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Indium-Mediated Addition of γ-Substituted Allylic Halides to *N*-Aryl α-Imino Esters. Diastereoselective Production of β,β′-Disubstituted α-Amino Acid Derivatives with Two Contiguous Stereocenters

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Keywords: Synthetic methods / Allylation / Indium / Amino acids / Diastereoselectivity

Chelation-controlled Barbier-type indium-mediated addition of γ-substituted allylic halides to *N*-aryl (including *N*-PMP) α-imino- and *N*-acylhydrazono esters and highly diastereoselective tailoring of functionalized γ,δ-unsaturated β,β′-disubstituted *N*-aryl α-amino acid derivatives, bearing two contiguous stereocenters is reported. Further *N*-allylation of the resulting γ,δ-unsaturated β,β′-disubstituted *N*-aryl amino acid derivatives followed by ring closing metathesis (RCM) led to the synthesis of 2,3-disubstituted *N*-aryltetrahydropyridine derivatives bearing two contiguous stereocenters. The stereochemistry of the key products was unequivocally established from X-ray structure analyses.

Introduction

Isoleucine (natural) and alloisoleucine[1a] (unnatural) are γ,δ-hydrogenated versions of the γ,δ-unsaturated β,β′-disubstituted α-amino acids, bearing two contiguous stereocenters. The β,β′-disubstituted α-amino acids and γ- or δ-hydroxy β,β′-disubstituted α-amino acids form the core or subunits in various important natural products, for example, nikkomycin B,[1b] 4-hydroxyisoleucine,[1c] lysobactin[1d] and halipeptin A.[1e] The inclusion of β,β′-disubstituted α-amino acids into peptides provides conformational rigidity, enhanced activity, and resistance towards proteolysis.[2,3] Due to this biological importance and because of their value as synthetic building blocks, various excellent enantio- and stereoselective methods[3,4] have been developed for the synthesis of β,β′-disubstituted α-amino acid and γ,δ-unsaturated β,β′-disubstituted α-amino acid derivatives. Among the available methods,[3,4] stereoselective addition of α- and/or γ-substituted allyl metals to the C=N bond[4–6] of α-imino esters is one of the direct methods used to obtain the unnatural γ,δ-unsaturated β,β′-disubstituted α-amino acid derivatives having two contiguous stereocenters. In this regard, to the best of our knowledge, there exists only a few significant reports,[6] such as the stereoselective addition of (a) γ-substituted allylstannanes to *N*-tosyl α-imino esters by Jørgensen et al.,[6a] (b) γ-substituted allyltrichlorosilanes to α-hydrazono esters by Kobayashi et al.,[6b] (c) sulfonimidoyl-substituted bis(allyl)titanium complexes to *N*-sulfonyl α-imino esters by Gais et al.,[6c,6d] (d) α-methylallylboronate to *N*-acylhyrazones and crotylboronate addition to glyoxylic acid by Kobayashi et al.[6e,6f] and (e) γ-substituted allylmetals to oxime ethers by Ricci et al.[6g] and Hanessian et al.[6h] and ketimine derived from trifluoropyruvate by Zhang et al.[6i] Notably, in some of these versatile methods there is a need for prior preparation of α- and/or γ-substituted allylmetals and some of the reagents are relatively expensive.

In recent years, indium-mediated Barbier-type stereoselective allylation of carbonyl (C=O) and imino (C=N) functionalities have attracted the attention of many synthetic chemists.[7] This method has the advantage of involving the direct use of indium powder and allylic halides − thereby avoiding the requirement for prior preparation of allylic reagents − and the reactions can be accomplished in aqueous media. The indium-mediated nonstereoselective as well as stereoselective additions of simple allylic halides to C=N bond systems (aldimines, ketimines, hydrazones, oximes, and sulfonimines) have been well-studied.[8,9] However, there exists only a limited number of reports on the indium-mediated stereoselective addition of γ-substituted allylic halides to C=N bond systems such as oxime ethers,[10] sulfonimines,[11] acylhydrazones,[12] and imines derived from alkyl as well as arylamines,[13] leading to homoallylic amines with two contiguous stereocenters.

In spite of the encouraging developments on the indium-mediated stereoselective addition of allylic halides to C=N systems, a survey of the literature indicated that the theme of indium-based addition of simple as well as γ-substituted

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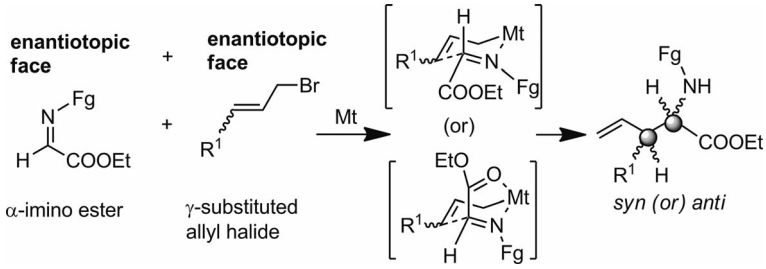
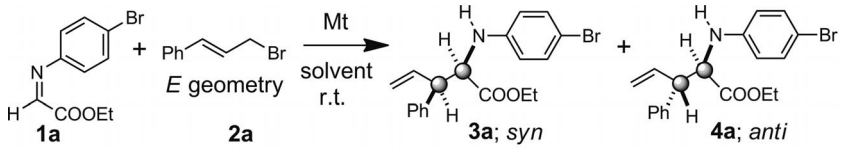
allylic reagents to C=N bond systems affording the γ,δ-unsaturated amino acid derivatives is an interesting and emerging topic of study.[14,15] Recently, Kang and coworkers[16] have reported the indium-mediated addition of γ,γ′-dimethyl allylindium to *N*-aryl α-imino esters for the synthesis of γ,δ-unsaturated β,β′-dimethyl *N*-aryl α-amino acid derivatives bearing only one chiral center.

We envisaged that addition of the γ-substituted allylindiums to α-imino esters would enable the construction of two contiguous stereogenic centers and the synthesis of highly functionalized γ,δ-unsaturated β,β′-disubstituted *N*-aryl α-amino acid derivatives having more than one stereocenter, as illustrated in Scheme 1. Control of the stereocenters during the addition of γ-substituted allylmetals to the C=N bond of *N*-aryl α-imino esters leading to diastereomers demands either a cyclic/rigid TS or a chelation-controlled TS. These two conditions require strong coordination acceptance and high nucleophilicity in the organo-



Scheme 1. Theme of this work: Barbier-type addition of γ-substituted allylindium compounds to *N*-aryl α-imino esters.

Table 1. Optimization of the addition of **2a** to **1a**.



Entry	Mt	Solvent [mL]	*t* [h]	**3a**; yield [%][a] [*syn*/*anti*]
1	In	DMF (1.5)	2	42 (98:2)
2	In	DMF (1.5)	12	48 (98:2)
3	In	THF (3)	12	52 (27)[b] (98:2)
4	In	THF (3)	12	53 (98:2)[c]
5	In	THF (3)	12	55 (98:2)[d]
6	In	DMF (1.5)/H_2O (1.5)	12	47 (98:2)
7	In	THF (2)/H_2O (4)	12	53 (98:2)
8	In	THF (4)/H_2O (2)	12	50 (98:2)
9	In	THF (3)/H_2O (3)	5	47 (98:2)
10	In	THF (3)/H_2O (3)	12	64 (98:2)[18b]
11	In	THF (3)/H_2O (3)	12	38 (98:2)[c]
12	In	THF (3)/H_2O (3)	12	67 (98:2)[e]
13	In	THF (3)/H_2O (3)	24	63 (98:2)[f]
14	In	THF (3)/H_2O (0.2)	12	66 (98:2)
15	In	THF (0.2)/H_2O (3)	12	50 (98:2)
16	In	THF (3)/satd. aq. NH_4Cl (3)	12	38 (98:2)
17	In	THF (3)/satd. aq. NH_4Cl (3)/MeCOOH (0.18)	12	40 (98:2)
18	Zn	THF (3)/H_2O (3)	12	27 (98:2)
19	Zn	THF (3)/satd. aq. NH_4Cl (3)	12	5
20	Zn	THF (3)/satd. aq. NH_4Cl (3)/MeCOOH (0.18)	12	26 (98:2)
21	Sn	THF (3)/H_2O (3)	12	5

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), metal (0.75 mmol). Isolated yields are given. [b] THF dried with activated molecular seives was used. In other cases, THF dried with sodium was used. [c] The reaction was carried out at 80 °C. [d] The reaction was carried out at –10 to 0 °C. [e] The reaction was carried out at 5 °C. [f] Indium powder was added in three portions (each portion was added after a 4 h interval).

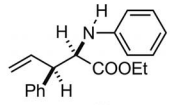
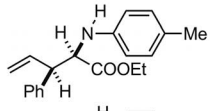
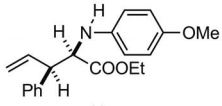
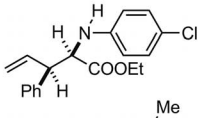
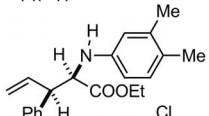
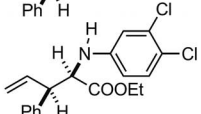
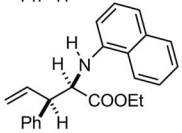
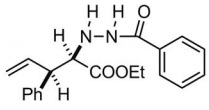
metallic reagents. Strikingly, the *N*-aryl α-amino acids form the core framework in various medicinal agents.[17] Hence, the development of new protocols for the synthesis of *N*-aryl α-amino acid derivatives will be highly beneficial (Scheme 1).

We herein report the direct Barbier-type indium-mediated addition of various γ-substituted allylic halides to *N*-aryl (including *N*-PMP) α-imino- and α-hydrazono esters. Our procedure has led to the highly diastereoselective production of γ,δ-unsaturated β,β′-disubstituted *N*-aryl α-amino acid derivatives and 2,3-disubstituted *N*-aryltetrahydropyridine derivatives bearing two contiguous stereocenters.

Results and Discussion

At the outset, to a mixture of α-imino ester **1a** and cinnamyl bromide (**2a**, *E* geometry) in anhydrous *N*,*N*-dimethylformamide (DMF), was added indium metal powder and the mixture was stirred at room temp. for 2 h; this gave the product **3a** in a 42% yield (*ds* 98:2, Table 1, entry 1). Prolonging the reaction time to 12 h resulted the formation of product **3a** in 48% yield (Table 1, entry 2). The cinnamylation of **1a** in anhydrous tetrahydrofuran (THF) gave the product **3a** in a 52% yield (Table 1, entry 3). In anhydrous THF, increasing or lowering the reaction temperature did not alter the yield (Table 1, entries 4 and 5). We then employed a DMF/H_2O mixture, which also furnished the product **3a** (47%, Table 1, entry 6). Next, various THF/H_2O combinations were tested (Table 1, entries 7–10). THF/water combinations were also found to promote the stereoselective formation of the *syn* isomer **3a**, bearing two contiguous stereocenters. At ambient temperature, 64% yield of the *syn* isomer **3a**[18a] (*ds* 98:2) was obtained for a 12 h reaction time (Table 1, entry 10). The reaction in THF/water at 80 °C gave only 38% yield of the product **3a** (Table 1, entry 11). The reaction in THF/water at 5 °C yielded a slight increment in yield of **3a** (67%; Table 1, en-

Table 2. Stereoselective cinnamylation of **1b**–**i**.[18a]

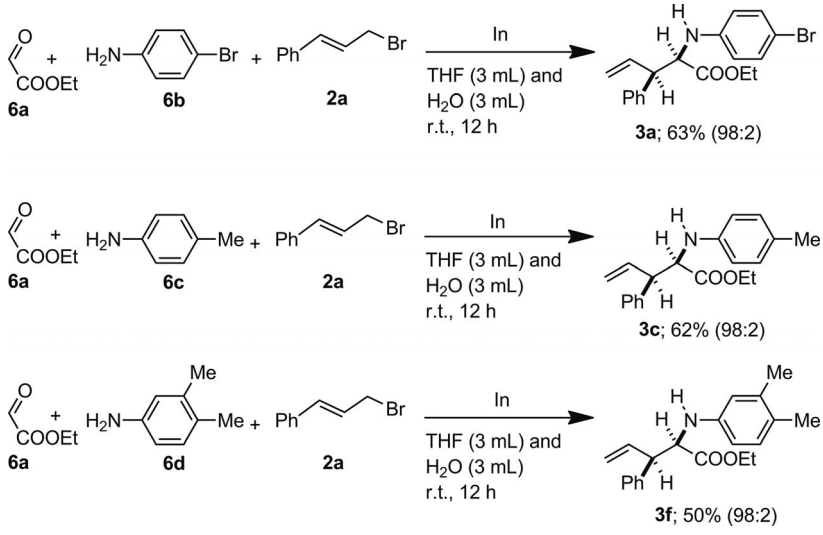
Entry	—Fg	Product	Yield [%][a] [*syn* / *anti*]
1	**1b**		**3b**; 71 (98:2)
2	**1c**		**3c**; 65 (98:2)
3	**1d**		**3d**; 60 (98:2)
4	**1e**		**3e**; 65 (98:2)
5	**1f**		**3f**; 70 (98:2)
6	**1g**		**3g**; 57 (98:2)
7	**1h**		**3h**; 50 (98:2)
8	**1i**		**3i**; 71 (75:25)

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), metal (0.75 mmol). Isolated yields are given.

try 12). Portionwise addition of indium powder to the reaction in THF/water at ambient temperature also gave only 63% of the product **3a** (Table 1, entry 13). Significantly, small amounts of water in THF or small amounts of THF in water gave the product **3a** in 66 and 50% yields, respectively (Table 1, entries 14 and 15). Inclusion of various additives did not improve the yield of **3a** (Table 1, entries 16 and 17). Employing Zn dust afforded low yields, and Sn powder failed to yield the product **3a** in good yields (Table 1, entries 18–21). Hence, indium metal powder and THF/water system were established as the best choice for the diastereoselective production of **3a** (*syn* isomer) bearing two contiguous stereocenters.

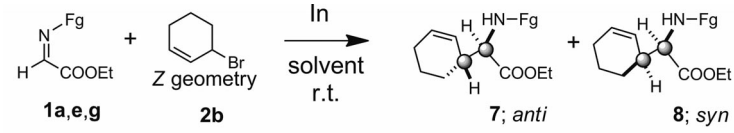
The scope of the Barbier-type cinnamylation was tested by using various α-imino esters **1b**–**i** (Table 2). The indium-mediated cinnamylation of α-imino esters prepared from anilines with electron-withdrawing or -donating groups furnished the respective α-amino acid derivatives **3b**–**g** (*syn* isomers, *ds* 98:2; Table 2, entries 1–6). The cinnamylation of **1h**, obtained from α-naphthylamine, gave the *syn* isomer **3h** (Table 2, entry 7). The reaction of **2a** with α-hydrazono ester **1i** afforded the α-amino acid derivative **3i** with moderate diastereoselectivity (*ds* 75:25; Table 2, entry 8).

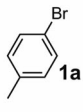
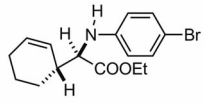
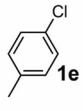
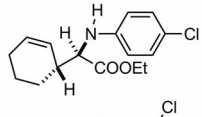
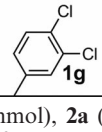
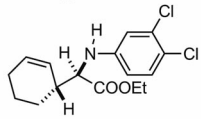
The exclusive formation of the *syn* products **3a**–**i**[18a,18e] in the cinnamylation of α-imino esters **1a**–**i** could be explained by a chelation TS in aqueous media (Model B, Figure 1). The allylindium compounds are tolerant to water[7] and, in these reactions, the aqueous media contributes to the rapid quenching of the transient indium amide, formed after the addition of allylindium; furthermore, the very high



Scheme 2. One-pot multicomponent reactions. *Reagents and conditions:* **6a** (0.5 mmol), **6b**–**d** (0.5 mmol), **2a** (1.25 mmol), In (0.75 mmol). Isolated yields are given.

Table 3. Stereoselective addition of **2b** to **1**.[18a]



Entry	—Fg	Solvent [mL]	*t* [h]	Product	Yield [%][a] [*anti* / *syn*]
1		THF (3)/H_2O (3)	12		**7a**; < 5
2		THF (3)/H_2O (3)	24		**7a**; < 5
3		THF (3)	12		**7a**; 50 (98:2)
4		THF (3)	12		**7a**; 40 (98:2)[b]
5		THF (1)	12		**7a**; 44 (98:2)
6		THF (3)	24		**7b**; 45 (98:2)
7		THF (3)	24		**7c**; 45 (98:2)

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), metal (0.75 mmol). Isolated yields are given. [b] This reaction was carried out using Zn dust (2 mmol) instead of In.

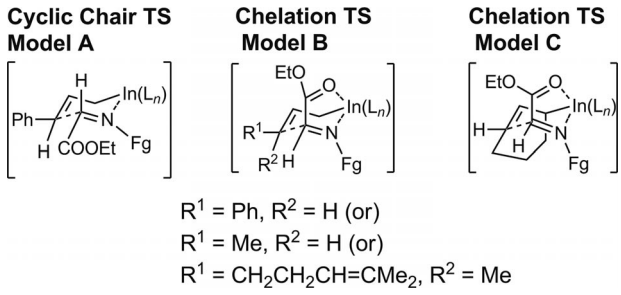
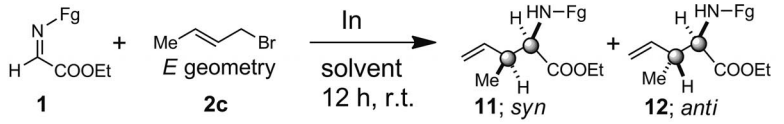
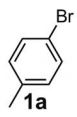
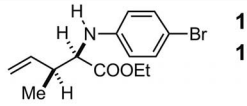
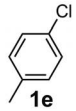
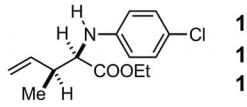
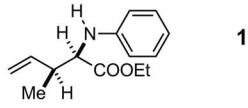
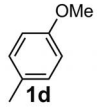
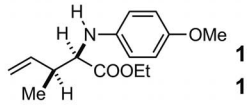
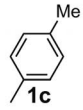
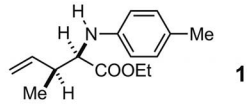
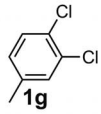
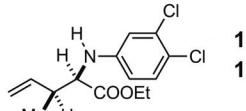
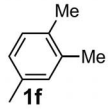
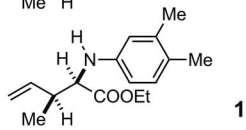
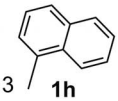
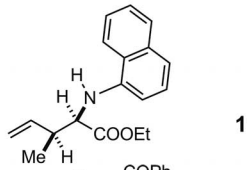
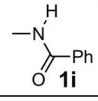
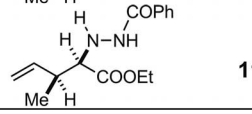


Figure 1. Plausible transition states for the observed diastereoselectivity.

stereoselectivity observed revealed that the addition process was kinetically controlled. In the transition state, involvement of both the indium(III) species as well as indium(I) species is possible, as proposed in various reports. The formation of two discrete species from cinnamyl bromide and indium in [D_8]THF/D_2O was observed (see NMR spectra of the Supporting Information in reference[7i]) in ^{1}H NMR studies by various groups,[19a–19i] including us, and the addition of a carbonyl compound to both the species revealed that one species was more reactive than the other species. The nature of the active indium species remains elusive because of its fleeting character.[7a,7j,19a–19i] Recent reports

Table 4. Stereoselective crotylation of α-imino ester **1**.[18a]

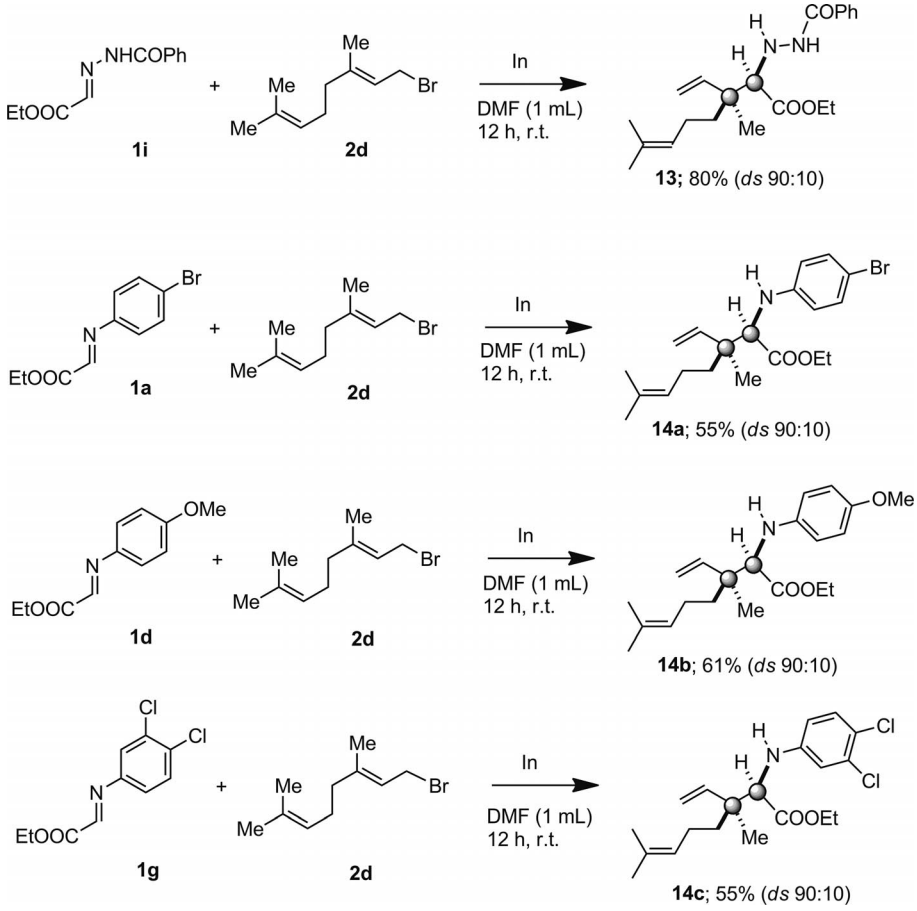


Entry	—Fg	Solvent [mL]	Product	Yield [%][a] [*syn* / *anti*]
1	 **1a**	THF (3)/H_2O (3)		**11a**; 43 (98:2)[b]
2		THF (3)/H_2O (3)		**11a**; 61 (98:2)[18b]
3	 **1e**	THF (3)/H_2O (3)		**11b**; 60 (98:2)
4		THF (4)/H_2O (2)		**11b**; 52 (98:2)
5		THF (2)/H_2O (4)		**11b**; 46 (98:2)
6	 **1b**	THF (3)/H_2O (3)		**11c**; 54 (98:2)
7	 **1d**	THF (3)/H_2O (3)		**11d**; 59 (98:2)
8		DMF (2)		**11d**; 82 (75:25)[c,d]
9	 **1c**	THF (3)/H_2O (3)		**11e**; 59 (98:2)
10	 **1g**	THF (3)		**11f**; 43 (98:2)
11		THF (3)/H_2O (3)		**11f**; 49 (98:2)
12	 **1f**	THF (3)/H_2O (3)		**11g**; 48 (98:2)
13	 **1h**	THF (3)/H_2O (3)		**11h**; 40 (98:2)
14	 **1i**	THF (3)/H_2O (3)		**11i**; 65 (75:25)[d]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), metal (0.75 mmol). Isolated yields are given. [b] Reaction time was 6 h. [c] Reaction time was 2 h. [d] The products **11d** and **11i** were isolated as a mixture of diastereomers.

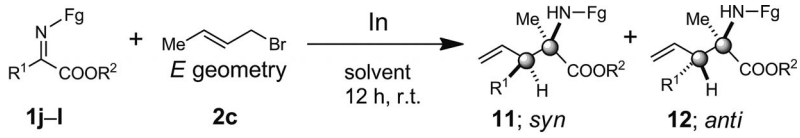
strongly suggest the involvement of an In^{III} species in the TS (proposed by Singaram,[19a] Baba[7r,19b–19f] and Koszinowski[19g]); however, in the present reactions, the involvement of an In^{I} species (proposed by Chan[19h] and Hilt[19i]) is also very likely, as a chelation-controlled/rigid TS, which is essential for the high diastereoselectivity,[7i,19e,19f] might favor a low-valent indium species.

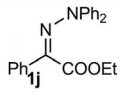
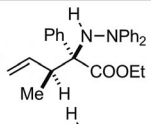
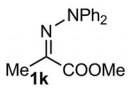
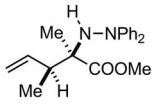
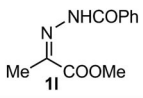
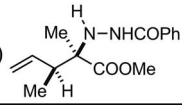
The direct indium-mediated three-component one-pot reaction of ethyl glyoxalate (**6a**), amines **6b–d** and cinnamyl bromide (**2a**) was then performed. The one-pot indium-me-



Scheme 3. Stereoselective geranylation of α-imino ester **1**. *Reagents and conditions:* **1** (1 mmol), **2d** (2 mmol), NaI (2 mmol), In (1.5 mmol). Isolated yields are given.

Table 5. Stereoselective crotylation of α-imino esters **1j–l**.[18a]



Entry	1j–l	Solvent [mL]	Product	Yield [%][a] [*syn* / *anti*]
1		THF (3)		**11j**; 0
2		THF (3)/H_2O (3)		**11j**; 0
3		THF (3)/H_2O (3)		**11k**; 0
4		THF (3)		**11l**; 81 (70:30)
5		THF (3)/H_2O (3)		**11l**; 63 (72:28)

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), metal (0.75 mmol). Isolated yields are given.

diated cinnamylation in aqueous media exclusively afforded the respective α-amino acid derivatives **3a**, **3c**, and **3f** (*syn* isomers, *ds* 98:2, Scheme 2).

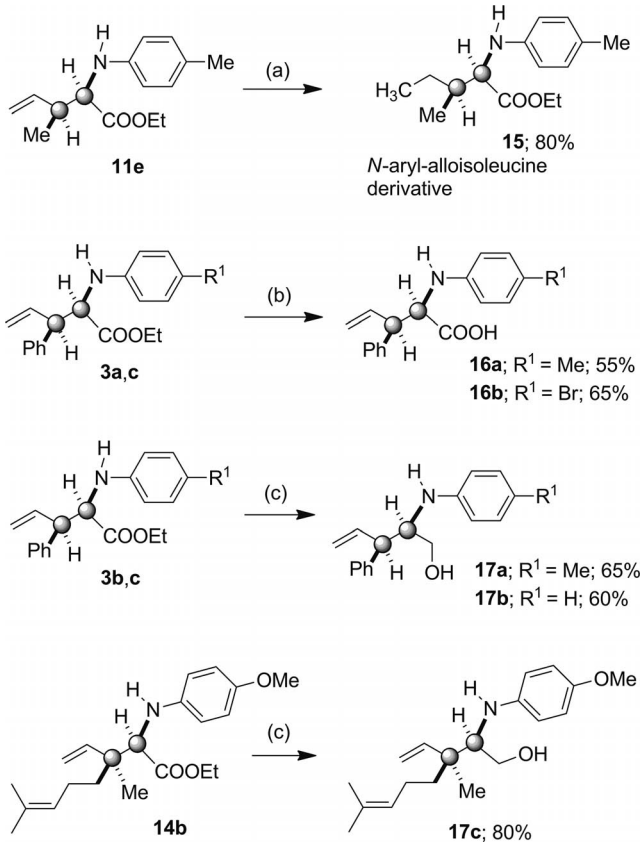
We then focused our attention on the optimization of the Barbier-type indium-mediated direct addition of cyclohexenyl bromide (**2b**, *Z* geometry) to the α-imino esters **1a**, **1e**, and **1g** (Table 3). In contrast to the cinnamyl bromide case, the indium-mediated addition of **2b** to **1a** in aqueous media failed to give the products **7/8** (Table 3, entries 1 and 2), perhaps because the cyclohexenylindium was unstable in aqueous media.[7i] However, a smooth reaction of the α-imino ester **1a** and **2b** in anhydrous THF furnished the α-amino acid derivative **7a** (*anti* isomer) bearing two contiguous stereocenters (*ds* 98:2, Table 3, entry 3). The indium-mediated one-pot treatment of cyclohexenyl bromide (**2b**), 4-bromo aniline, and ethyl glyoxalate in THF also afforded the product **7a** in a 44% yield (Table 3, entry 5). Similarly, the α-imino esters **1e** and **1g** also reacted with **2b** to furnish the *anti* isomers **7b** and **7c**, respectively (Table 3, entries 6 and 7). The exclusive formation of *anti* products **7a**–**c** could be accounted for by a chelation TS (Model C, Figure 1).

The reactivity pattern of the crotyl bromide (**2c**, *E* geometry) with α-imino esters was subsequently investigated (Table 4). The reaction of crotylindium with **1a** in THF/water (1:1) was optimized to afford the *syn* isomer of the α-amino acid derivative **11a** (61%, *ds* 98:2, Table 4, entries 1 and 2). Similarly, the product **11b** was obtained in a 60% yield (Table 4, entry 3). Changing the ratio of the THF/water did not improve the yield of **11b** (Table 4, entries 4 and 5). The indium-mediated crotylation of **1b**–**d** gave the respective products **11c**–**e** (Table 4, entries 6–9). Although the yield of **11d** was high in DMF, a somewhat lower diastereoselectivity was observed (*ds* 75:25). The crotylation of α-imino esters **1f**–**h** furnished the respective *syn* isomers **11f**–**h** (Table 4, entries 10–13). Successful addition of crotylindium to the α-hydrazono ester **1i** gave the product **11i** (65%) with reasonably good diastereoselectivity (*ds* 75:25, Table 4, entry 14). The exclusive formation of *syn* products **11a**–**i** in these reactions could be accounted for by a chelation TS (Model B, Figure 1).

Next, we studied the reaction of geranyl bromide (**2d**, *E* geometry) with α-hydrazono- and α-imino esters (Scheme 3). The α-hydrazono ester **1i** and α-imino esters **1a**, **1d**, and **1g** underwent stereoselective geranylation to give the respective β,β′-disubstituted α-amino acid derivatives **13** and **14a**–**c** (*ds* 90:10), bearing a terpene unit and two contiguous stereocenters (including an all carbon quaternary center).[18c]

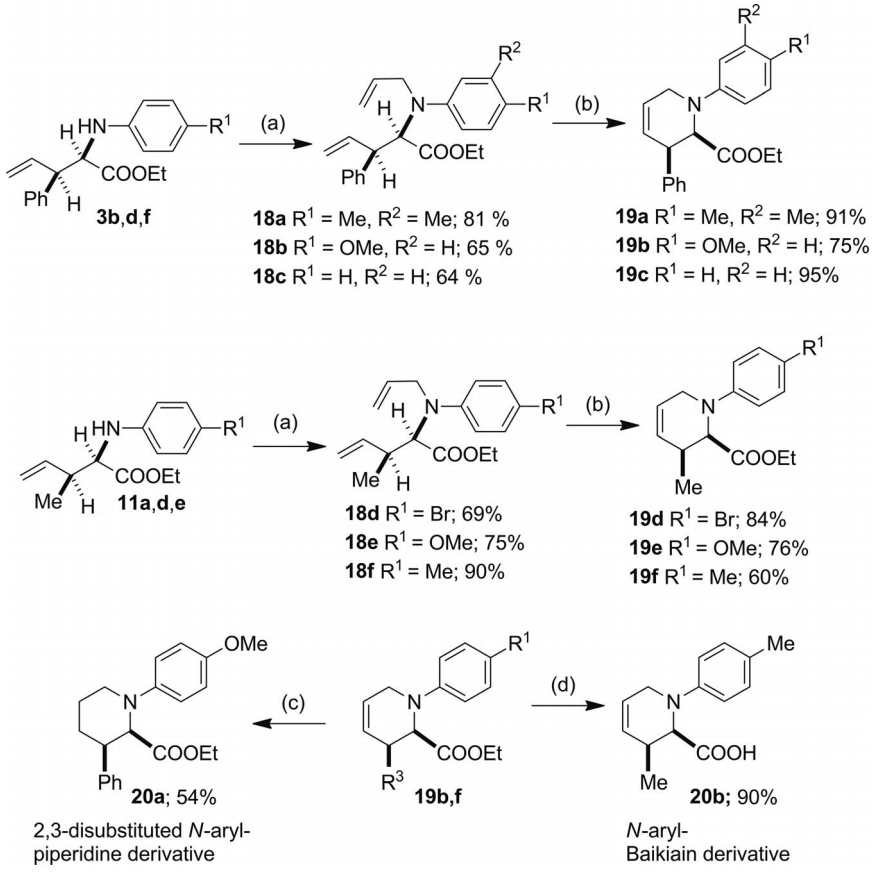
Subsequently, the addition of crotyl bromide (**2c**, *E* geometry) to hydrazono esters **1j**–**l**, prepared from ethyl benzoylformate and methyl pyruvate, was studied (Table 5). The reaction of crotylindium with *N*,*N*-diphenyl hydrazono esters **1j** and **1k** in anhydrous THF or THF/water (1:1) did not afford any product (Table 5, entries 1–3) and the starting materials **1j** and **1k** were recovered. This was perhaps due to their low reactivity with crotyl indium. Treatment of acylhydrazone derived from methyl pyruvate **1l** with crotylindium afforded the product **11l** in anhydrous THF, as well as in THF/water mixture (Table 5, entries 4 and 5). In these cases, a moderate diastereoselectivity was observed, probably due to the involvement of a less rigid cyclic TS species.

The scope of this method is delineated in Scheme 4. The hydrogenation of a representative compound **11e** led to the synthesis of a novel *N*-aryl alloisoleucine derivative **15**. The hydrolysis of compounds **3a** and **3c** gave the respective unnatural β,β′-disubstituted *N*-aryl α-amino acids **16a** and **16b**. Reduction of the ester group of the representative compounds **3b**, **3c**, and **14b** afforded the respective novel δ,ω-unsaturated γ,γ′-disubstituted *N*-aryl β-amino alcohols **17a**–**c**, bearing two contiguous stereocenters.[18d]



Scheme 4. Scope and generality. *Reagents and conditions:* (a) H_2 (1 atm), Pd/C (10 mol-%), THF, room temp.; (b) 1 M Aq. KOH, MeOH, reflux, 48 h; (c) $LiAlH_4$ (2 equiv.), THF, 0 °C to room temp., 12 h.

Finally, we were interested in extending the utility of this synthetic protocol and constructing 2,3-disubstituted *N*-aryltetrahydropyridine derivatives bearing two contiguous stereocenters (Scheme 5). N-Allylation of γ,δ-unsaturated β,β′-disubstituted *N*-aryl α-amino acid derivatives **3b**, **3d**, **3f** and **11a**, **11d**, and **11e**, obtained from the stereoselective cinnamylation and crotylation of the α-imino esters **1**, respectively, gave the products **18a**–**f**. The reaction of **18a**–**f** in the presence of a catalytic amount of Grubb's 2nd generation catalyst[20a–d] successfully afforded, the 2,3-disubstituted *N*-aryltetrahydropyridine derivatives **19a**–**f**, bearing two contiguous stereocenters, in very good yields. Next, the hydrogenation of



Scheme 5.[18d] Scope and generality. *Reagents and conditions:* (a) K_2CO_3 (3 equiv.), NaI (0.1 equiv.), allyl bromide (6 equiv.), MeCN, reflux, 24–48 h; (b) Grubb's 2nd generation catalyst (0.05–0.1 equiv.), CH_2Cl_2, room temp., overnight; (c) H_2 (1 atm), Pd/C (10 mol-%), THF, room temp.; (d) 1 M aq. KOH, MeOH, 90–95 °C, 48 h.

a representative compound **19b** led to the synthesis of 2,3-disubstituted *N*-aryl piperidine derivative **20a**. Hydrolysis of **19f** gave 3-methyl-1-(*p*-tolyl)-1,2,3,6-tetrahydropyridine-2-carboxylic acid (**20b**)[19j] (*N*-aryl Baikiain analogue[19k]).

Conclusions

A highly diastereoselective C–C bond formation synthetic protocol was established by using the direct Barbier-type indium-mediated addition of various γ-substituted allylic halides to *N*-aryl α-imino esters and α-hydrazono esters. Production of γ,δ-unsaturated β,β′-disubstituted *N*-aryl (including *N*-PMP) α-amino acid derivatives bearing two contiguous stereocenters, with remarkable diastereoselectivity, was accomplished. Furthermore, the synthetic utility of this protocol has been illustrated by efficiently constructing various 2,3-disubstituted *N*-aryltetrahydropyridine, 2,3-disubstituted *N*-aryl piperidine, and *N*-aryl Baikiain derivatives, bearing two contiguous stereocenters.

Experimental Section

General: Melting points are uncorrected. IR spectra were recorded as thin films or KBr pellets. ^1H and ^{13}C NMR spectra were recorded with 400 and 100 MHz spectrometers, respectively, with TMS as an internal or external standard. Column chromatography was carried out on silica gel (100–200 mesh) or neutral Al_2O_3. Reactions were conducted in anhydrous solvent under nitrogen atmosphere where required. Solutions were dried using anhydrous sodium sulfate. Reagents were added to the reaction flask by using a syringe. Thin layer chromatography (TLC) was performed on silica plates or neutral Al_2O_3 and components were visualized by observation under iodine. Isolated yields of all the products are reported (yields were not optimized). Ratios of diastereomers were determined from the ^1H and ^{13}C NMR spectra of either crude reaction mixtures or after isolation; in all the reactions, only the major diastereomer was isolated in pure form. The ratio of diastereoselectivity (*ds* 98:2) refers to the predominant presence of the major diastereomer and rarely, traces of the corresponding minor isomer in the NMR spectrum of the crude reaction mixture. After the column purification, we did not observe any minor diastereomer.

Procedure A. Indium-Mediated Addition of Cinnamyl Bromide (2a) to α-Imino Esters 1: To a vigorously stirring solution of α-imino ester **1**[20e] (0.5 mmol, 1 equiv.) and *E*-cinnamyl bromide (**2a**; 1.25 mmol, 2.5 equiv.) in THF (3 mL) and H_2O (3 mL), was added indium powder (0.75 mmol, 1.5 equiv.). The mixture was stirred vigorously for 12 h at room temp., then transferred to a separating funnel and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4, then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on neutral alumina or silica gel (EtOAc/hexane) gave the product **3** (see Tables 1 and 2 for individual entries).

Procedure B. One-Pot Synthesis of *N*-Aryl α-Amino Esters (3a, 3c, and 3f): Ethyl glyoxylate **6a** (0.6 mmol, 1.2 equiv.) and the respective amine **6b**–**d** (0.5 mmol, 1 equiv.) were dissolved in THF (2 mL) and stirred for 15 min at room temp. To the resulting solution, *E*-cinnamyl bromide (**2a**; 1.25 mmol, 2.5 equiv.), THF (1 mL) and H_2O (3 mL) were added. Indium powder (0.75 mmol, 1.5 equiv.) was added while stirring the reaction mixture vigorously, and stirring was continued for 12 h at room temp. After this period, the reaction mixture was transferred to a separating funnel and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4, then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on neutral alumina (EtOAc/hexane) gave the products (**3a, 3c**, and **3f**) (see Scheme 2 for individual entries).

Procedure C. Indium-Mediated Addition of Cyclohexenyl Bromide (2b) to α-Imino Esters 1: To a vigorously stirring solution of α-imino ester **1** (0.5 mmol, 1 equiv.) and *Z*-cyclohexenyl bromide (**2b**; 1.25 mmol, 2.5 equiv.) in THF (3 mL), was added indium powder (0.75 mmol, 1.5 equiv.). The mixture was stirred vigorously for 12 h at room temp. under a nitrogen atmosphere. After this period, water (10 mL) was added to the reaction mixture, which was then transferred to a separating funnel and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and the solvent was then evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on neutral alumina (EtOAc/hexane) gave the product **7** (see Table 3 for individual entries).

Procedure D. Indium-Mediated Addition of Crotyl Bromide (2c) to α-Imino Esters 1: To a vigorously stirring solution of α-imino ester **1** (0.5 mmol, 1 equiv.) and *E*-crotyl bromide (**2c**; 1.25 mmol, 2.5 equiv.) in THF (3 mL) and H_2O (3 mL) was added indium powder (0.75 mmol, 1.5 equiv.). The mixture was stirred vigorously for 12 h at room temp., then transferred to a separating funnel and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4, then the solvent was then evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on neutral alumina or silica gel (EtOAc/hexane) gave the product **11** (see Table 4 and Table 5 for individual entries).

Procedure E. Indium-Mediated Addition of Geranyl Bromide (2d) to α-Imino Esters 1: To a vigorously stirring solution of α-imino ester **1** (1 mmol, 1 equiv.) in anhydrous DMF (2 mL) was sequentially added indium powder (1.5 mmol, 1.5 equiv.), sodium iodide (2 mmol, 2 equiv.), and *E*-geranyl bromide (**2d**; 2 mmol, 2 equiv.). The mixture was stirred vigorously for 12–24 h at room temp. under a nitrogen atmosphere, then water (5–10 mL) was added. The resulting reaction mixture was transferred to a separating funnel and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4, then the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on neutral alumina (EtOAc/hexane as eluent) gave the products **13** and **14** [major diastereomers, see Scheme 3 for individual entries].

Procedure F. Hydrogenation[21] of *N*-Aryl α-Amino Esters 11e to *N*-Aryl Alloisolucine Derivative 15: A dry flask containing *N*-aryl α-amino ester **11e** (0.5 mmol, 1 equiv.) in anhydrous THF (4 mL) was charged with Pd-C (10 mol-%) and the contents were stirred under H_2 (1 atm) at room temp. After disappearance of starting material (reaction monitored by TLC) the reaction mixture was filtered through a Celite pad and rinsed with EtOAc (20 mL). The solvent was removed by rotary evaporation and the product was purified by column chromatography on silica gel (EtOAc/hexane) to afford the *N*-aryl alloisolucine derivative **15** (Scheme 4). Compound **19b** (0.15 mmol, 1 equiv.) was hydrogenated in anhydrous THF (2 mL) using Pd-C (10 mol-%) and the contents were stirred under H_2 (1 atm) at room temp. to afford the product **20a** (Scheme 5).

Procedure G. Hydrolysis[22] of the *N*-Aryl α-Amino Esters 3a,c and the Synthesis of Unnatural *N*-Aryl α-Amino Acids 16a,b: The respective *N*-aryl α-amino ester **3a**,**c** (0.5 mmol, 1 equiv.) was hydrolyzed by heating to reflux with 1 M aq. potassium hydroxide (3 mL) and methanol (1 mL) for 48 h. After this period the reaction mixture was cooled to room temp., transferred to a separating flask, and washed with CH_2Cl_2 (2 × 10 mL). To the reaction mixture was added aq. HCl dropwise and the solid products were filtered to afford the corresponding *N*-aryl α-amino acids **16a**,**b** (Scheme 4). Compound **19f** (0.2 mmol, 1 equiv.) was hydrolyzed by heating to reflux with 1 M aq. potassium hydroxide (2 mL) and methanol (0.05 mL) for 48 h to afford the product **20b** (Scheme 5).

Procedure H. Reduction[23] of *N*-Aryl α-Amino Esters 3/14 to *N*-Aryl β-Amino Alcohols 17: A dry flask was charged with anhydrous THF (4 mL) and the respective *N*-aryl α-amino ester **3b**, **3c** or **14b** (0.5 mmol) under a nitrogen atmosphere, at 0 °C. To this solution was added $LiAlH_4$ (1 mmol) in portions and the mixture was stirred overnight at room temp. EtOH (few drops) and water (1–2 mL) were then added sequentially and the resulting white suspension was filtered through a Celite pad and rinsed with THF (20 mL). The filtrate was dried with anhydrous Na_2SO_4, the solvent was removed by rotary evaporation, and the product was purified by column chromatography on silica gel (EtOAc/hexane) to afford the respective *N*-aryl α-amino alcohols **17a**–**c** (Scheme 4).

Procedure I. *N*-Allylation of γ,δ-Unsaturated β,β′-Disubstituted *N*-Aryl α-Amino Acid Derivatives 3b,d,f and 11a,d,e: To the respective *N*-aryl α-amino ester **3b**,**d**,**f** and **11a**,**d**,**e** (1 mmol, 1 equiv.) in MeCN (5 mL) was added allyl bromide (6 equiv.), NaI (0.1 equiv.), and activated K_2CO_3 (3 equiv.). The resulting reaction mixture was heated to reflux for 24–48 h. After completion of the reaction as indicated by the TLC, the reaction mixture was cooled to room temp., water (5–6 mL) was added, and the resulting reaction was transferred to a separating flask and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane) gave the products **18a**–**f** (see Scheme 5 for individual entries).

Procedure J. Synthesis of 19a–f by RCM of Compounds 18a–f: To the respective compounds **18a**–**f** (0.5 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (2 mL) was added Grubb's 2nd generation catalyst (0.05–0.1 equiv.), and the resulting reaction mixture was stirred overnight at room temp. After completion of the reaction as indicated by the TLC, the reaction mixture was subjected to rotary evaporation. Purification of the resulting crude reaction mixture by column chromatography on silica gel (EtOAc/hexane) gave the products **19a**–**f** (see Scheme 5 for individual entries).

(2*R*,3*R*)-Ethyl 2-[(4-Bromophenyl)amino]-3-phenylpent-4-enoate (3a): Following the general procedure A as described above, **3a** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless solid; yield 66%; m.p. 89–91 °C (Hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 3363, 2958, 1725, 1594, 1181, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32 (t, J = 6.9 Hz, 2 H), 7.26–7.19 (m, 5 H), 6.46 (d, J = 8.8 Hz, 2 H), 6.18–6.09 (m, 1 H), 5.22–5.17 (m, 2 H), 4.29 (t, J = 8.4 Hz, 1 H), 4.14–4.06 (m, 2 H), 4.02 (d, J = 8.4 Hz, 1 H), 3.78 (t, J = 8.4 Hz, 1 H), 1.17 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 145.8, 139.1, 136.6, 132.0, 128.8, 128.0, 127.3, 118.0, 115.4,

110.3, 61.2, 61.1, 53.0, 14.2 ppm. HRMS (ESI): calcd. for $C_{19}H_{20}BrNO_2Na$ [M + Na]$^+$ 396.0575; found 396.0570. Along with the main product **3a**, minor products such as **5a** (5%), **5b** (12%) and **5c** (8%) were also observed (in all other cases, only the diastereoisomer **3** was isolated in pure form). See the Supporting Information for the structures of **5a**–**c**.

4-Bromo-*N*,*N*-dicinnamylaniline (5a):[18b,24] Obtained after column chromatography (EtOAc/hexanes, 0.5:99.5) as a colorless solid; yield 5%; m.p. 96–98 °C. IR (KBr): $\tilde{\nu}$ = 2923, 1588, 1494, 967, 732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.19 (m, 12 H), 6.65 (d, J = 9.0 Hz, 2 H), 6.49 (d, J = 15.9 Hz, 2 H), 6.21 (td, J_1 = 15.9, J_2 = 5.0 Hz, 2 H), 4.08 (d, J = 5.0 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 136.7, 131.9, 131.4, 128.6, 127.6, 126.4, 125.2, 114.3, 108.5, 52.4 ppm. MS (CI): *m*/*z* (%) = 406 (85) [M + 3]$^+$, 404 (100) [M + 1]$^+$.

4-Bromo-*N*-cinnamylaniline (5b):[18b,24,25] Obtained after column chromatography (EtOAc/hexanes, 1:99) as a colorless solid; yield 12%; m.p. 75–77 °C. IR (KBr): $\tilde{\nu}$ = 3401, 2926, 1591, 1492, 969, 746 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.21 (m, 7 H), 6.59 (d, J = 15.9 Hz, 1 H), 6.52 (d, J = 8.8 Hz, 2 H), 6.27 (td, J_1 = 15.9, J_2 = 4.4 Hz, 1 H), 3.89 (d, J = 4.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.0, 136.7, 132.0, 131.7, 128.6, 127.7, 126.4, 126.3, 114.6, 109.2, 46.1 ppm. MS (CI): *m*/*z* (%) = 288 (100) [M + 1]$^+$, 286 (90), 210 (10), 208 (13).

Ethyl 2-Hydroxy-3-phenylpent-4-enoate (5c):[26] Obtained after column chromatography (EtOAc/hexanes, 4:96) as a colorless liquid; yield 8%. IR (neat): $\tilde{\nu}$ = 3459, 2979, 1731, 1494, 1257 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 5 H), 6.26–6.17 (m, 1 H), 5.22 (d, J = 7.5 Hz, 1 H), 5.19 (s, 1 H), 4.50 (d, J = 4.1 Hz, 1 H), 4.13 (q, J = 7.1 Hz, 2 H), 3.77 (dd, J_1 = 7.5, J_2 = 4.1 Hz, 1 H), 2.69 (s, 1 H), 1.21 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 138.3, 137.4, 128.8, 128.4, 127.3, 117.0, 74.0, 61.7, 53.4, 14.2 ppm. MS (CI): *m*/*z* (%) = 221 (35) [M + 1]$^+$, 203 (60), 175 (35), 157 (37). This compound was isolated as a mixture of diastereomers; the NMR data refer to the major isomer.

Ethyl (2*R*,3*R*)-3-Phenyl-2-(phenylamino)pent-4-enoate (3b): Following the general procedure A as described above, **3b** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless oil; yield 71%. IR (CH_2Cl_2): $\tilde{\nu}$ = 3388, 2980, 1734, 1602, 1506, 1181 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (t, J = 6.5 Hz, 2 H), 7.23 (d, J = 6.5 Hz, 3 H), 7.12 (t, J = 7.5 Hz, 2 H), 6.71 (t, J = 7.5 Hz, 1 H), 6.59 (d, J = 7.5 Hz, 2 H), 6.20–6.11 (m, 1 H), 5.22–5.16 (m, 2 H), 4.34 (t, J = 8.5 Hz, 1 H), 4.14–4.05 (m, 2 H), 4.0 (d, J = 8.5 Hz, 1 H), 3.79 (t, J = 8.5 Hz, 1 H), 1.16 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 146.7, 139.4, 136.9, 129.3, 128.8, 128.0, 127.3, 118.6, 117.8, 113.8, 61.3, 61.0, 53.2, 14.2 ppm. MS (CI): *m*/*z* (%) = 296 (5) [M + 1]$^+$, 223 (20), 222 (100), 180 (20), 178 (22), 104 (80). HRMS (ESI): calcd. for $C_{19}H_{21}NO_2Na$ [M + Na]$^+$ 318.1470; found 318.1460.

Ethyl (2*R*,3*R*)-3-Phenyl-2-(*p*-tolylamino)pent-4-enoate (3c): Following the general procedure A as described above, **3c** was obtained after purification by neutral alumina column chromatography (EtOAc/hexanes, 2:98) as a colorless solid; yield 65%; m.p. 67–69 °C. IR (KBr): $\tilde{\nu}$ = 3359, 2911, 1724, 1619, 1524, 1181 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (t, J = 7.6 Hz, 2 H), 7.23 (d, J = 7.6 Hz, 3 H), 6.93 (d, J = 8.4 Hz, 2 H), 6.51 (d, J = 8.4 Hz, 2 H), 6.19–6.10 (m, 1 H), 5.22–5.15 (m, 2 H), 4.30 (d, J = 7.2 Hz, 1 H), 4.12–4.04 (m, 2 H), 3.88 (s, 1 H), 3.77 (t, J = 7.2 Hz, 1 H), 2.19 (s, 3 H), 1.15 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 144.5, 139.5, 137.0, 129.8, 128.8, 128.0, 127.8, 127.2, 117.8, 114.0, 61.7, 60.9, 53.2, 20.4, 14.2 ppm. MS (CI): *m*/*z* (%) = 310 (5) [M + 1]$^+$, 237 (22), 236 (100), 220 (12), 192 (22), 118 (88). HRMS (ESI): calcd. for $C_{20}H_{23}NO_2Na$ [M + Na]$^+$ 332.1626; found 332.1626.

Ethyl (2*R*,3*R*)-2-[(4-Methoxyphenyl)amino]-3-phenylpent-4-enoate (3d): Following the general procedure A as described above, **3d** was obtained after purification by neutral alumina column chromatography (EtOAc/hexanes, 3:97) as a colorless solid; yield 60%; m.p. 74–76 °C (Hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 3361, 2955, 1727, 1520, 1238, 1187 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (t, J = 8.0 Hz, 2 H), 7.22 (d, J = 8.0 Hz, 3 H), 6.70 (d, J = 8.9 Hz, 2 H), 6.54 (d, J = 8.9 Hz, 2 H), 6.16–6.10 (m, 1 H), 5.20–5.14 (m, 2 H), 4.24 (d, J = 7.3 Hz, 1 H), 4.10–4.04 (m, 2 H), 3.77–3.71 (m, 1 H), 3.68 (s, 3 H), 3.38 (s, 1 H), 1.14 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 152.9, 140.9, 139.6, 137.0, 128.7, 128.0, 127.2, 117.7, 115.5, 114.8, 62.6, 60.9, 55.7, 53.2, 14.2 ppm. MS (CI): *m*/*z* (%) = 326 (10) [M + 1]$^+$, 253 (22), 252 (98), 208 (20), 134 (100), 122 (30). HRMS (ESI): calcd. for $C_{20}H_{23}NO_3Na$ [M + Na]$^+$ 348.1576; found 348.1568.

Ethyl (2*R*,3*R*)-2-[(4-Chlorophenyl)amino]-3-phenylpent-4-enoate (3e): Following the general procedure A as described above, **3e** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless solid; yield 65%; m.p. 86–87 °C (Hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 3364, 2960, 1726, 1602, 1516, 1180, 820 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.31 (m, 2 H), 7.30–7.22 (m, 3 H), 7.07 (d, J = 8.9 Hz, 2 H), 6.51 (d, J = 8.9 Hz, 2 H), 6.18–6.09 (m, 1 H), 5.23–5.18 (m, 2 H), 4.31–4.27 (m, 1 H), 4.14–4.07 (m, 2 H), 4.0 (d, J = 8.5 Hz, 1 H), 3.79 (d, J = 8.5 Hz, 1 H), 1.17 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 145.3, 139.1, 136.7, 129.1, 128.8, 128.0, 127.4, 123.2, 118.0, 114.9, 61.4, 61.1, 53.1, 14.2 ppm. MS (CI): *m*/*z* (%) = 330 (3) [M + 1]$^+$, 258 (30), 257 (15), 256 (100), 140 (50), 138 (100). HRMS (ESI): calcd. for $C_{19}H_{20}ClNO_2Na$ [M + Na]$^+$ 352.1080; found 352.1072.

Ethyl (2*R*,3*R*)-2-[(3,4-Dimethylphenyl)amino]-3-phenylpent-4-enoate (3f): Following the general procedure A as described above, **3f** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless solid; yield 70%; m.p. 68–70 °C. IR (KBr): $\tilde{\nu}$ = 3353, 2919, 1722, 1617, 1518, 1320, 1185 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (t, J = 8.4 Hz, 2 H), 7.24–7.20 (m, 3 H), 6.88 (d, J = 8.0 Hz, 1 H), 6.41 (s, 1 H), 6.36 (d, J = 8.0 Hz, 1 H), 6.19–6.10 (m, 1 H), 5.21–5.15 (m, 2 H), 4.30 (d, J = 8.0 Hz, 1 H), 4.14–4.04 (m, 2 H), 3.84 (s, 1 H), 3.77 (t, J = 8.0 Hz, 1 H), 2.13 (s, 3 H), 2.10 (s, 3 H), 1.16 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 144.8, 139.5, 137.3, 137.0, 130.3, 128.7, 128.0, 127.2, 126.6, 117.7, 115.7, 111.1, 61.5, 60.9, 53.2, 20.0, 18.7, 14.2 ppm. MS (CI): *m*/*z* (%) = 324 (5) [M + 1]$^+$, 323 (5) [M]$^+$, 250 (5), 206 (100), 132 (80), 105 (20). HRMS (ESI): calcd. for $C_{21}H_{25}NO_2Na$ [M + Na]$^+$ 346.1782; found 346.1769.

Ethyl (2*R*,3*R*)-2-[(3,4-Dichlorophenyl)amino]-3-phenylpent-4-enoate (3g): Following the general procedure A as described above, **3g** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless solid; yield 57%; m.p. 70–72 °C. IR (KBr): $\tilde{\nu}$ = 3358, 2909, 1726, 1598, 1476, 1188, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 2 H), 7.25–7.18 (m, 3 H), 7.12 (d, J = 8.7 Hz, 1 H), 6.64 (d, J = 2.7 Hz, 1 H), 6.39 (dd, J_1 = 8.7, J_2 = 2.7 Hz, 1 H), 6.15–6.06 (m, 1 H), 5.22–5.17 (m, 2 H), 4.26–4.22 (m, 1 H), 4.15–4.03 (m, 3 H), 3.76 (t, J = 8.3 Hz, 1 H), 1.17 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 146.2, 138.8, 136.4, 132.8, 130.6, 129.0, 127.9, 127.5, 121.1, 118.2, 114.9, 113.3, 61.3, 61.0, 53.0, 14.2 ppm. MS (CI): *m*/*z* (%) = 366 (65) [M + 3]$^+$, 365 (25) [M +

2]+, 364 (100) [M + 1]+, 292 (45), 290 (70), 246 (15). HRMS (ESI): calcd. for $C_{19}H_{19}Cl_2NO_2Na$ [M + Na]+ 386.0691; found 386.0685.

Ethyl (2*R*,3*R*)-2-(Naphthalen-1-ylamino)-3-phenylpent-4-enoate (3h): Following the general procedure A as described above, **3h** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 1:99) as a brown solid; yield 50%; m.p. 77–79 °C. IR (KBr): $\tilde{\nu}$ = 3419, 2979, 1732, 1582, 1528, 1483, 1179 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, J = 7.6 Hz, 1 H), 7.64 (d, J = 7.6 Hz, 1 H), 7.43–7.23 (m, 9 H), 6.61 (d, J = 7.6 Hz, 1 H), 6.30–6.21 (m, 1 H), 5.30–5.23 (m, 2 H), 4.75 (d, J = 7.6 Hz, 1 H), 4.50 (t, J = 7.6 Hz, 1 H), 4.19–4.06 (m, 2 H), 3.96 (t, J = 7.6 Hz, 1 H), 1.16 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 142.0, 139.4, 136.7, 134.3, 128.9, 128.6, 128.0, 127.4, 126.3, 125.8, 124.9, 123.8, 120.0, 118.6, 118.1, 105.6, 61.1, 61.1, 53.3, 14.2 ppm. MS (CI): *m*/*z* (%) = 347 (25) [M + 2]+, 346 (100) [M + 1]+, 272 (65), 228 (15), 143 (10). HRMS (ESI): calcd. for $C_{23}H_{23}NO_2Na$ [M + Na]+ 368.1626; found 368.1620.

Ethyl (2*R*,3*R*)-2-(2-Benzoylhydrazinyl)-3-phenylpent-4-enoate (3i): Following the general procedure A as described above, **3i** (major, *syn* isomer) was obtained after purification by silica column chromatography (EtOAc/hexane, 18:82) as a colorless solid; yield 71%; m.p. 105–107 °C (Hexane/EtOAc). IR (KBr): $\tilde{\nu}$ = 3362, 2987, 1726, 1664, 1463, 1202 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 4.8 Hz, 1 H), 7.67 (d, J = 7.1 Hz, 2 H), 7.50 (t, J = 7.1 Hz, 1 H), 7.42–7.25 (m, 7 H), 6.12–6.03 (m, 1 H), 5.18–5.12 (m, 2 H), 4.89 (s, 1 H), 4.24–4.15 (m, 3 H), 3.74 (t, J = 8.4 Hz, 1 H), 1.22 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 167.3, 138.8, 137.2, 132.5, 132.0, 128.9, 128.7, 128.4, 127.5, 126.9, 117.3, 66.8, 61.1, 51.9, 14.2 ppm. MS (CI): *m*/*z* (%) = 340 (25) [M + 2]+, 339 (100) [M + 1]+, 290 (5), 265 (25). HRMS (ESI): calcd. for $C_{20}H_{22}N_2O_3Na$ [M + Na]+ 361.1528; found 361.1532. Only a fraction of the major isomer was obtained in the pure form, **3i** refers to the major (*syn*) isomer, which was characterized by the X-ray structure analysis. The minor isomer could not be separated from the major isomer.

Ethyl (*R*)-2-[(4-Bromophenyl)amino]-2-[(*R*)-cyclohex-2-en-1-yl]acetate (7a): Following the general procedure C as described above, **7a** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 3:97) as a colorless solid; yield 50%; m.p. 79–81 °C (EtOAc). IR (KBr): $\tilde{\nu}$ = 3350, 2929, 1725, 1594, 1516, 1487, 1184, 677 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, J = 8.9 Hz, 2 H), 6.48 (d, J = 8.9 Hz, 2 H), 5.92–5.89 (m, 1 H), 5.63 (dd, J_1 = 10.2, J_2 = 1.6 Hz, 1 H), 4.2–4.1 (m, 3 H), 3.89 (dd, J_1 = 9.7, J_2 = 5.2 Hz, 1 H), 2.67 (s, 1 H), 2.02–1.99 (m, 2 H), 1.81–1.78 (m, 2 H), 1.55–1.51 (m, 2 H), 1.24 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 146.3, 132.0, 131.4, 125.7, 115.0, 109.8, 61.1, 60.6, 38.7, 26.4, 25.0, 21.6, 14.3 ppm. MS (CI): *m*/*z* (%) = 340 (98) [M + 3]+, 339 (15) [M + 2]+, 338 (100) [M + 1]+, 266 (50), 264 (52), 258 (10), 182 (5). HRMS (ESI): calcd. for $C_{16}H_{20}BrNO_2Na$ [M + Na]+ 360.0575; found 360.0567.

Ethyl (*R*)-2-[(4-Chlorophenyl)amino]-2-[(*R*)-cyclohex-2-en-1-yl]acetate (7b): Following the general procedure C as described above, **7b** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 3:97) as a colorless solid; yield 45%; m.p. 78–80 °C. IR (KBr): $\tilde{\nu}$ = 3384, 2933, 1731, 1600, 1503, 1179, 815 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, J = 8.8 Hz, 2 H), 6.53 (d, J = 8.8 Hz, 2 H), 5.93–5.90 (m, 1 H), 5.64 (dd, J_1 = 10.1, J_2 = 1.6 Hz, 1 H), 4.21–4.10 (m, 3 H), 3.90 (dd, J_1 = 9.8, J_2 = 5.2 Hz, 1 H), 2.68 (s, 1 H), 2.03–2.00 (m, 2 H), 1.83–1.79 (m, 2 H), 1.61–1.52 (m, 2 H), 1.25 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 145.9, 131.4, 129.1, 125.7, 122.7, 114.6, 61.1, 60.7, 38.7, 26.4, 25.0, 21.6, 14.3 ppm. MS (CI): *m*/*z* (%) = 296 (30) [M + 3]+, 295 (15) [M + 2]+, 294 (100) [M + 1]+, 280 (30), 220 (40), 212 (25). HRMS (ESI): calcd. for $C_{16}H_{20}ClNO_2Na$ [M + Na]+ 316.1080; found 316.1084.

Ethyl (*R*)-2-[(*R*)-Cyclohex-2-en-1-yl]-2-[(3,4-dichlorophenyl)amino]-acetate (7c): Following the general procedure C as described above, **7c** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 3:97) as a colorless solid; yield 45%; m.p. 73–75 °C. IR (KBr): $\tilde{\nu}$ = 3356, 2932, 1724, 1599, 1476, 1186, 853 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, J = 8.7 Hz, 1 H), 6.68 (d, J = 2.7 Hz, 1 H), 6.44 (dd, J_1 = 8.7, J_2 = 2.7 Hz, 1 H), 5.94–5.91 (m, 1 H), 5.61 (dd, J_1 = 10.2, J_2 = 1.3 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 3 H), 3.88 (dd, J_1 = 9.6, J_2 = 5.1 Hz, 1 H), 2.69 (s, 1 H), 2.03–2.00 (m, 2 H), 1.82–1.79 (m, 2 H), 1.56–1.51 (m, 2 H), 1.26 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 146.8, 132.8, 131.7, 130.6, 125.3, 120.6, 114.6, 113.0, 61.3, 60.4, 38.6, 26.4, 24.9, 21.5, 14.3 ppm. MS (CI): *m*/*z* (%) = 330 (60) [M + 3]+, 329 (15) [M + 2]+, 328 (100) [M + 1]+, 255 (20), 254 (37), 246 (14). HRMS (ESI): calcd. for $C_{16}H_{19}Cl_2NO_2Na$ [M + Na]+ 350.0691; found 350.0679.

Ethyl (2*R*,3*S*)-2-[(4-Bromophenyl)amino]-3-methylpent-4-enoate (11a): Following the general procedure D as described above, **11a** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless liquid; yield 61%. IR (neat): $\tilde{\nu}$ = 3387, 2979, 1731, 1595, 1502, 1193, 674 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, J = 8.8 Hz, 2 H), 6.50 (d, J = 8.8 Hz, 2 H), 5.79–5.70 (m, 1 H), 5.15–5.09 (m, 2 H), 4.20–4.13 (m, 3 H), 3.93 (dd, J_1 = 9.5, J_2 = 5.6 Hz, 1 H), 2.65 (q, J = 6.9 Hz, 1 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.14 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 146.0, 138.9, 132.0, 116.7, 115.3, 110.0, 61.1, 61.0, 41.3, 16.4, 14.3 ppm. MS (CI): *m*/*z* (%) = 313 (10) [M + 2]+, 311 (10) [M]+, 258 (100), 256 (100), 240 (10), 238 (10), 184 (75), 182 (75), 159 (10). HRMS (ESI): calcd. for $C_{14}H_{18}BrNO_2Na$ [M + Na]+ 334.0419; found 334.0410. Along with the diastereomer **11a**, minor products such as **9** (11%) and **10** (5%) were also observed[18b] (In all other cases, only the diastereomer **11** was isolated in pure form). See the Supporting Information for the structures of **9** and **10**.

4-Bromo-*N*,*N*-bis[(*E*)-but-2-en-1-yl]aniline (9): Obtained after purification by chromatography (EtOAc/hexanes, 0.5:99.5) as a colorless liquid; yield 11%; IR (neat): $\tilde{\nu}$ = 2917, 1593, 1503, 1225, 805 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, J = 8.9 Hz, 2 H), 6.55 (d, J = 8.9 Hz, 2 H), 5.60–5.54 (m, 2 H), 5.47–5.41 (m, 2 H), 3.79 (d, J = 3.5 Hz, 4 H), 1.69 (d, J = 6.2 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 131.6, 127.3, 126.3, 113.9, 107.6, 51.9, 17.7 ppm. MS (CI): *m*/*z* (%) = 281(100) [M + 2]+, 279 (100) [M]+, 266 (20), 264 (20), 227 (80), 225 (80), 145 (40), 130 (50).

(*E*)-4-Bromo-*N*-(but-2-en-1-yl)aniline (10): Obtained after purification by chromatography (EtOAc/hexane, 1:99) as a colorless liquid; yield 5%; IR (neat): $\tilde{\nu}$ = 3400, 2925, 1593, 1490, 807 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, J = 9.0 Hz, 2 H), 6.48 (d, J = 9.0 Hz, 2 H), 5.75–5.66 (m, 1 H), 5.59–5.51 (m, 1 H), 3.72 (s, 1 H), 3.64 (d, J = 5.8 Hz, 2 H), 1.70 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2, 131.9, 128.3, 127.5, 114.5, 108.9, 45.9, 17.8 ppm. MS (CI): *m*/*z* (%) = 227 (100) [M + 2]+, 225 (100) [M]+, 211 (45), 209 (45), 173 (55), 171 (55), 130 (80).

Ethyl (2*R*,3*S*)-2-[(4-Chlorophenyl)amino]-3-methylpent-4-enoate (11b): Following the general procedure D as described above, **11b** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless liquid; yield 60%. IR (neat): $\tilde{\nu}$ = 3388, 2980, 1731, 1600, 1504, 1193, 678 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, J = 8.9 Hz, 2 H), 6.54

(d, J = 8.9 Hz, 2 H), 5.79–5.70 (m, 1 H), 5.15–5.09 (m, 2 H), 4.20–4.14 (m, 3 H), 3.93 (dd, J_1 = 9.5, J_2 = 5.6 Hz, 1 H), 2.65 (q, J = 6.9 Hz, 1 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.15 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6, 145.6, 138.9, 129.1, 123.0, 116.7, 114.8, 61.1, 61.0, 41.3, 16.4, 14.3 ppm. MS (CI): m/z (%) = 269 (12) $[M + 2]^+$, 268 (30) $[M + 1]^+$, 267 (17) $[M]^+$, 214 (35), 212 (100), 194 (15), 140 (25), 138 (85). HRMS (ESI): calcd. for $C_{14}H_{18}ClNO_2Na$ $[M + Na]^+$ 290.0923; found 290.0916.

Ethyl (2*R*,3*S*)-3-Methyl-2-(phenylamino)pent-4-enoate (11c): Following the general procedure D as described above, **11c** was obtained after purification by neutral alumina column chromatography (EtOAc/hexanes, 2:98) as a colorless liquid; yield 54%. IR (CH_2Cl_2): $\tilde{\nu}$ = 3387, 2979, 1732, 1603, 1505, 1191 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (t, J = 7.3 Hz, 2 H), 6.74 (t, J = 7.3 Hz, 1 H), 6.64 (d, J = 7.3 Hz, 2 H), 5.84–5.75 (m, 1 H), 5.17–5.10 (m, 2 H), 4.21–4.14 (m, 3 H), 4.0 (s, 1 H), 2.68 (q, J = 6.9 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.17 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 147.0, 139.2, 129.3, 118.4, 116.4, 113.7, 61.1, 60.9, 41.4, 16.5, 14.3 ppm. MS (CI): m/z (%) = 235 (10) $[M + 2]^+$, 234 (65) $[M + 1]^+$, 178 (30), 161 (12), 160 (100). HRMS (ESI): calcd. for $C_{14}H_{19}NO_2Na$ $[M + Na]^+$ 256.1313; found 256.1301.

Ethyl (2*R*,3*S*)-2-[(4-Methoxyphenyl)amino]-3-methylpent-4-enoate (11d): Following the general procedure D as described above, **11d** was obtained after purification by neutral alumina column chromatography (EtOAc/hexanes, 3:97) as a colorless liquid; yield 59%. IR (neat): $\tilde{\nu}$ = 3375, 2979, 1732, 1514, 1240, 1037 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (d, J = 8.9 Hz, 2 H), 6.60 (d, J = 8.9 Hz, 2 H), 5.82–5.73 (m, 1 H), 5.15–5.08 (m, 2 H), 4.17–4.11 (m, 2 H), 3.89 (s, 2 H), 3.73 (s, 3 H), 2.64 (s, 1 H), 1.22 (t, J = 7.1 Hz, 3 H), 1.15 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 152.8, 141.1, 139.3, 116.4, 115.4, 114.8, 62.3, 60.8, 55.7, 41.4, 16.5, 14.3 ppm. MS (CI): m/z (%) = 263 (20) $[M]^+$, 208 (70), 134 (100), 77 (10). HRMS (ESI): calcd. for $C_{15}H_{21}NO_3Na$ $[M + Na]^+$ 286.1419; found 286.1410.

Ethyl (2*R*,3*S*)-3-Methyl-2-(*p*-tolylamino)pent-4-enoate (11e): Following the general procedure D as described above, **11e** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless liquid; yield 59%. IR (neat): $\tilde{\nu}$ = 3376, 2979, 1728, 1514, 1230, 1020 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (d, J = 8.0 Hz, 2 H), 6.53 (d, J = 8.0 Hz, 2 H), 5.80–5.71 (m, 1 H), 5.13–5.06 (m, 2 H), 4.12 (q, J = 7.1 Hz, 2 H), 4.00 (s, 1 H), 3.92 (d, J = 5.4 Hz, 1 H), 2.63 (q, J = 6.9 Hz, 1 H), 2.20 (s, 3 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.13 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 144.7, 139.3, 129.8, 127.6, 116.4, 113.9, 61.5, 60.8, 41.4, 20.4, 16.5, 14.3 ppm. MS (CI): m/z (%) = 249 (16) $[M + 2]^+$, 248 (100) $[M + 1]^+$, 216 (55), 192 (10), 174 (6).

Ethyl (2*R*,3*S*)-2-[(3,4-Dichlorophenyl)amino]-3-methylpent-4-enoate (11f): Following the general procedure D as described above, **11f** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a colorless liquid; yield 49%. IR (neat): $\tilde{\nu}$ = 3401, 2980, 1731, 1599, 1494, 1133, 675 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, J = 8.7 Hz, 1 H), 6.69 (d, J = 2.7 Hz, 1 H), 6.45 (dd, J_1 = 8.7, J_2 = 2.7 Hz, 1 H), 5.77–5.68 (m, 1 H), 5.15–5.10 (m, 2 H), 4.25 (d, J = 9.4 Hz, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 3.90 (dd, J_1 = 9.4, J_2 = 5.6 Hz, 1 H), 2.65 (q, J = 6.9 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.14 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 146.4, 138.6, 132.8, 130.7, 120.8, 116.9, 114.8, 113.3, 61.2, 60.7, 41.2, 16.3, 14.3 ppm. MS (CI): m/z (%) = 304 (60) $[M + 3]^+$, 303 (15) $[M + 2]^+$, 302 (100) $[M + 1]^+$, 248 (15), 246 (25), 230 (30), 230 (30), 228 (45), 174 (7), 172 (11). HRMS (ESI): calcd. for $C_{14}H_{17}Cl_2NO_2Na$ $[M + Na]^+$ 324.0534; found 324.0525.

Ethyl (2*R*,3*S*)-2-[(3,4-Dimethylphenyl)amino]-3-methylpent-4-enoate (11g): Following the general procedure D as described above, **11g** was obtained after purification by neutral alumina column chromatography (EtOAc/hexanes, 2:98) as a colorless liquid; yield 48%. IR (neat): $\tilde{\nu}$ = 3384, 2978, 1732, 1619, 1512, 1191 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90 (d, J = 8.0 Hz, 1 H), 6.45 (d, J = 2.4 Hz, 1 H), 6.38 (dd, J_1 = 8.0, J_2 = 2.4 Hz, 1 H), 5.81–5.72 (m, 1 H), 5.13–5.06 (m, 2 H), 4.18–4.11 (m, 2 H), 3.99–3.91 (m, 2 H), 2.63 (q, J = 6.9 Hz, 1 H), 2.16 (s, 3 H), 2.12 (s, 3 H), 1.23 (t, J = 7.1 Hz, 3 H), 1.14 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 145.1, 139.3, 137.3, 130.3, 126.4, 116.3, 115.7, 111.1, 61.4, 60.8, 41.4, 20.0, 18.7, 16.5, 14.3 ppm. MS (CI): m/z (%) = 262 (100) $[M + 1]^+$, 206 (15), 188 (40), 132 (5). HRMS (ESI): calcd. for $C_{16}H_{23}NO_2Na$ $[M + Na]^+$ 284.1626; found 284.1618.

Ethyl (2*R*,3*S*)-3-Methyl-2-(naphthalen-1-ylamino)pent-4-enoate (11h): Following the general procedure D as described above, **11h** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 2:98) as a brownish red solid; yield 40%; m.p. 89–91 °C. IR (KBr): $\tilde{\nu}$ = 3369, 2963, 1719, 1581, 1530, 1193 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (dd, J_1 = 6.0, J_2 = 3.3 Hz, 1 H), 7.77 (dd, J_1 = 6.0, J_2 = 3.3 Hz, 1 H), 7.46–7.43 (m, 2 H), 7.31–7.24 (m, 2 H), 6.56 (d, J = 7.2 Hz, 1 H), 5.89–5.80 (m, 1 H), 5.24–5.15 (m, 2 H), 4.95 (d, J = 8.7 Hz, 1 H), 4.21–4.14 (m, 3 H), 2.82 (q, J = 6.9 Hz, 1 H), 1.27–1.24 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 142.1, 139.2, 134.4, 128.6, 126.4, 125.8, 124.9, 123.8, 120.1, 118.3, 116.7, 105.4, 61.0, 60.8, 41.5, 16.8, 14.3 ppm. MS (CI): m/z (%) = 284 (100) $[M + 1]^+$, 228 (15), 210 (40), 154 (5), 143 (10). HRMS (ESI): calcd. for $C_{18}H_{21}NO_2Na$ $[M + Na]^+$ 306.1470; found 306.1460.

Ethyl (2*R*,3*S*)-2-(2-Benzoylhydrazinyl)-3-methylpent-4-enoate (11i):[6b,6e] Following the general procedure D as described above, **11i** was obtained as a mixture of diastereomers (*ds* 75:25) after purification by silica gel column chromatography (EtOAc/hexane, 12:88) as a colorless oil; yield 65%. IR (neat): $\tilde{\nu}$ = 3289, 2979, 1731, 1643, 1462, 1202 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 1 H), 7.74 (d, J = 7.4 Hz, 2 H), 7.51 (t, J = 7.4 Hz, 1 H), 7.43 (t, J = 7.4 Hz, 2 H), 6.01–5.80 (m, 1 H), 5.23–5.09 (m, 3 H), 4.29–4.17 (m, 2 H), 3.78 (d, J = 4.0 Hz, 1 H), 2.80 (q, J = 7.0 Hz, 1 H), 1.29 (t, J = 7.1 Hz, 3 H), 1.16 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 166.9, 138.9, 132.6, 131.9, 128.7, 126.9, 116.2, 66.7, 61.0, 38.8, 14.5, 14.3 ppm. MS (CI): m/z (%) = 278 (15) $[M + 2]^+$, 277 (100) $[M + 1]^+$, 259 (5), 203 (25). HRMS (ESI): calcd. for $C_{15}H_{20}N_2O_3Na$ $[M + Na]^+$ 299.1371; found 299.1365. ^{1}H and ^{13}C NMR spectroscopic data given here refer to the major isomer of **11i**.

Methyl (2*R*,3*S*)-2-(2-Benzoylhydrazinyl)-2,3-dimethylpent-4-enoate (11l):[6e] Following the general procedure as described D above, **11l** was obtained as a mixture of diastereomers after purification by silica gel column chromatography (EtOAc/hexane, 12:88) as a colorless solid; yield 63%. IR (KBr): $\tilde{\nu}$ = 3283, 2950, 1731, 1644, 1450, 1260, 1130 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (br. s, 1 H), 7.65 (d, J = 7.2 Hz, 2 H), 7.44–7.33 (m, 3 H), 5.81–5.72 (m, 1 H), 5.11–5.03 (m, 2 H), 3.67 (s, 3 H), 2.66–2.57 (m, 1 H), 1.29 (s, 3 H), 1.03 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 166.6, 137.7, 132.8, 131.7, 128.7, 126.9, 117.7, 67.8, 52.2, 44.1, 18.7, 14.9 ppm. MS (CI): m/z (%) = 277 (100) $[M + 1]^+$, 246 (1). ^{1}H and ^{13}C NMR spectroscopic data given here refer to the

major diastereomer of **11l** (the NMR was recorded for the mixture of diastereomers).

Ethyl (2*R*,3*S*)-2-(2-Benzoylhydrazinyl)-3,7-dimethyl-3-vinyloct-6-enoate (13): Following the general procedure E as described above, **13** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 5:95) as a colorless oil; yield 80%. IR (neat): $\tilde{\nu}$ = 3295, 2975, 1730, 1638, 1447, 1192 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (s, 1 H), 7.71 (d, J = 7.2 Hz, 2 H), 7.49 (t, J = 7.2 Hz, 1 H), 7.40 (t, J = 7.2 Hz, 2 H), 5.94–5.87 (m, 1 H), 5.17–5.04 (m, 4 H), 4.23–4.14 (m, 2 H), 3.60 (s, 1 H), 1.98–1.92 (m, 2 H), 1.66 (s, 3 H), 1.58 (s, 3 H), 1.58–1.46 (m, 2 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.20 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 167.1, 142.1, 132.7, 131.8, 131.5, 128.6, 126.9, 124.3, 114.6, 71.2, 60.8, 42.9, 37.7, 25.7, 22.5, 19.0, 17.6, 14.2 ppm. HRMS (ESI): calcd. for $C_{21}H_{31}N_2O_3$ [M + H]$^+$ 359.2335; found 359.2352.

Ethyl (2*R*,3*S*)-2-[(4-Bromophenyl)amino]-3,7-dimethyl-3-vinyloct-6-enoate (14a): Following the general procedure E as described above, **14a** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 1:99) as a colorless oil; yield 55%. IR (neat): $\tilde{\nu}$ = 3390, 2926, 1731, 1595, 1496, 1180, 813 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, J = 8.9 Hz, 2 H), 6.49 (d, J = 8.9 Hz, 2 H), 5.93–5.86 (m, 1 H), 5.27 (dd, J_1 = 10.6, J_2 = 1.2 Hz, 1 H), 5.12 (dd, J_1 = 16.2, J_2 = 1.2 Hz, 1 H), 5.08–5.02 (m, 1 H), 4.16–4.10 (m, 3 H), 3.81 (d, J = 10.6 Hz, 1 H), 2.03–1.95 (m, 1 H), 1.91–1.86 (m, 1 H), 1.67 (s, 3 H), 1.58 (s, 3 H), 1.58–1.52 (m, 1 H), 1.39–1.32 (m, 1 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.16 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 146.3, 141.5, 132.0, 131.7, 124.1, 116.1, 115.3, 109.9, 64.0, 60.8, 43.6, 38.4, 25.7, 22.6, 18.9, 17.6, 14.3 ppm. HRMS (ESI): calcd. for $C_{20}H_{28}BrNO_2Na$ [M + Na]$^+$ 416.1201; found 416.1183.

Ethyl (2*R*,3*S*)-2-[(4-Methoxyphenyl)amino]-3,7-dimethyl-3-vinyloct-6-enoate (14b): Following the general procedure E as described above, **14b** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 1:99) as a colorless oil; yield 61%. IR (neat): $\tilde{\nu}$ = 3397, 2927, 1731, 1514, 1240, 1039 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74 (d, J = 8.7 Hz, 2 H), 6.59 (d, J = 8.7 Hz, 2 H), 5.95–5.87 (m, 1 H), 5.24 (dd, J_1 = 10.2, J_2 = 1.2 Hz, 1 H), 5.13–5.05 (m, 2 H), 4.10 (q, J = 7.1 Hz, 2 H), 3.86 (s, 1 H), 3.79 (s, 1 H), 3.72 (s, 3 H), 2.05–1.85 (m, 3 H), 1.67 (s, 3 H), 1.58 (s, 3 H), 1.41–1.32 (m, 1 H), 1.19 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 152.7, 141.9, 141.4, 131.6, 124.3, 115.6, 115.3, 114.8, 65.4, 60.5, 55.7, 43.5, 38.5, 25.7, 22.7, 18.8, 17.6, 14.3 ppm. HRMS (ESI): calcd. for $C_{21}H_{32}NO_3$ [M + H]$^+$ 346.2382; found 346.2369.

Ethyl (2*R*,3*S*)-2-[(3,4-Dichlorophenyl)amino]-3,7-dimethyl-3-vinyloct-6-enoate (14c): Following the general procedure E as described above, **14c** was obtained after purification by neutral alumina column chromatography (EtOAc/hexane, 1:99) as a colorless oil; yield 55%. IR (neat): $\tilde{\nu}$ = 3391, 2926, 1731, 1599, 1494, 1132, 678 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, J = 8.7 Hz, 1 H), 6.70 (d, J = 2.7 Hz, 1 H), 6.45 (dd, J_1 = 8.7, J_2 = 2.7 Hz, 1 H), 5.93–5.86 (m, 1 H), 5.27 (dd, J_1 = 10.5, J_2 = 1.2 Hz, 1 H), 5.12 (dd, J_1 = 17.4, J_2 = 1.2 Hz, 1 H), 5.08–5.02 (m, 1 H), 4.16–4.10 (m, 3 H), 3.79 (d, J = 10.5 Hz, 1 H), 2.05–1.87 (m, 2 H), 1.68 (s, 3 H), 1.59 (s, 3 H), 1.58–1.51 (m, 1 H), 1.40–1.33 (m, 1 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.17 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 146.8, 141.3, 132.8, 131.8, 130.7, 124.0, 120.8, 116.4, 114.8, 113.3, 63.8, 60.9, 43.6, 38.4, 25.7, 22.6, 18.9, 17.6, 14.3 ppm. HRMS (ESI): calcd. for $C_{20}H_{27}Cl_2NO_2Na$ [M + Na]$^+$ 406.1317; found 406.1307.

Ethyl (2*R*,3*S*)-3-Methyl-2-(*p*-tolylamino)pentanoate (15): Following the general procedure F as described above, **15** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 2:98) as a colorless liquid; yield 80%. IR (neat): $\tilde{\nu}$ = 3376, 2979, 1728, 1514, 1230, 1020 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (d, J = 8.4 Hz, 2 H), 6.55 (d, J = 8.4 Hz, 2 H), 4.14 (q, J = 7.1 Hz, 2 H), 3.95 (s, 2 H), 2.21 (s, 3 H), 1.90–1.87 (m, 1 H), 1.57–1.50 (m, 1 H), 1.31–1.26 (m, 1 H), 1.22 (t, J = 7.1 Hz, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.94 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 145.3, 129.8, 127.4, 113.9, 61.2, 60.8, 38.0, 26.2, 20.4, 15.0, 14.3, 11.8 ppm. MS (CI): m/z (%) = 251 (16) [M + 2]$^+$, 250 (100) [M + 1]$^+$, 176 (10). HRMS (ESI): calcd. for $C_{15}H_{24}NO_2$ [M + H]$^+$ 250. 1807; found 250.1791.

(2*R*,3*R*)-3-Phenyl-2-(*p*-tolylamino)pent-4-enoic Acid (16a): Following the general procedure G as described above, **16a** was obtained as a yellowish white solid; yield 55%; m.p. 116–118 °C. IR (KBr): $\tilde{\nu}$ = 3247, 3134, 2604–2361, 1709, 1544, 1509, 1246 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$ + [D$_6$]DMSO): δ = 7.27 (d, J = 4.3 Hz, 4 H), 7.22–7.19 (m, 1 H), 6.99 (d, J = 8.2 Hz, 2 H), 6.84 (d, J = 8.2 Hz, 2 H), 6.22–6.16 (m, 1 H), 5.69 (br. s, 2 H), 5.28–5.19 (m, 2 H), 4.28 (d, J = 7.0 Hz, 1 H), 4.02 (t, J = 7.0 Hz, 1 H), 2.22 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + [D$_6$]DMSO): δ = 177.1, 144.1, 141.1, 134.9, 134.5, 133.4, 132.9, 131.9, 128.1, 123.1, 121.8, 68.7, 56.4, 25.3 ppm. MS (CI): m/z (%) = 282 (45) [M + 1]$^+$, 236 (100), 207 (10).

(2*R*,3*R*)-2-[(4-Bromophenyl)amino]-3-phenylpent-4-enoic Acid (16b): Following the general procedure G as described above, **16b** was obtained as a colorless solid; yield 65%; m.p. 100–102 °C. IR (KBr): $\tilde{\nu}$ = 3571, 3378, 3079–2549, 1713, 1595, 1502, 1273, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 7 H), 6.46 (d, J = 8.9 Hz, 2 H), 6.16–6.07 (m, 1 H), 5.23–5.18 (m, 2 H), 5.01 (br. s, 2 H), 4.29 (d, J = 7.5 Hz, 1 H), 3.82 (t, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 145.7, 138.7, 136.7, 132.0, 128.9, 128.1, 127.5, 118.0, 115.4, 110.5, 61.3, 52.7 ppm. MS (CI): m/z (%) = 348 (45) [M + 2]$^+$, 346 (50) [M]$^+$, 302 (95), 300 (100), 206 (11).

(2*R*,3*R*)-3-Phenyl-2-(*p*-tolylamino)pent-4-en-1-ol (17a): Following the general procedure H as described above, **17a** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 6:94) as a colorless liquid; yield 65%. IR (neat): $\tilde{\nu}$ = 3399, 2922, 1616, 1519, 1039 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (t, J = 7.6 Hz, 2 H), 7.26 (m, 3 H), 7.01 (d, J = 8.2 Hz, 2 H), 6.59 (d, J = 8.2 Hz, 2 H), 6.18–6.09 (m, 1 H), 5.23–5.19 (m, 2 H), 3.82–3.77 (m, 2 H), 3.72–3.68 (m, 1 H), 3.64–3.60 (m, 1 H), 2.27 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 140.6, 137.5, 129.9, 128.7, 128.0, 127.8, 126.9, 117.8, 114.6, 61.8, 59.5, 52.0, 20.4 ppm. MS (CI): m/z (%) = 269 (20) [M + 2]$^+$, 268 (100) [M + 1]$^+$, 250 (4), 236 (5), 150 (9). HRMS (ESI): calcd. for $C_{18}H_{21}NONa$ [M + Na]$^+$ 290.1521; found 290.1534.

(2*R*,3*R*)-3-Phenyl-2-(phenylamino)pent-4-en-1-ol (17b): Following the general procedure H as described above, **17b** was obtained after purification by silica gel column chromatography (EtOAc/hexane, 6:94) as a colorless liquid; yield 60%. IR (neat): $\tilde{\nu}$ = 3400, 2926, 1600, 1503, 1316, 1040 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (t, J = 7.2 Hz, 2 H), 7.28–7.24 (m, 3 H), 7.18 (t, J = 8.2 Hz, 2 H), 6.76 (t, J = 7.2 Hz, 1 H), 6.14 (d, J = 7.2 Hz, 2 H), 6.18–6.09 (m, 1 H), 5.23–5.19 (m, 2 H), 3.86–3.79 (m, 2 H), 3.72–3.68 (m, 1 H), 3.64 (dd, J_1 = 10.9, J_2 = 5.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.5, 140.5, 137.6, 129.4, 128.8, 128.0, 126.9, 118.4, 117.7, 114.3, 62.0, 59.1, 52.1 ppm. MS (CI): m/z (%) = 255 (20) [M + 2]$^+$, 254 (100) [M + 1]$^+$, 236 (4), 222 (5). HRMS (ESI): calcd. for $C_{17}H_{19}NONa$ [M + Na]$^+$ 276.1364; found 276.1371.

(2*R*,3*S*)-2-[(4-Methoxyphenyl)amino]-3,7-dimethyl-3-vinyloct-6-en-1-ol (17c): Following the general procedure H as described above, **17c** was obtained after purification by silica gel column chromatography (EtOAc/hexanes, 5:95) as a colorless liquid; yield 80%. IR (neat): $\tilde{\nu}$ = 3399, 2925, 1620, 1513, 1239, 1041 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (d, J = 9.0 Hz, 2 H), 6.65 (d, J = 9.0 Hz, 2 H), 5.84–5.77 (m, 1 H), 5.24 (dd, J_1 = 9.5, J_2 = 1.3 Hz, 1 H), 5.08 (dd, J_1 = 16.2, J_2 = 1.3 Hz, 1 H), 5.05–4.95 (m, 1 H), 3.82–3.78 (m, 1 H), 3.74 (s, 3 H), 3.40 (t, J = 9.0 Hz, 1 H), 3.31–3.27 (m, 1 H), 1.93–1.81 (m, 2 H), 1.65 (s, 3 H), 1.55 (s, 3 H), 1.48–1.33 (m, 2 H), 0.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 143.7, 143.0, 131.6, 124.3, 115.6, 115.2, 115.0, 64.2, 62.0, 55.8, 45.0, 38.8, 25.7, 22.6, 19.4, 17.6 ppm. HRMS (ESI): calcd. for $C_{19}H_{29}NO_2Na$ [M + Na]$^+$ 326.2096; found 326.2101.

(2*R*,3*R*)-Ethyl 2-[Allyl(3,4-dimethylphenyl)amino]-3-phenylpent-4-enoate (18a): Following the general procedure I as described above, **18a** was obtained after purification by silica gel column chromatography (EtOAc/hexanes, 1.5:98.5) as a colorless liquid; yield 81%. IR (neat): $\tilde{\nu}$ = 2922, 1732, 1614, 1505, 1154, 1029 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.19 (m, 2 H), 7.16–7.12 (m, 3 H), 6.88 (d, J = 8.3 Hz, 1 H), 6.55 (d, J = 2.6 Hz, 1 H), 6.50 (dd, J_1 = 8.3, J_2 = 2.6 Hz, 1 H), 5.96–5.87 (m, 1 H), 5.39–5.30 (m, 1 H), 5.13–5.03 (m, 2 H), 4.91–4.85 (m, 2 H), 4.66 (d, J = 11.0 Hz, 1 H), 4.13 (q, J = 7.1 Hz, 2 H), 4.02 (dd, J_1 = 11.0, J_2 = 8.4 Hz, 1 H), 3.87–3.85 (m, 2 H), 2.15 (s, 3 H), 2.11 (s, 3 H), 1.23 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 146.8, 139.9, 138.4, 136.7, 136.1, 129.8, 128.4, 128.3, 126.7, 126.5, 117.4, 116.9, 115.8, 113.3, 65.6, 60.6, 51.0, 48.4, 20.3, 18.7, 14.3 ppm. MS (CI): m/z (%) = 364 (100) [M + 1]$^+$, 336 (5), 206 (5).

Ethyl (2*R*,3*R*)-2-[Allyl(4-methoxyphenyl)amino]-3-phenylpent-4-enoate (18b): Following the general procedure I as described above, **18b** was obtained after purification by silica gel column chromatography (EtOAc/hexanes, 2.5:97.5) as a colorless oil; yield 65%. IR (neat): $\tilde{\nu}$ = 2929, 1731, 1680, 1513, 1244, 1039 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.20 (m, 2 H), 7.17–7.12 (m, 3 H), 6.68 (d, J = 1.1 Hz, 4 H), 5.94–5.86 (m, 1 H), 5.39–5.29 (m, 1 H), 5.12–5.02 (m, 2 H), 4.91–4.85 (m, 2 H), 4.50 (d, J = 11.2 Hz, 1 H), 4.14 (q, J = 7.1 Hz, 2 H), 3.99 (dd, J_1 = 11.2, J_2 = 8.2 Hz, 1 H), 3.81 (d, J = 5.4 Hz, 2 H), 3.70 (s, 3 H), 1.21 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 153.1, 142.7, 140.0, 138.2, 135.9, 128.4, 128.3, 126.7, 118.9, 116.9, 116.1, 114.0, 67.5, 60.5, 55.5, 50.8, 49.0, 14.3 ppm. MS (CI): m/z (%) = 366 (100) [M + 1]$^+$, 208 (15), 163 (5).

Ethyl (2*R*,3*R*)-2-[Allyl(phenyl)amino]-3-phenylpent-4-enoate (18c): Following the general procedure I as described above, **18c** was obtained after purification by silica gel column chromatography (EtOAc/hexanes, 1.5:98.5) as a colorless liquid; yield 64%. IR (neat): $\tilde{\nu}$ = 2981, 1732, 1598, 1504, 1163, 1026 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.10 (m, 7 H), 6.76–6.70 (m, 3 H), 5.97–5.88 (m, 1 H), 5.42–5.34 (m, 1 H), 5.16–5.06 (m, 2 H), 4.94–4.89 (m, 2 H), 4.74 (d, J = 11.1 Hz, 1 H), 4.16 (q, J = 7.1 Hz, 2 H), 4.07 (dd, J_1 = 11.1, J_2 = 8.3 Hz, 1 H), 3.92–3.89 (m, 2 H), 1.24 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 148.6, 139.7, 138.2, 135.6, 128.7, 128.5, 128.2, 126.8, 118.3, 117.0, 116.0, 115.4, 65.3, 60.7, 50.9, 48.3, 14.3 ppm. MS (CI): m/z (%) = 336 (100) [M + 1]$^+$, 262 (5), 246 (5).

Ethyl (2*R*,3*S*)-2-[Allyl(4-bromophenyl)amino]-3-methylpent-4-enoate (18d): Following the general procedure I as described above, **18d** was obtained after purification by silica gel column chromatography (EtOAc/hexanes, 1.5:98.5) as a colorless liquid; yield 69%. IR (neat): $\tilde{\nu}$ = 2979, 1732, 1589, 1495, 1242, 1027, 670 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, J = 9.1 Hz, 2 H), 6.74 (d, J = 9.1 Hz, 2 H), 5.77–5.67 (m, 2 H), 5.16–5.03 (m, 4 H), 4.11–4.00 (m, 5 H), 2.94–2.84 (m, 1 H), 1.19 (t, J = 7.1 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 147.9, 139.4, 134.8, 131.7, 116.5, 116.4, 116.3, 110.0, 66.6, 60.6, 48.5, 38.6, 17.2, 14.2 ppm. MS (CI): m/z (%) = 353 (95) [M + 2]$^+$, 352 (100) [M + 1]$^+$, 274 (10), 246 (15), 172 (5).

Ethyl (2*R*,3*S*)-2-[Allyl(4-methoxyphenyl)amino]-3-methylpent-4-enoate (18e): Following the general procedure I as described above, **18e** was obtained after purification by silica gel column chromatography (EtOAc/hexanes, 2.5:97.5) as a colorless liquid; yield 75%. IR (neat): $\tilde{\nu}$ = 2980, 1731, 1513, 1243, 1039 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (d, J = 9.2 Hz, 2 H), 6.79 (d, J = 9.2 Hz, 2 H), 5.78–5.67 (m, 2 H), 5.18–5.01 (m, 4 H), 4.07 (q, J = 7.1 Hz, 2 H), 4.00–3.88 (m, 3 H), 3.74 (s, 3 H), 2.91–2.81 (m, 1 H), 1.18 (t, J = 7.1 Hz, 3 H), 1.08 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 152.9, 143.2, 139.9, 136.0, 118.2, 116.2, 116.0, 114.3, 68.6, 60.2, 55.5, 49.1, 38.6, 17.3, 14.3 ppm. MS (CI): m/z (%) = 304 (100) [M + 1]$^+$, 262 (4), 208 (6).

Ethyl (2*R*,3*S*)-2-[Allyl(*p*-tolyl)amino]-3-methylpent-4-enoate (18f): Following the general procedure I as described above, **18f** was obtained after purification by silica gel column chromatography (EtOAc/hexanes, 1.5:98.5) as a colorless liquid; yield 90%. IR (neat): $\tilde{\nu}$ = 2980, 1731, 1513, 1243, 1039 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (d, J = 8.4 Hz, 2 H), 6.79 (d, J = 8.4 Hz, 2 H), 5.79–5.68 (m, 2 H), 5.17–5.01 (m, 4 H), 4.09–3.94 (m, 5 H), 2.91–2.85 (m, 1 H), 2.23 (s, 3 H), 1.18 (t, J = 7.1 Hz, 3 H), 1.03 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 146.8, 139.8, 135.7, 129.5, 127.4, 116.1, 116.0, 115.3, 67.0, 60.4, 48.5, 38.8, 20.3, 17.3, 14.3 ppm. MS (CI): m/z (%) = 289 (20) [M + 2]$^+$, 288 (100) [M + 1]$^+$.

Ethyl (2*R*,3*R*)-1-(3,4-Dimethylphenyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylate (19a): Following the general procedure J as described above, **19a** was obtained after purification by silica gel column chromatography (EtOAc/hexanes, 2:98) as a yellow semisolid; yield 91%. IR (neat): $\tilde{\nu}$ = 2922, 1732, 1615, 1512, 1024 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.22 (m, 5 H), 7.00 (d, J = 8.3 Hz, 1 H), 6.75 (s, 1 H), 6.70 (d, J = 8.3 Hz, 1 H), 6.14 (dd, J_1 = 10.3, J_2 = 2.8 Hz, 1 H), 5.94 (dd, J_1 = 10.3, J_2 = 1.7 Hz, 1 H), 4.74 (d, J = 6.9 Hz, 1 H), 4.13 (br. s, 1 H), 4.05 (br. s, 2 H), 3.73–3.69 (m, 1 H), 3.54–3.49 (m, 1 H), 2.21 (s, 3 H), 2.15 (s, 3 H), 0.74 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 147.3, 140.2, 137.3, 130.4, 128.5, 128.4, 127.2, 127.1, 126.5, 124.1, 116.0, 111.9, 60.6, 59.8, 45.6, 43.6, 20.4, 18.7, 13.7 ppm. HRMS (ESI): calcd. for $C_{22}H_{26}NO_2$ [M + H]$^+$ 336.1964; found 336.1968.

Ethyl (2*R*,3*R*)-1-(4-Methoxyphenyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylate (19b): Following the general procedure J as described above, **19b** was obtained after purification by silica gel column chromatography (EtOAc/hexanes, 3:97) as a colorless solid; yield 75%; m.p. 67–69 °C. IR (KBr): $\tilde{\nu}$ = 2983, 1723, 1514, 1184, 1040 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 2 H), 7.29–7.25 (m, 3 H), 6.93 (d, J = 9.2 Hz, 2 H), 6.84 (d, J = 9.2 Hz, 2 H), 6.16 (dd, J_1 = 10.3, J_2 = 3.7 Hz, 1 H), 5.96 (dd, J_1 = 10.3, J_2 = 2.2 Hz, 1 H), 4.68 (d, J = 6.9 Hz, 1 H), 4.18–3.94 (m, 3 H), 3.76 (s, 3 H), 3.73–3.65 (m, 1 H), 3.58–3.50 (m, 1 H), 0.73 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 153.2, 143.4, 140.1, 128.5, 128.4, 127.2, 126.4, 124.2, 116.4, 114.7, 61.6, 59.7, 55.6, 46.0, 43.7, 13.6 ppm. MS (CI): m/z (%) = 338 (100) [M + 1]$^+$, 278 (7), 208 (10), 246 (10). HRMS (ESI): calcd. for $C_{21}H_{24}NO_3$ [M + H]$^+$ 338.1756; found 338.1773.

Ethyl (2*R*,3*R*)-1,3-Diphenyl-1,2,3,6-tetrahydropyridine-2-carboxylate (19c): Following the general procedure J as described above,

19c was obtained after purification by silica gel column chromatography (EtOAc/hexanes, 2:98) as a colorless solid; yield 95%; m.p. 83–84 °C. IR (KBr): $\tilde{\nu}$ = 2977, 1734, 1599, 1502, 1292, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 7 H), 6.94 (d, J = 8.1 Hz, 2 H), 6.81 (t, J = 8.1 Hz, 1 H), 6.16 (dd, J_1 = 10.1, J_2 = 2.8 Hz, 1 H), 5.97 (dd, J_1 = 10.1, J_2 = 2.1 Hz, 1 H), 4.79 (d, J = 6.9 Hz, 1 H), 4.13–4.02 (m, 3 H), 3.73–3.66 (m, 1 H), 3.57–3.49 (m, 1 H), 0.74 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 149.0, 140.0, 129.3, 128.5, 128.4, 127.2, 126.3, 124.0, 119.0, 114.1, 60.2, 59.9, 45.3, 43.5, 13.6 ppm. HRMS (ESI): calcd. for $C_{20}H_{22}NO_2$ $[M + H]^+$ 308.1651; found 308.1663.

Ethyl (2*R*,3*S*)-1-(4-Bromophenyl)-3-methyl-1,2,3,6-tetrahydropyridine-2-carboxylate (19d): Following the general procedure J as described above, **19d** was obtained after purification by silica gel column chromatography (EtOAc/hexanes, 2:98) as an orange oil; yield 84%. IR (neat): $\tilde{\nu}$ = 2977, 1732, 1590, 1494, 1022, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, J = 9.2 Hz, 2 H), 6.76 (d, J = 9.2 Hz, 2 H), 5.88 (dd, J_1 = 10.2, J_2 = 3.1 Hz, 1 H), 5.58 (dd, J_1 = 10.2, J_2 = 2.2 Hz, 1 H), 4.51 (d, J = 6.6 Hz, 1 H), 4.08 (q, J = 7.1 Hz, 2 H), 3.95–3.79 (m, 2 H), 2.91–2.86 (m, 1 H), 1.91–1.14 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 148.1, 131.9, 126.8, 123.9, 115.2, 110.6, 60.4, 59.0, 45.4, 32.0, 17.4, 14.4 ppm. MS (CI): m/z (%) = 325 (95) $[M + 2]^+$, 324 (100) $[M + 1]^+$, 246 (30), 172 (10). HRMS (ESI): calcd. for $C_{15}H_{19}NO_2Br$ $[M + H]^+$ 324.0599; found 324.0594.

Ethyl (2*R*,3*S*)-1-(4-Methoxyphenyl)-3-methyl-1,2,3,6-tetrahydropyridine-2-carboxylate (19e): Following the general procedure as described above, **19e** was obtained after purification by silica gel column chromatography (EtOAc/hexanes, 3:97) as a brown solid; yield 76%; m.p. 55–57 °C. IR (KBr): $\tilde{\nu}$ = 2961, 1727, 1514, 1171, 1032 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.88–6.81 (m, 4 H), 5.88 (dd, J_1 = 10.1, J_2 = 3.1 Hz, 1 H), 5.56 (dd, J_1 = 10.1, J_2 = 2.1 Hz, 1 H), 4.45 (d, J = 6.6 Hz, 1 H), 4.05 (q, J = 7.1 Hz, 2 H), 3.89–3.85 (m, 2 H), 3.75 (s, 3 H), 2.91 (br. s, 1 H), 1.16 (t, J = 7.1 Hz, 3 H), 1.11 (d, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 152.9, 143.6, 126.8, 124.4, 115.8, 114.6, 60.3, 60.1, 55.6, 46.0, 32.2, 17.4, 14.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{22}NO_3$ $[M + H]^+$ 276.1600; found 276.1613.

Ethyl (2*R*,3*S*)-3-Methyl-1-(*p*-tolyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (19f): Following the general procedure J as described above, **19f** was obtained after purification by silica gel column chromatography (EtOAc/hexanes, 2:98) as a colorless oil; yield 60%. IR (neat): $\tilde{\nu}$ = 2976, 1738, 1519, 1450, 1156, 1023 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, J = 8.6 Hz, 2 H), 6.81 (d, J = 8.6 Hz, 2 H), 5.88 (dd, J_1 = 10.1, J_2 = 3.1 Hz, 1 H), 5.56 (dd, J_1 = 10.1, J_2 = 2.1 Hz, 1 H), 4.53 (d, J = 6.6 Hz, 1 H), 4.06 (q, J = 7.1 Hz, 2 H), 3.97–3.84 (m, 2 H), 2.89 (br. s, 1 H), 2.24 (s, 3 H), 1.16 (t, J = 7.1 Hz, 3 H), 1.12 (d, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 147.0, 129.8, 127.8, 126.8, 124.4, 113.9, 60.1, 59.4, 45.6, 32.1, 20.3, 17.4, 14.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{22}NO_2$ $[M + H]^+$ 260.1651; found 260.1663.

Ethyl (2*R*,3*R*)-1-(4-Methoxyphenyl)-3-phenylpiperidine-2-carboxylate (20a): Following the general procedure F as described above, **20a** was obtained after purification by silica gel column chromatography (EtOAc/hexanes, 4:96) as a colorless oil; yield 54%. IR (neat): $\tilde{\nu}$ = 2930, 1727, 1602, 1512, 1148, 1037 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.13 (m, 5 H), 6.87 (d, J = 9.0 Hz, 2 H), 6.72 (d, J = 9.0 Hz, 2 H), 4.44 (d, J = 5.6 Hz, 1 H), 3.66 (s, 3 H), 3.64–3.52 (m, 3 H), 3.26–3.23 (m, 2 H), 2.30–2.19 (m, 1 H), 2.01–1.97 (m, 1 H), 1.79–1.73 (m, 1 H), 1.17 (s, 1 H), 0.62 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 153.6, 144.5, 141.5, 128.3, 127.8, 126.9, 118.3, 114.3, 65.6, 59.4, 55.5, 44.6, 44.3, 25.6, 23.4, 13.7 ppm. MS (CI): m/z (%) = 340 (100) $[M + 1]^+$, 288 (10).

(2*R*,3*S*)-3-Methyl-1-(*p*-tolyl)-1,2,3,6-tetrahydropyridine-2-carboxylic Acid (20b): Following the general procedure G as described above, **20b** was obtained (as a mixture of diastereomers, *ds* 80:20)[19j] as a semisolid; yield 90%. IR ($CDCl_3$): $\tilde{\nu}$ = 3543–2852, 1714, 1518, 1215, 1037 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.65 (br. s, 1 H), 7.03 (d, J = 8.1 Hz, 2 H), 6.72 (d, J = 8.1 Hz, 2 H), 5.82–5.71 (m, 2 H), 4.33 (s, 1 H), 3.87–3.76 (m, 2 H), 2.87 (br. s, 1 H), 2.23 (s, 3 H), 1.20 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.2, 147.9, 129.8, 127.8, 126.9, 124.0, 113.7, 60.9, 45.1, 33.3, 20.3, 17.4 ppm. MS (CI): m/z (%) = 232 (100) $[M + 1]^+$, 200 (50), 188 (70), 120 (5). NMR spectroscopic data given here refers to the major diastereomer.

Supporting Information (see footnote on the first page of this article): X-ray structures, copies of ^1H and ^{13}C NMR spectra of all compounds.

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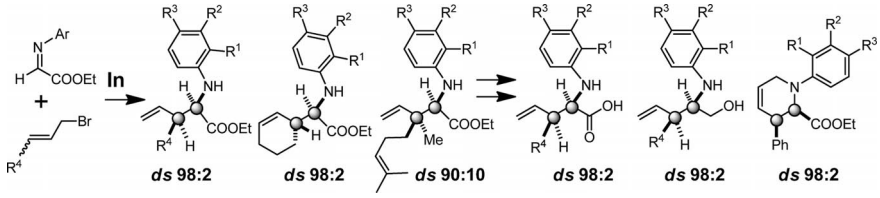
Diastereoselective Allylation



Highly diastereoselective C–C bond formation through Barbier-type indium-mediated addition of γ-substituted allylic halides to *N*-aryl α-imino and α-hydrazono esters was established. Diastereoselective production of γ,δ-unsaturated β,β′-disubstituted *N*-aryl (including *N*-PMP) α-amino acid- and 2,3-disubstituted *N*-aryltetrahydropyridine derivatives bearing two contiguous stereocenters was accomplished.

Keywords: Synthetic methods / Allylation / Indium / Amino acids / Diastereoselectivity

