DAICEL CHIRALPAK OJ, hexane/*i*-PrOH = 95/5, 210 nm, 1.0 mL/min; t_{R1} = 8.9 min (major), t_{R2} = 10.3 min (minor)]. $[\alpha]_D^{20}$ = -19.0 (*c* 1.0, $CHCl_3$).

(2*S*,3*S*)-*tert*-Butyl 2-amino-3-phenylpent-4-enoate [(*S*,*S*)-3a]: ^{1}H NMR analysis of the crude mixture showed a dr of >20:1. Light yellow oil, 54.4 mg, 88% yield. HRMS (Q–TOF Premier) calcd for $C_{15}H_{22}NO_2$ $(M+H)^+$: 248.1650; found: 248.1651. >99% ee [DAICEL CHIRALPAK OJ, hexane/*i*-PrOH = 95/5, 210 nm, 1.0 mL/min; t_{R1} = 8.9 min (minor), t_{R2} = 10.2 min (major)]. $[\alpha]_D^{20}$ = 29.0 (*c* 1.0, $CHCl_3$). Spectral data were in agreement with those of the enantiomer reported above.

(2*R*,3*S*)-*tert*-Butyl 2-amino-3-phenylpent-4-enoate [(*S*,*R*)-3a]: ^{1}H NMR analysis of the crude mixture showed a dr of 12:1. Light yellow oil, 56.2 mg, 91% yield. HRMS (Q–TOF Premier) calcd for $C_{15}H_{22}NO_2$ $(M+H)^+$: 248.1650; found: 248.1649. 98% ee [DAICEL CHIRALPAK OJ, hexane/*i*-PrOH = 95/5, 210 nm, 1.0 mL/min; t_{R1} = 7.2 min (minor), t_{R2} = 7.8 min (major)]. $[\alpha]_D^{20}$ = 14.4 (*c* 1.0, $CHCl_3$). Spectral data were in agreement with those of the enantiomer reported above.

(2*S*,3*S*)-*tert*-Butyl 2-amino-3-(*p*-tolyl)pent-4-enoate [(*S*,*S*)-3b]: ^{1}H NMR analysis of the crude mixture showed a dr of 12:1. Light yellow oil, 50.3 mg, 77% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.16 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.10 (ddd, *J* = 17.0, 10.4, 8.4 Hz,

1H), 5.16 (dd, *J* = 17.0, 1.6 Hz, 1H), 5.14 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.65 (d, *J* = 8.0 Hz, 1H), 3.56 (dd, *J* = 8.4, 8.0 Hz, 1H), 2.34 (s, 3H), 1.71 (s, 2H), 1.46 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 138.2, 137.0, 136.6, 129.4, 128.3, 116.5, 81.5, 59.6, 54.9, 28.1, 21.0. HRMS (Q–TOF Premier) calcd for $C_{16}H_{24}NO_2$ $(M+H)^+$: 262.1812; found: 262.1809. 93% ee [DAICEL CHIRALPAK OJ, hexane/*i*-PrOH = 97/3, 210 nm, 1.0 mL/min; t_{R1} = 11.5 min (major), t_{R2} = 13.0 min (minor)]. $[\alpha]_D^{20}$ = 35.8 (*c* 1.0, $CHCl_3$).

(2*S*,3*R*)-*tert*-Butyl 2-amino-3-(*p*-tolyl)pent-4-enoate [(*R*,*S*)-3b]: ^{1}H NMR analysis of the crude mixture showed a dr of 11:1. Light yellow oil, 50.1 mg, 77% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.16 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.10 (ddd, *J* = 17.0, 10.2, 8.8 Hz, 1H), 5.21 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.17 (dd, *J* = 17.0, 1.8 Hz, 1H), 3.63 (d, *J* = 7.2 Hz, 1H), 3.52 (dd, *J* = 8.8, 7.2 Hz, 1H), 2.34 (s, 3H), 1.63 (s, 2H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 137.7, 137.3, 136.3, 129.1, 128.1, 117.7, 81.1, 59.5, 55.0, 27.8, 21.0. HRMS (Q–TOF Premier) calcd for $C_{16}H_{24}NO_2$ $(M+H)^+$: 262.1812; found: 262.1813. 98% ee [DAICEL CHIRALPAK OJ, hexane/*i*-PrOH = 97/3, 210 nm, 1.0 mL/min; t_{R1} = 8.4 min (major), t_{R2} = 10.7 min (minor)]. $[\alpha]_D^{20}$ = -21.6 (*c* 1.0, $CHCl_3$).

(2*S*,3*S*)-*tert*-Butyl 2-amino-3-(4-methoxyphenyl)pent-4-enoate [(*S*,*S*)-3c]: ^{1}H NMR analysis of the crude mixture showed a dr of 15:1. Light yellow oil, 57.3 mg, 83% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.16 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.08 (ddd, *J* = 17.8, 10.0, 8.2 Hz, 1H), 5.14 (dd, *J* = 17.8, 1.2 Hz, 1H), 5.13 (dd, *J* = 10.0, 1.2 Hz, 1H), 3.80 (s, 3H), 3.65 (d, *J* = 7.4 Hz, 1H), 3.57 (dd, *J* = 8.2, 7.4 Hz, 1H), 1.72 (s, 2H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 158.6, 138.2, 131.8, 129.4, 116.6, 114.1, 81.5, 59.5, 55.2, 54.1, 28.1. HRMS (Q–TOF Premier) calcd for $C_{16}H_{24}NO_3$ $(M+H)^+$: 278.1761; found: 278.1751. >99% ee [DAICEL CHIRALPAK IE, hexane/*i*-PrOH = 99/1, 210 nm, 0.8 mL/min; t_{R1} = 65.6 min (minor), t_{R2} = 47.5 min (major)]. $[\alpha]_D^{20}$ = 53.5 (*c* 1.0, $CHCl_3$).

(2*S*,3*R*)-*tert*-Butyl 2-amino-3-(4-methoxyphenyl)pent-4-enoate [(*R*,*S*)-3c]: ^{1}H NMR analysis of the crude mixture showed a dr of 8:1. Light yellow oil, 58.0 mg, 84% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.19 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.08 (ddd, *J* = 17.0, 10.2, 8.8 Hz, 1H), 5.21 (dd, *J* = 10.2, 1.6 Hz, 1H), 5.21 (ddd, *J* = 17.0, 1.6, 1.0 Hz, 1H), 3.80 (s, 3H), 3.61 (d, *J* = 7.2 Hz, 1H), 3.51 (dd, *J* = 8.8, 7.2 Hz, 1H), 1.63 (s, 2H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 158.5, 137.4, 132.8, 129.4, 129.2, 117.6, 114.0, 113.9, 81.1, 59.6, 55.3, 54.5, 27.8. HRMS (Q–TOF Premier) calcd for $C_{16}H_{24}NO_3$ $(M+H)^+$: 278.1761; found: 278.1756. 95% ee [DAICEL CHIRALPAK IE, hexane/*i*-PrOH = 99/1, 210 nm, 0.8 mL/min; t_{R1} = 54.9 min (minor), t_{R2} = 57.8 min (major)]. $[\alpha]_D^{20}$ = -16.7 (*c* 1.0, $CHCl_3$).

(2*S*,3*S*)-*tert*-Butyl 2-amino-3-(4-fluorophenyl)pent-4-enoate [(*S*,*S*)-3d]: ^{1}H NMR analysis of the crude mixture showed a dr of 16:1. Light yellow oil, 52.5 mg, 79% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.27 – 7.20 (m, 2H), 7.06 – 7.00 (m, 2H), 6.09 (ddd, *J* = 17.0, 10.4, 7.8 Hz, 1H), 5.17 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.14 (dd, *J* = 17.0, 1.3 Hz, 1H), 3.65 (d, *J* = 7.2 Hz, 1H), 3.61 (dd, *J* = 7.8, 7.2 Hz, 1H), 1.47 (s, 2H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 162.8, 160.9, 137.8, 135.8, 135.7, 130.0, 129.9, 117.0, 115.5, 115.3, 81.5, 59.5, 53.9, 28.0. ^{19}F NMR (471 MHz, $CDCl_3$) δ -115.9. HRMS (Q–TOF Premier) calcd for $C_{15}H_{21}FNO_2$ $(M+H)^+$: 266.1561; found: 266.1556. >99% ee [DAICEL CHIRALPAK IC-3, hexane/*i*-PrOH = 98.5/1.5, 210 nm, 0.8 mL/min; t_{R1} = 33.5 min (minor), t_{R2} = 33.9 min (major)]. $[\alpha]_D^{20}$ = 42.5 (*c* 1.0, $CHCl_3$).

(2*S*,3*R*)-*tert*-Butyl 2-amino-3-(4-fluorophenyl)pent-4-enoate [(*R*,*S*)-3d]: ^{1}H NMR analysis of the crude mixture showed a dr of >20:1. Light yellow oil, 54.0 mg, 81% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.02 (dd, *J* = 8.8, 8.7 Hz, 2H), 6.06 (ddd, *J* = 17.0, 10.2, 8.8 Hz, 1H), 5.23 (dd, *J* = 10.2, 1.6 Hz, 1H), 5.17 (dd, *J* = 17.0, 1.6 Hz, 1H), 3.60 (d, *J* = 7.6 Hz, 1H), 3.52 (dd, *J* = 8.8, 7.6 Hz, 1H), 1.66 (s, 2H), 1.29 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 163.0, 160.5, 137.1, 136.5, 136.5, 129.8, 129.7, 118.0, 115.3, 115.1, 81.3, 59.5, 54.5, 27.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.2. HRMS (Q–TOF Premier) calcd for $C_{15}H_{21}FNO_2$ $(M+H)^+$: 266.1561; found: 266.1553. 99% ee [DAICEL CHIRALPAK IC-3, hexane/*i*-PrOH = 98.5/1.5, 210 nm, 0.8 mL/min; t_{R1} = 31.1 min (minor), t_{R2} = 37.6 min (major)]. $[\alpha]_D^{20}$ = -19.0 (*c* 1.0, $CHCl_3$).

(2*S*,3*S*)-*tert*-Butyl 2-amino-3-(4-chlorophenyl)pent-4-enoate [(*S*,*S*)-3e]: ^{1}H NMR analysis of the crude mixture showed a dr of >20:1. Light yellow oil, 57.7 mg, 82% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.07 (ddd, *J* = 17.0, 10.4, 8.0 Hz, 1H), 5.17 (dd, *J* = 10.4, 1.4 Hz, 1H), 5.14 (dd, *J* = 17.0, 1.4 Hz, 1H), 3.66 (d, *J* = 7.2 Hz, 1H), 3.60 (dd, *J* = 8.0, 7.2 Hz, 1H), 1.63 (s, 2H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 138.6, 137.5, 132.8, 129.8, 128.7, 117.3, 81.6, 59.3, 54.1, 28.0. HRMS (Q–TOF Premier) calcd for $C_{15}H_{21}ClNO_2$ $(M+H)^+$: 282.1266; found: 282.1265. 98% ee [DAICEL CHIRALPAK OJ, hexane/*i*-PrOH = 98.5/1.5, 210 nm, 0.8 mL/min; t_{R1} = 11.4 min (minor), t_{R2} = 10.6 min (major)]. $[\alpha]_D^{20}$ = 46.7 (*c* 1.0, $CHCl_3$).

(2*S*,3*R*)-*tert*-Butyl 2-amino-3-(4-chlorophenyl)pent-4-enoate [(*R*,*S*)-3e]: ^{1}H NMR analysis of the crude mixture showed a dr of 9:1. Light yellow oil, 48.9 mg, 70% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.06 (ddd, *J* = 17.0, 10.2, 8.8 Hz, 1H), 5.24 (dd, *J* = 10.2, 1.4 Hz, 1H), 5.17 (dd, *J* = 17.0, 1.4 Hz, 1H), 3.60 (d, *J* = 7.2 Hz, 1H), 3.53 (dd, *J* = 8.8, 7.2 Hz, 1H), 1.74 (s, 2H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 139.4, 136.7, 132.6, 129.7, 128.7, 128.5, 118.3, 81.4, 59.3, 54.6, 27.8. HRMS (Q–TOF Premier) calcd for $C_{15}H_{21}ClNO_2$ $(M+H)^+$: 282.1266; found: 282.1264. 96% ee [DAICEL CHIRALPAK OJ, hexane/*i*-PrOH = 98.5/1.5, 210 nm, 0.8 mL/min; t_{R1} = 10.4 min (minor), t_{R2} = 8.5min (major)]. $[\alpha]_D^{20}$ = -22.6 (*c* 1.0, $CHCl_3$).

(2*S*,3*S*)-*tert*-Butyl 2-amino-3-(4-bromophenyl)pent-4-enoate [(*S*,*S*)-3f]: ^{1}H NMR analysis of the crude mixture showed a dr of 10:1. Light yellow oil, 61.8 mg, 76% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.07 (ddd, *J* = 17.0, 10.4, 8.0 Hz, 1H), 5.18 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.16 (dd, *J* = 17.0, 1.2 Hz, 1H),3.65 (d, *J* = 7.2 Hz, 1H), 3.58 (dd, *J* = 8.0, 7.2 Hz, 1H), 1.53 (s, 2H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 139.2, 137.4, 131.6, 131.5, 130.2, 120.9, 117.3, 81.6, 59.3, 54.2, 28.1. HRMS (Q–TOF Premier)

calcd for $C_{15}H_{21}BrNO_2$ $(M+H)^+$: 326.0760; found: 326.0763. 97% ee [DAICEL CHIRALPAK IC-3, hexane/*i*-PrOH = 97/3, 210 nm, 1.0 mL/min; t_{R1} = 13.0 min (minor), t_{R2} = 14.8 min (major)]. $[\alpha]_D^{20}$ = 32.7 (*c* 1.0, $CHCl_3$).

(2*S*,3*R*)-*tert*-Butyl 2-amino-3-(4-bromophenyl)pent-4-enoate [(*R*,*S*)-3f]: ^{1}H NMR analysis of the crude mixture showed a dr of 12:1. Light yellow oil, 61.9 mg, 76% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.06 (ddd, *J* = 17.0, 10.2, 8.6 Hz, 1H), 5.23 (dd, *J* = 10.2, 1.2 Hz, 1H) 5.20 (dd, *J* = 17.0, 1.2 Hz, 1H) 3.60 (d, *J* = 7.2 Hz, 1H), 3.52 (dd, *J* = 8.6, 7.2 Hz, 1H), 1.64 (s, 2H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 139.9, 136.6, 131.6, 131.5, 130.0, 120.6, 118.3, 81.4, 59.3, 54.6, 27.8. HRMS (Q–TOF Premier) calcd for $C_{15}H_{21}BrNO_2$ $(M+H)^+$: 326.0760; found: 326.0757. >99% ee [DAICEL CHIRALPAK IC-3, hexane/*i*-PrOH = 97/3, 210 nm, 1.0 mL/min; t_{R1} = 14.7 min (minor), t_{R2} = 12.1 min (major)]. $[\alpha]_D^{20}$ = -14.1 (*c* 1.0, $CHCl_3$).

(2*S*,3*S*)-*tert*-Butyl 2-amino-3-(*m*-tolyl)pent-4-enoate [(*S*,*S*)-3g]: ^{1}H NMR analysis of the crude mixture showed a dr of 10:1. Light yellow oil, 54.3 mg, 83% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.27 – 7.15 (m, 2H), 7.08 – 7.04 (m, 2H), 6.11 (ddd, *J* = 17.2, 10.4, 8.4 Hz, 1H), 5.16 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.14 (dd, *J* = 10.4, 1.5 Hz, 1H), 3.66 (d, *J* = 7.6 Hz, 1H), 3.55 (dd, *J* = 8.4, 7.6 Hz, 1H), 2.36 (s, 3H), 1.80 (s, 2H), 1.46 (s, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 138.0, 129.2, 128.5, 127.8, 125.4, 116.7, 81.5, 59.6, 55.3, 28.1, 21.5. HRMS (Q–TOF Premier) calcd for $C_{16}H_{24}NO_2$ $(M+H)^+$: 262.1812; found: 262.1806. 98% ee, HPLC [DAICEL CHIRALPAK AD, hexane/*i*-PrOH = 98/2, 210 nm, 0.6 mL/min; t_{R1} = 10.4 min (minor), t_{R2} = 12.9 min (major)]. $[\alpha]_D^{20}$ = 28.4 (*c* 1.0, $CHCl_3$).

(2*S*,3*R*)-*tert*-Butyl 2-amino-3-(*m*-tolyl)pent-4-enoate [(*R*,*S*)-3g]: ^{1}H NMR analysis of the crude mixture showed a dr of 10:1. Light yellow oil, 52.4 mg, 80% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.21 (dd, *J* = 8.8, 7.2 Hz, 1H), 7.07 (s, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.10 (ddd, *J* = 17.0, 10.2, 9.0 Hz, 1H), 5.23 (dd, *J* = 10.2, 1.6 Hz, 1H), 5.19 (dd, *J* = 17.0, 1.6 Hz, 1H), 3.63 (d, *J* = 7.4 Hz, 1H), 3.49 (dd, *J* = 9.0, 7.4 Hz, 1H), 2.35 (s, 3H), 1.83 (s, 2H), 1.27 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 140.6, 138.0, 137.3, 129.0, 128.4, 127.5, 125.2, 117.8, 81.1, 59.4, 55.5, 27.8, 21.4. HRMS (Q–TOF Premier) calcd for $C_{16}H_{24}NO_2$ $(M+H)^+$: 262.1812; found: 262.1805. 91% ee, HPLC [DAICEL CHIRALPAK AD, hexane/*i*-PrOH = 98/2, 210 nm, 0.6 mL/min; t_{R1} = 14.1 min (minor), t_{R2} = 15.6 min (major)]. $[\alpha]_D^{20}$ = -14.0 (*c* 1.0, $CHCl_3$).

(2*S*,3*S*)-*tert*-Butyl 2-amino-3-(3-fluorophenyl)pent-4-enoate [(*S*,*S*)-3h]: ^{1}H NMR analysis of the crude mixture showed a dr of 7:1. Light yellow oil, 49.6 mg, 75% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 (dd, *J* = 8.0, 6.0 Hz, 1H), 7.08 – 6.95 (m, 3H), 6.08 (ddd, *J* = 16.6, 10.4, 8.2 Hz, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 5.19 (d, *J* = 16.6 Hz, 1H), 3.67 (d, *J* = 7.4 Hz, 1H), 3.63 (d, *J* = 7.4 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 164.1, 161.6, 137.2, 130.1, 130.0, 124.1, 117.5, 115.5, 115.3, 114.0, 113.8, 81.7, 59.4, 54.6, 28.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.9. HRMS (Q–TOF Premier) calcd for $C_{15}H_{21}FNO_2$ $(M+H)^+$: 266.1561; found: 266.1557. 87% ee [DAICEL CHIRALPAK IC-3, hexane/*i*-PrOH = 95/5, 210 nm, 1.0 mL/min; t_{R1} = 9.0 min (minor), t_{R2} = 16.8 min (major)]. $[\alpha]_D^{20}$ = 33.4 (*c* 1.0, $CHCl_3$).

(2*S*,3*R*)-*tert*-Butyl 2-amino-3-(3-fluorophenyl)pent-4-enoate [(*R*,*S*)-3h]: ^{1}H NMR analysis of the crude mixture showed a dr of >20:1. Light yellow oil, 51.1 mg, 77% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 - 7.28 (m, 1H), 7.07 – 7.05 (m, 1H), 7.02 -7.01 (m, 1H), 6.96 - 6.94 (m, 1H), 6.07 (ddd, *J* = 17.0, 10.2, 8.8 Hz, 1H), 5.26 (dd, *J* = 10.2, 1.4 Hz, 1H), 5.19 (dd, *J* = 17.0, 1.4 Hz, 1H), 3.63 (d, *J* = 7.2 Hz, 1H), 3.54 (dd, *J* = 8.8, 7.2 Hz, 1H), 1.63 (s, 2H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 164.0, 161.6, 143.5, 143.4, 136.5, 129.9, 129.8, 123.9, 123.9, 118.4, 115.3, 115.1, 113.8, 113.6, 81.3, 59.3, 55.0, 54.9, 27.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.3. HRMS (Q–TOF Premier) calcd for $C_{15}H_{21}FNO_2$ $(M+H)^+$: 266.1561; found: 266.1555. >99% ee [DAICEL CHIRALPAK IC-3, hexane/*i*-PrOH = 95/5, 210 nm, 1.0 mL/min; t_{R1} = 8.3 min (minor), t_{R2} = 12.1 min (major)]. $[\alpha]_D^{20}$ = -15.9 (*c* 1.0, $CHCl_3$).

(2*S*,3*S*)-*tert*-Butyl 2-amino-3-(2-fluorophenyl)pent-4-enoate [(*S*,*S*)-3i]: ^{1}H NMR analysis of the crude mixture showed a dr of >20:1. Light yellow oil, 54.9 mg, 83% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.02 (m, 4H), 6.10 (ddd, *J* = 17.4, 10.0, 8.4 Hz, 1H), 5.19 (d, *J* = 17.4 Hz, 1H), 5.18 (d, *J* = 10.0 Hz, 1H), 3.90 (dd, *J* = 8.4, 8.0 Hz, 1H), 3.74 (d, *J* = 8.0 Hz, 1H), 1.68 (s, 2H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 162.1, 159.6, 136.4, 129.7, 129.7, 128.5, 128.4, 127.4, 127.3, 124.2, 124.2, 117.7, 115.8, 115.5, 81.5, 58.5, 48.6, 28.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.9. HRMS (Q–TOF Premier) calcd for $C_{15}H_{21}FNO_2$ $(M+H)^+$: 266.1561; found: 266.1556. >99% ee [DAICEL CHIRALPAK IC-3, hexane/*i*-PrOH = 95/5, 210 nm, 1.0 mL/min; t_{R1} = 14.2 min (minor), t_{R2} = 11.1 min (major)]. $[\alpha]_D^{20}$ = 24.4 (*c* 1.0, $CHCl_3$).

(2*S*,3*R*)-*tert*-Butyl 2-amino-3-(2-fluorophenyl)pent-4-enoate [(*R*,*S*)-3i]: ^{1}H NMR analysis of the crude mixture showed a dr of >20:1. Light yellow oil, 50.1 mg, 76% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 – 7.21 (m, 2H), 7.12 – 7.02 (m, 2H), 6.13 (ddd, *J* = 17.0, 10.2, 8.4 Hz, 1H), 5.24 (d, *J* = 17.0 Hz, 1H), 5.21 (d, *J* = 10.2 Hz, 1H), 3.73 (dd, *J* = 8.4, 7.8 Hz, 1H), 3.71 (d, *J* = 7.8 Hz, 1H), 1.72 (s, 2H), 1.24 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 161.6, 159.6, 136.1, 130.2, 130.1, 128.4, 128.4, 128.0, 127.8, 124.1, 124.0, 118.5, 115.7, 115.5, 81.1, 57.9, 50.3, 27.7. ^{19}F NMR (471 MHz, $CDCl_3$) δ -116.4. HRMS (Q–TOF Premier) calcd for $C_{15}H_{21}FNO_2$ $(M+H)^+$: 266.1561; found: 266.1557. 91% ee [DAICEL CHIRALPAK IC-3, hexane/*i*-PrOH = 95/5, 210 nm, 1.0 mL/min; t_{R1} = 13.6 min (minor), t_{R2} = 11.2 min (major)] $[\alpha]_D^{20}$ = -16.9 (*c* 1.0, $CHCl_3$).

(2*S*,3*S*)-*tert*-Butyl 2-amino-3-(3,4-dimethylphenyl)pent-4-enoate [(*S*,*S*)-3j]: ^{1}H NMR analysis of the crude mixture showed a dr of 15:1. Light yellow oil, 58.4 mg, 85% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.11 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 1.8 Hz, 1H), 6.98 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.10 (ddd, *J* = 17.6, 10.8, 8.4 Hz, 1H), 5.14 (d, *J* = 17.6 Hz, 1H), 5.11 (d, *J* = 10.8 Hz, 1H), 3.63 (d, *J* = 7.8 Hz, 1H), 3.51 (dd, *J* = 8.4, 7.8 Hz, 1H), 2.26 (s, 3H), 2.25 (s, 3H), 1.57 (s, 2H), 1.47 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5, 138.4, 137.4, 136.8, 135.3, 129.9, 129.6, 125.7, 116.3, 81.4, 59.6, 55.0, 28.1, 19.9, 19.4. HRMS (Q–

TOF Premier) calcd for $C_{17}H_{26}NO_2$ $(M+H)^+$: 276.1963; found: 276.1963. 92% ee [DAICEL CHIRALPAK AD, hexane/*i*-PrOH = 98/2, 210 nm, 0.5 mL/min; t_{R1} = 19.7 min (minor), t_{R2} = 20.9 min (major)]. $[\alpha]_D^{20}$ = 26.7 (*c* 1.0, $CHCl_3$).

(2*S*,3*R*)-*tert*-Butyl 2-amino-3-(3,4-dimethylphenyl)pent-4-enoate [(*R*,*S*)-3j]: ^{1}H NMR analysis of the crude mixture showed a dr of 7:1. Light yellow oil, 51.3 mg, 75% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.09 (d, *J* = 7.6 Hz, 1H), 7.05 – 6.98 (m, 2H), 6.10 (ddd, *J* = 16.8, 10.4, 9.2 Hz, 1H), 5.22 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.19 (dd, *J* = 16.8, 1.6 Hz, 1H), 3.63 (d, *J* = 7.0 Hz, 1H), 3.50 (dd, *J* = 9.2, 7.0 Hz, 1H), 2.26 (s, 3H), 2.25 (s, 3H), 1.69 (s, 2H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 138.2, 137.2, 136.5, 135.0, 129.7, 129.5, 125.5, 117.6, 81.0, 59.5, 54.9, 27.8, 19.8, 19.3. HRMS (Q–TOF Premier) calcd for $C_{17}H_{26}NO_2$ $(M+H)^+$: 276.1963; found: 276.1960. 97% ee [DAICEL CHIRALPAK AD, hexane/*i*-PrOH = 98/2, 210 nm, 0.5 mL/min; t_{R1} = 22.4 min (minor), t_{R2} = 26.9 min (major)]. $[\alpha]_D^{20}$ = -19.3 (*c* 1.0, $CHCl_3$).

(2*S*,3*S*)-*tert*-Butyl 2-amino-3-(naphthalen-2-yl)pent-4-enoate [(*S*,*S*)-3k]: ^{1}H NMR analysis of the crude mixture showed a dr of 14:1. Light yellow oil, 57.0 mg, 77% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 (td, *J* = 8.2, 7.5, 2.8 Hz, 3H), 7.71 (d, *J* = 1.7 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.41 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.23 (ddd, *J* = 17.0, 10.2, 5.2 Hz, 1H), 5.22 (d, *J* = 10.2 Hz, 1H), 5.21 (d, *J* = 17.0 Hz, 1H), 3.79 (d, *J* = 2.8 Hz, 1H), 3.78 (dd, *J* = 5.2, 2.8 Hz, 1H), 1.57 (s, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 137.9, 133.5, 132.6, 128.3, 127.7, 127.4, 126.2, 125.7, 117.1, 81.5, 59.6, 55.3, 28.1. HRMS (Q–TOF Premier) calcd for $C_{19}H_{24}NO_2$ $(M+H)^+$: 298.1812; found: 298.1799. >99% ee [DAICEL CHIRALPAK IE, hexane/*i*-PrOH = 99/1, 210 nm, 0.8 mL/min; t_{R1} = 30.0 min (minor), t_{R2} = 35.2 min (major)]. $[\alpha]_D^{20}$ = 33.1 (*c* 1.0, $CHCl_3$).

(2*S*,3*R*)-*tert*-Butyl 2-amino-3-(naphthalen-2-yl)pent-4-enoate [(*R*,*S*)-3k]: ^{1}H NMR analysis of the crude mixture showed a dr of 7:1. Light yellow oil, 58.5 mg, 79% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.80 (m, 3H), 7.72 (d, *J* = 1.8 Hz, 1H), 7.49 – 7.42 (m, 3H), 6.23 (ddd, *J* = 17.0, 10.2, 8.4 Hz, 1H), 5.29 (dd, *J* = 10.2, 1.4 Hz, 1H), 5.25 (dd, *J* = 17.0, 1.4 Hz, 1H), 3.84 – 3.70 (m, 2H), 1.74 (s, 2H), 1.22 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 138.2, 136.9, 133.4, 132.4, 128.1, 127.7, 127.6, 126.9, 126.4, 126.1, 125.7, 118.3, 81.2, 59.3, 55.4, 27.8. HRMS (Q–TOF Premier) calcd for $C_{19}H_{24}NO_2$ $(M+H)^+$: 298.1812; found: 298.1803. >99% ee [DAICEL CHIRALPAK IE, hexane/*i*-PrOH = 99/1, 210 nm, 0.8 mL/min; t_{R1} = 33.6 min (minor), t_{R2} = 38.1 min (major)]. $[\alpha]_D^{20}$ = -19.1 (*c* 1.0, $CHCl_3$).

(2*S*,3*R*)-*tert*-Butyl 2-amino-3-(furan-2-yl)pent-4-enoate [(*R*,*S*)-3l]: ^{1}H NMR analysis of the crude mixture showed a dr of >20:1. Light yellow oil, 50.2 mg, 85% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 1.8 Hz, 1H), 6.33 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.13 (d, *J* = 3.2 Hz, 1H), 6.03 (ddd, *J* = 16.8, 10.6, 8.2 Hz, 1H), 5.31 – 5.19 (m, 2H), 3.84 (dd, *J* = 8.2, 5.5 Hz, 1H), 3.71 (d, *J* = 5.5 Hz, 1H), 1.64 (s, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 153.3, 141.7, 134.8, 118.3, 110.2, 107.1, 81.4, 58.0, 48.2, 28.0. HRMS (Q–TOF Premier) calcd for $C_{13}H_{20}NO_3$ $(M+H)^+$: 238.1443; found: 238.1441. 99% ee [DAICEL CHIRALPAK AD, hexane/*i*-PrOH = 97/3, 210 nm, 0.8 mL/min; t_{R1} = 18.3 min (minor), t_{R2} = 15.7 min (major)]. $[\alpha]_D^{20}$ = 16.9 (*c* 1.0, $CHCl_3$).

(2*S*,3*S*)-*tert*-Butyl 2-amino-3-(furan-2-yl)pent-4-enoate [(*S*,*S*)-3l]: ^{1}H NMR analysis of the crude mixture showed a dr of >20:1. Light yellow oil, 49.4 mg, 83% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 2.1 Hz, 1H), 6.32 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.14 (d, *J* = 3.2 Hz, 1H), 6.00 (ddd, *J* = 17.4, 10.3, 7.4 Hz, 1H), 5.27 (dd, *J* = 10.3, 1.6 Hz, 1H), 5.21 (dd, *J* = 17.4, 1.6 Hz, 1H), 3.82 – 3.79 (m, 2H), 1.63 (s, 2H), 1.42 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 154.1, 141.6, 133.6, 119.0, 110.2, 106.8, 81.4, 57.7, 48.4, 28.0. HRMS (Q–TOF Premier) calcd for $C_{13}H_{20}NO_3$ $(M+H)^+$: 238.1443; found: 238.1443. >99% ee, HPLC [DAICEL CHIRALPAK AD, hexane/*i*-PrOH = 97/3, 210 nm, 0.8 mL/min; t_{R1} = 16.9 min (minor), t_{R2} = 22.2 min (major)]. $[\alpha]_D^{20}$ = -29.8 (*c* 1.0, $CHCl_3$).

(2*S*,3*R*)-*tert*-Butyl 2-(((benzyloxy)carbonyl)amino)-3-methylpent-4-enoate [(*R*,*S*)-3m-Cbz]: ^{1}H NMR analysis of the crude mixture showed a dr of 10:1. Light yellow oil, 62.2 mg, 78% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 4.4 Hz, 4H), 7.35 – 7.32 (m, 1H), 5.77 (ddd, *J* = 17.6, 10.4, 7.6 Hz, 1H), 5.13 (s, 2H), 5.10 (dd, *J* = 17.6, 1.4 Hz, 1H), 5.09 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.30 (dd, *J* = 9.0, 4.8 Hz, 1H), 2.68 (q, *J* = 6.8 Hz, 1H), 1.48 (s, 9H), 1.08 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 156.0, 138.7, 136.4, 128.5, 128.1, 128.1, 116.0, 82.2, 66.9, 58.2, 40.9, 28.1, 15.3. HRMS (Q–TOF Premier) calcd for $C_{18}H_{26}NO_4$ $(M+H)^+$: 320.1862; found: 320.1864. >99% ee [DAICEL CHIRALPAK IC-3, hexane/*i*-PrOH = 97/3, 210 nm, 1.0 mL/min; t_{R1} = 8.9 min (minor), t_{R2} = 10.1 min (major)].

(2*S*,3*S*)-*tert*-Butyl 2-(((benzyloxy)carbonyl)amino)-3-methylpent-4-enoate [(*S*,*S*)-3m-Cbz]: ^{1}H NMR analysis of the crude mixture showed a dr of 17:1. Light yellow oil, 58.3 mg, 73% yield. H NMR (500 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 4.4 Hz, 4H), 7.35 – 7.32 (m, 1H), 5.71 (ddd, *J* = 17.4, 10.8, 7.2 Hz, 1H), 5.20 (d, *J* = 10.8 Hz, 1H), 5.13 (s, 2H), 5.11 (d, *J* = 17.4 Hz, 1H), 4.28 (dd, *J* = 7.2, 4.4 Hz, 1H), 2.79 (q, *J* = 6.4 Hz, 1H), 1.48 (s, 9H), 1.11 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 156.4, 137.9, 136.5, 128.6, 128.3, 128.2, 116.7, 82.3, 67.1, 58.6, 40.4, 28.2, 16.1. HRMS (Q–TOF Premier) calcd for $C_{18}H_{26}NO_4$ $(M+H)^+$: 320.1862; found: 320.1866. >99% ee, HPLC [DAICEL CHIRALPAK IC-3, hexane/*i*-PrOH = 97/3, 210 nm, 1.0 mL/min; t_{R1} = 12.1 min (minor), t_{R2} = 9.6 min (major)].

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21472123, 21620102003, 81872418 and 21831005), Shanghai Municipal Education Commission (201701070002E00030), Science and Technology Commission of Shanghai Municipality (18ZR1431700) and Shanghai Municipal Commission of Health and Family Planning (2017YQ048). We also thank the Instrumental Analysis Center of SJTU for characterization.

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Enantioselective and Diastereodivergent Access to α-Substituted α-Amino Acids via Dual Iridium and Copper Catalysis

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