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Chiral Synthesis of Functionalized Tetrahydropyridines: γ-Aminobutyric Acid Uptake Inhibitor Analogues

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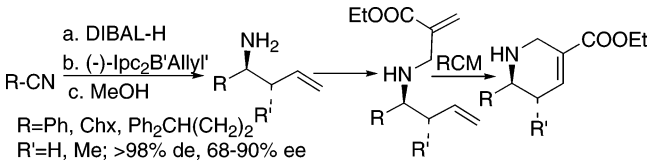

A convenient preparation of functionalized chiral tetrahydropyridine-3-carboxylates from nitriles in 68−90% enantiomeric excess (ee) via allylboration, followed by a conjugate addition−elimination and ring-closing metathesis, has been developed. Thus, the treatment of the acetate derived from vinylalumination of formaldehyde by use of [α-(ethoxycarbonyl)vinyl]diisobutylaluminum with chiral β-substituted and β-unsubstituted homoallylic amines, prepared in >98% diastereomeric excess (de) and 68−90% ee via allylboration of the corresponding *N*-aluminoimines, furnished functionalized aminodienes, which underwent ring-closing metathesis to provide chiral C_5−C_6 disubstituted tetrahydropyridine-3-carboxylates. This methodology has been applied for the synthesis of a chiral C_6-substituted tetrahydropyridine with known GABA-inhibiting properties at low concentrations.

Introduction

One of the major mammalian inhibitory neurotransmitters is γ-aminobutyric acid (GABA).[1] A plethora of diseases, such as Parkinson's, Huntington's, epilepsy, and schizophrenia, has been linked to dysfunction of GABAergic synapses.[1,2] The tetrahydropyridine moiety[3] has been identified as the pharmacophore for GABA inhibition with the aid of computer modeling, and these results have been confirmed by in vitro studies.[4] Among the evaluated compounds, nipecotic acid (**1**, $IC_{50} = 1.7\ \mu M$),[5] guvacine (**2**, $IC_{50} = 4.9\ \mu M$),[6] and various guvacine derivatives showed the best results in their activity toward GABAergic receptors. Unfortunately, high in vitro activity of **1** and **2** did not extend to the in vivo action.[7] Among several evaluated analogues, compounds such as SKF 100330-A (**3**, $IC_{50} = 0.21\ \mu M$)[8] and **4** ($IC_{50} = 0.1\ \mu M$)[4] were found to provide good results in GABA inhibition, and **3** was reported to have high bioavailability as well.[2c,9] Subsequent studies have shown that a modification at the C_6 position (as in compound **5**) eliminated the GABA-uptake inhibition, but inhibition of M_1 and M_2 muscarinic receptors at 100 nM was observed (Figure 1).[10]

Unfortunately, a systematic study of such compounds has been limited, probably, due to the somewhat cumbersome routes for their preparation.[11] Indeed, to the best of our knowledge, preparation and biological evaluation of C_6-chiral analogues of guvacine has never been reported.

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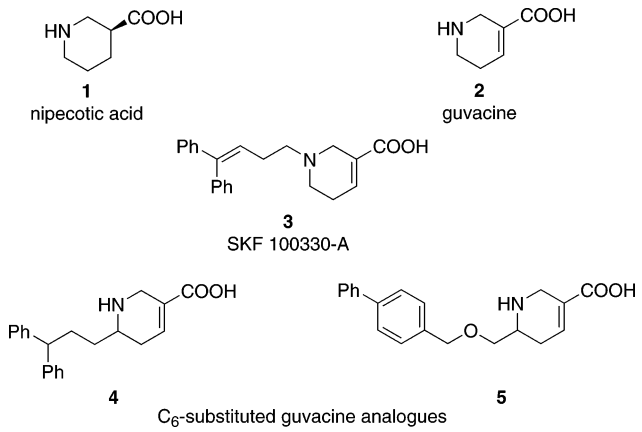
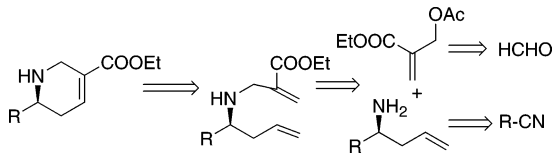


FIGURE 1. GABA-uptake inhibitors.

SCHEME 1. Retrosynthetic Analysis



We envisaged a convenient preparation of such molecules via the conjugate addition−elimination reaction[12] of the acetate obtained from the alcohol synthesized via vinylalumination or Baylis−Hillman reaction with chiral homoallylic amines to furnish aminodienes, which would then undergo ring-closing metathesis (RCM) reaction to yield the desired products. The RCM reaction of aminodienes has been previously applied for the syntheses of numerous piperidine and pyrrolidine alkaloids.[13] However, to the best of our knowledge, RCM has never been used for the preparation of tetrahydropyridine-3-carboxylic acids such as **2**−**5** and their esters. We were also curious to know the effect of the carboxylate on the alkene during the RCM reaction. Accordingly, we undertook such a study and our general retrosynthetic analysis for the preparation of tetrahydropyridine-3-carboxylates is presented in Scheme 1.

Results and Discussion

Recently, we reported the preparation of chiral homoallylic amines from nitriles via the allylboration or crotylboration of *N*-aluminoimines with (−)-*B*-allyldiisopinocampheylborane (**8**, Figure 2)[14] or the "allyl" "ate" complexes (**9**−**11**, Figure 2) in the presence of 1 equiv of methanol.[15] We adopted this protocol for the current project.

For the synthesis of the required acetate (**12**), we chose to synthesize ethyl 2-(hydroxymethyl)acrylate (**13**) via [α-(ethoxycarbonyl)vinyl]diisobutylaluminum (**14**).[16] This vinylalumination reaction, which has been modified and

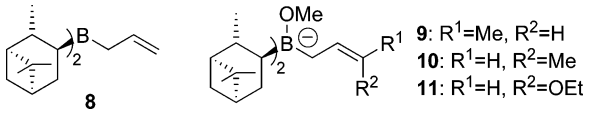
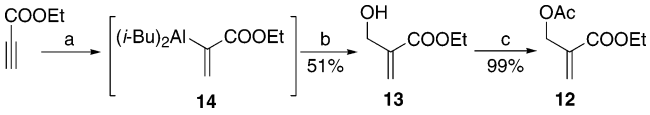


FIGURE 2. α-Pinene-based reagents for allylboration of *N*-aluminoimines.

SCHEME 2. Preparation of Acetate 12 via Vinylalumination[a]



[a] Reagents and conditions: (a) DIBAL-H (1.5 equiv), NMO (1.8 equiv); THF, 0 °C, 1 h. (b) (1) HCHO (excess); THF, 50 °C, 0.5 h; (2) aq. dil. HCl; (c) AcCl (1.2 equiv); pyridine (0.8 equiv), CH_2Cl_2, 1 h, 0 °C.

developed in our laboratory over the past few years, is an attractive alternative for the Baylis−Hillman protocol[17] as it furnishes similar or the same products, while reaction times are significantly shortened and a broader range of carbonyl compounds is tolerated. Although anhydrous formaldehyde had to be generated for the vinylalumination, the reaction was cleaner, workup and purification were significantly easier, and the product was obtained in satisfactory yield (Scheme 2).[18] The obtained alcohol **13** was acetylated under standard conditions to yield **12**.

Partial reduction of benzonitrile (**15a**) with 1 equiv of diisobutylaluminum hydride (DIBAL-H) at 0 °C furnished the corresponding *N*-aluminoimine, which was added to an ether−pentane solution of **8** at −100 °C, followed by 1 equiv of methanol. Upon completion of the reaction, as shown by the disappearance of the peak at δ 78 and the appearance of a peak at δ 47 in ^{11}B NMR spectra, and alkaline oxidative workup, followed by purification, the desired homoallylic amine **16a** was obtained in 90% yield and 88% enantiomeric excess (ee) (Scheme 3).[15] Addition of **16a** to the acetate **12** furnished the desired aminodiene **17a** in 92% yield (Scheme 4).

The commercially available ruthenium-based alkylidene catalyst **18** (Figure 3),[19] devised by Grubbs and co-workers, is stable to air and moisture and it tolerates acidic environment. It is widely used for the synthesis of various cycloalkenes, even from densely substituted dienes,[20] including aminodienes.[13] Recent modification of this catalyst achieved in Hoveyda's laboratory furnished **19** (Figure 3),[21] which was reported to show more reactivity toward densely substituted dienes and was herein evaluated on selected aminodienes.

(12) This reaction is referred to as an S_N2' reaction in the literature (see ref 17a). However, this is a conjugated addition−elimination that is giving an S_N2' product.

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(18) It is noteworthy that the preparation of alcohol **13** via the Baylis−Hillman reaction of formaldehyde with ethyl acrylate always resulted in the formation of a significant amount of the dimerized product. Basavaiah, D.; Krishnamacharyulu, M.; Rao, A. J. *Synth. Commun.* **2000**, *30*, 2061.

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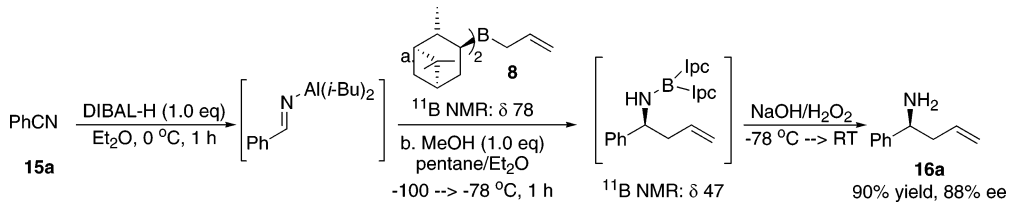
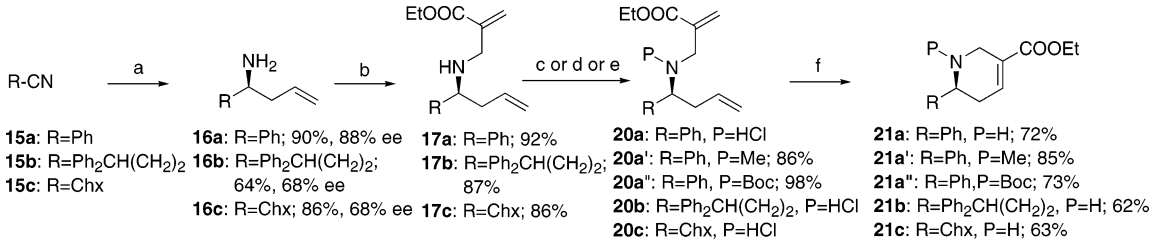
SCHEME 3. Synthesis of Homoallylic Amines via Allylboration of *N*-Aluminoimines



SCHEME 4. Preparation of Chiral Tetrahydropyridine-3-carboxylates[a]



[a] Reagents and conditions: (a) (1) DIBAL-H (1.0 equiv); pentane, 0 °C, 1 h. (2) **8** (1.2 equiv); pentane. (3) MeOH (1.0 equiv); −100 → −78 °C (for **15a**), −78 °C (for **15b**), or −55 °C (for **15c**), 3 h. (4) $NaOH/H_2O_2$; −78 °C → RT, 14 h. (b) **12** (1.0 equiv); CH_2Cl_2, 0 °C, 12 h. (c) HCl (1.2 equiv); Et_2O, RT, 0.5 h. (d) Boc_2O (1.2 equiv); Et_2O, RT, 12 h. (e) Aqueous HCHO (7.0 equiv), $NaBH_3CN$ (2.0 equiv); CH_3CN, 14 h, RT. (f) **18** or **19** (0.1 equiv); $CHCl_3$, 60 °C, 14 h or PhMe, 100 °C, 14 h.

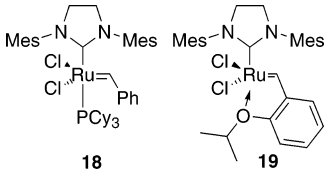


FIGURE 3. Catalysts for ring-closing metathesis.

The RCM reaction using Grubbs' second-generation catalyst (**18**) on the aminodiene containing free secondary amine (**17a**) failed to provide any cyclized product (Table 1, entry 1). This may be expected since the chelation between the catalyst and basic nitrogen atom might render **18** inactive.[22] Three methods for circumventing this deficiency of RCM were examined: (1) conversion of the amine to an ammonium salt, (2) conversion of the secondary amine to a tertiary one, and (3) protection of the amine. Thus, **17a** was treated with ethereal HCl to obtain the ammonium salt **20a**, which was refluxed with 0.1 equiv of **18** in $CHCl_3$ for 14 h and then neutralized with aqueous $NaHCO_3$. Purification on silica gel provided the desired amine **21a** in 72% yield (Table 1, entry 2). Similarly, the reaction of **20a** with 0.1 equiv of catalyst **19** in toluene at 100 °C yielded the desired tetrahydropyridine **21a** in 70% yield (Table 1, entry 3). Preparation of the *N*-methylamine (**20a′**) was achieved in 86% yield by the reductive amination of aqueous formaldehyde with **17a** in the presence of $NaBH_3CN$ in dilute acetonitrile. The compound **20a′** underwent RCM to furnish **21a′** in 85% yield; however, elevated reaction temperature was required (Scheme 4; Table 1, entries 4 and 5). Protection of **17a** with Boc_2O furnished a quantitative yield of **20a″**, which, after RCM in refluxing $CHCl_3$, provided **21a″** in 73% yield (Table 1, entry 6).

The ee of the prepared tetrahydropyridine-3-carboxylates **21a**, **21a′**, and **21a″** is assumed to be 88% on the basis of our earlier demonstration that similar RCM of acrylates prepared from homoallylic alcohols have yielded α-pyrones without the loss of optical activity.[23]

Next, this protocol was applied for the preparation of other chiral C_5-substituted GABA inhibitor analogues. Thus, allylboration of the *N*-aluminoimines obtained from 3,3-diphenylpropanenitrile (**15b**) and cyclohexanecarbonitrile (**15c**) with 1.2 equiv of **8** in the presence of 1.0 equiv of methanol yielded the corresponding homoallylic amines **16b** and **16c** in 64% and 86% yield, respectively, and both in 68% ee (Scheme 4). Compounds **16b,c** were reacted with acetate **12** to furnish the corresponding aminodienes **17b,c** in 87% and 86% yield, respectively. Since the RCM on the ammonium salt appeared to be the most convenient protocol, the aminodienes **17b,c** were converted to their hydrochloride salts **20b,c**, followed by RCM in the presence of 0.1 equiv of **18** in toluene at 100 °C for 14 h. Upon completion of the reaction, the free amines were recovered by neutralization with $NaHCO_3$ and purified on silica gel to provide the corresponding tetrahydropyridine-3-carboxylates **21b** and **21c** in 62% and 63% yield, respectively (Scheme 4; Table 1, entries 7 and 8). We are assuming 68% ee for **21b** and **21c** since we have previously observed no loss of optical activity during the RCM reaction.[23] The ester **21b** is a chiral analogue of the tetrahydropyridine carboxylic acid **4**, which was shown to have GABA-uptake inhibitory properties at low concentrations.[4]

Upon successful preparation of a series of C_6-substituted guvacine analogues from nitriles, the synthesis of compounds with functionalization at C_5 and C_6 was attempted. The reagent-controlled crotylboration[24] of *N*-aluminoimines by use of boron "ate" complexes **9**−**11** (Figure 2)[15] would furnish *β*-substituted homoallylic amines in high diastereomeric excess (de) and ee.[15] Hence, crotylboration of *N*-aluminoimines prepared by

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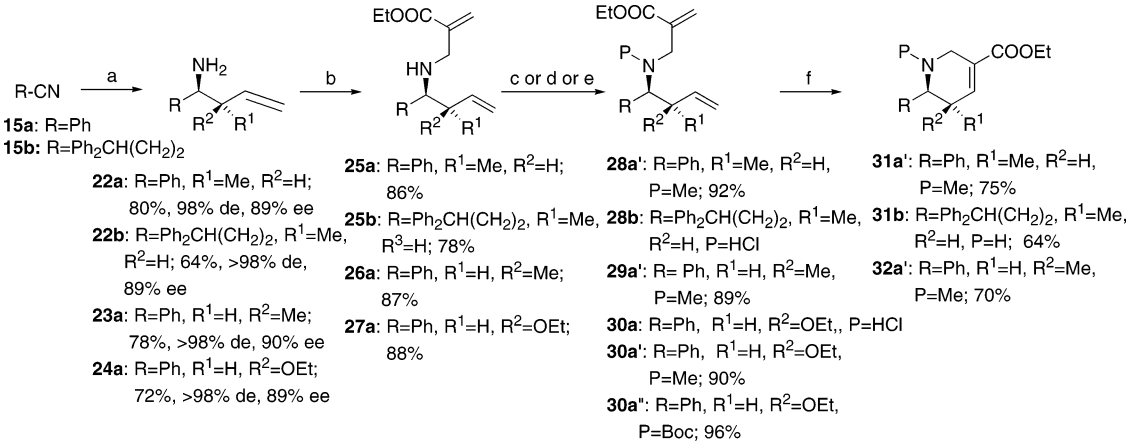
TABLE 1. Preparation of Chiral Tetrahydropyridine-3-carboxylates

		aminodiene					tetrahydropyridine			
entry	nitrile no.	no.	R	P	yield,[a] %	temp (°C)	no.	P	yield,[a] %	ee,[b] %
1	**15a**	**17a**	Ph	H	92[c]	60	**21a**	H	*d*	
2	**15a**	**20a**	Ph	HCl	92[c]	60	**21a**	H	72	88
3	**15a**	**20a**	Ph	HCl	92[c]	100	**21a**	H	70[e]	88
4	**15a**	**20a′**	Ph	Me	86	60	**21a′**	Me	*d*	88
5	**15a**	**20a′**	Ph	Me	86	100	**21a′**	Me	85	88
6	**15a**	**20a″**	Ph	Boc	98	60	**21a″**	Boc	73	88
7	**15b**	**20b**	$Ph_2CH(CH_2)_2$	HCl	87[c]	100	**21b**	H	62	68
8	**15c**	**20c**	Chx	HCl	86[c]	100	**21c**	H	63	68

[a] All yields are of pure isolated products. [b] The values are on the basis of the starting homoallylic amines, whose enantiomeric excess was verified by ^{19}F NMR spectroscopy after conversion to Mosher amides and/or obtained by HPLC analysis on a Chiracel OD-H column. [c] The yields are given for the free aminodienes; hydrochloride salts were not isolated. [d] No reaction; most of the unreacted starting material was recovered. [e] Catalyst **19** was used.

SCHEME 5. Preparation of C_5–C_6 Functionalized Tetrahydropyridine-3-carboxylates[a]



[a] Reagents and conditions: (a) (1) DIBAL-H (1.0 equiv); pentane or THF, 0 °C, 1 h. (2) **9**, **10**, or **11** (1.2 equiv); pentane or THF. (3) MeOH (1.0 equiv); −78 °C, 3 h. (4) $NaOH/H_2O_2$; −78 °C → RT, 14 h. (b) **12** (1.0 equiv); CH_2Cl_2, 0 °C, 6−12 h. (c) HCl (1.2 equiv); Et_2O, RT, 0.5 h. (d) Boc_2O (1.2 equiv); Et_2O, RT, 12 h. (e) Aqueous HCHO (7.0 equiv), $NaBH_3CN$ (2.0 equiv); CH_3CN, 14 h, RT. (f) **18** or **19** (0.1 equiv); PhMe, 100 °C, 14 h

partial reduction of **15a** and **15b** with DIBAL-H, by use of the reagent **9**, in the presence of 1.0 equiv of methanol, provided the corresponding *anti*-β-methyl homoallylic amines **22a** and **22b** in 80% and 64% yield, respectively, and in >98% de and 89% ee (Scheme 5).[15] Similarly, *syn*-β-methyl homoallylic amine **23a** was prepared from **15a** in 78% yield, >98% de, and 90% ee by use of the reagent **10** (Scheme 5). Alkoxyallylboration of the *N*-aluminoimine obtained from **15a** by use of the reagent **11**, in the presence of 1 equiv of methanol, furnished *syn*-β-ethoxy homoallylic amine **24a** in 72% yield, >98% de, and 89% ee (Scheme 5).[15]

These β-substituted homoallylic amines (**22a,b**, **23a**, and **24a**), upon the conjugate addition−elimination reaction with acetate **12**, yielded the corresponding aminodienes **25a,b**, **26a**, and **27a** in 78−88% yields. The RCM reactions of the aminodienes **25a**, **26a**, and **27a** as their ammonium salts (**28a**, **29a**, and **30a**, respectively) did not proceed satisfactorily even with 0.2 equiv of **18** in toluene and produced only low amounts of the desired tetrahydropyridine-3-carboxylates within 24 h, when decomposition of the starting materials was observed (Scheme 5; Table 2, entries 1 and 5). However, RCM of **28b** (the hydrochloride salt of the aliphatic aminodiene **25b**) furnished the desired tetrahydropyridine-3-carboxylate **31b** in 64% isolated yield (Scheme 5; Table 2, entry 4). Again, on the basis of our previously demonstrated work with RCM on similar dienes,[23] we assume that there is no loss of optical activity during the RCM reaction. The prepared compound **31b** is a C_5-functionalized analogue of **21b**, a chiral analogue of compound **4**.[4]

The aminodienes **25a**, **26a**, and **27a**, upon treatment with formaldehyde in the presence of $NaBH_3CN$, provided the corresponding *N*-methyl compounds **28a′**, **29a′**, and **30a′** in 89−92% yields. The tertiary amines **28a′** and **29a′**, upon reaction with 0.1 equiv of **18** in toluene at 100 °C, provided the corresponding densely functionalized tetrahydropyridine-3-carboxylates **31a′** and **32a′** in 75% and 70% yield, respectively (Scheme 5; Table 2, entries 2 and 6). The *N*-methylaminodiene **28a′** underwent RCM in the presence of 0.1 equiv of the catalyst **19** in toluene at 100 °C, providing the required product **31a′** in 74% isolated yield (Scheme 5; Table 2, entry 3). Unfortunately, compound **30a′** did not undergo RCM and only the starting material was recovered. Although attempted protection of aminodienes **25a** and **26a** with Boc_2O, according to numerous published procedures,[25] did not provide the expected *N*-Boc protected amines **28a″** and **29a″**, the β-alkoxy aminodiene **27a** reacted smoothly and furnished **30a″** in 96% yield. To our dismay, RCM on the β-alkoxy aminodienes **30a**, **30a′**, and **30a″** failed to proceed. The reaction would not advance despite the use of up to 0.3 equiv of **18** or **19**, added in portions over 3 days to a mixture stirring at 100 °C. In all of these cases,

TABLE 2. Preparation of C_5−C_6 Densely Functionalized Tetrahydropyridine-3-carboxylates

	aminodiene						tetrahydropyridine				
entry	no.	R	R^1	R^2	P	yield,[a] %	no.	P	yield,[b] %	de[c] (%)	ee[d] (%)
1	**28a**	Ph	Me	H	HCl	86[e]		H	*f*	98	89
2	**28a′**	Ph	Me	H	Me	79	**31a′**	Me	75	98	89
3	**28a′**	Ph	Me	H	Me	79	**31a′**	Me	74[g]	98	89
4	**28b**	$Ph_2CH(CH_2)_2$	Me	H	HCl	78[e]	**31b**	H	64	>98	89
5	**29a**	Ph	H	Me	HCl	87[e]		H	*f*	>98	90
6	**29a′**	Ph	H	Me	Me	77	**32a′**	Me	70	>98	90
7	**30a**	Ph	H	OEt	HCl	88[e]		H	*f*, *h*	>98	89
8	**30a′**	Ph	H	OEt	Me	79		Me	*f*, *h*	>98	89
9	**30a″**	Ph	H	OEt	Boc	84		Boc	*f*, *h*	>98	89

[a] All yields are of pure isolated products, obtained over two steps from homoallylic amines. [b] All yields are of pure isolated products. [c] Diastereomeric excess was verified by ^{1}H NMR analysis. [d] The values are for the starting homoallylic amines. Enantiomeric excess was verified by ^{19}F NMR spectroscopy after conversion to Mosher amides and/or obtained by HPLC analysis on a Chiracel OD-H column. [e] The ammonium salts were not isolated; the yields of free aminodienes are given. [f] No reaction, most of the unreacted starting material was recovered. [g] Catalyst **19** was used. [h] No reaction with catalysts **18** or **19**.

the starting aminodienes were recovered and no product formation was observed by TLC analysis (Table 2, entries 7−9).

In conclusion, we have developed a novel methodology for the preparation of chiral functionalized tetrahydropyridine-3-carboxylates in 68−90% ee, such as those present in GABA and muscarinic inhibitors. The methodology involves the preparation of homoallylic amines in high ee and de via allylboration of *N*-aluminoimines, followed by the conjugate addition−elimination reaction of an allylic acetate and ring-closing metathesis with Grubbs' second-generation catalyst. Substitutions on the nitrogen and C_6, as well as methyl group at C_5, are easily introduced in the tetrahydropyridines. Carboxylic esters on the double bond are accommodated during the ring-closing metathesis. We believe that our protocol will find wide application among organic and bioorganic chemists as it allows for a convenient synthesis of densely functionalized chiral nitrogen heterocycles.

Experimental Section

Preparation of homoallylic amines, vinylalumination, and ring-closing metathesis were carried out under nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use; all other chemicals and solvents were purchased commercially and used as such. Benzonitrile (**15a**) and cyclohexanecarbonitrile (**15c**) were purchased commercially, and 3,3-diphenylpropionitrile (**15b**) was prepared from commercially available 3,3-diphenylpropan-1-ol via the corresponding mesylate. The NMR chemical shifts (δ) are reported in parts per million (ppm). The enantiomeric excess of the homoallylic amines was obtained from high-performance liquid chromatography (HPLC) analysis (Chiracel OD-H column) and/or ^{19}F and ^{1}H NMR after conversion to Mosher amides.

Preparation of Ethyl 2-[(Acetyloxy)methyl]acrylate (12) via Vinylalumination. To a slurry of 4-methylmorpholine-*N*-oxide (2.5 g, 21.3 mmol) in THF (40 mL), cooled to 0 °C, was added DIBAL-H (3.0 mL, 16.8 mmol), and the mixture was stirred for 0.5 h, wherein DIBAL-H went into solution. Then, ethyl propiolate (1.1 mL, 11.2 mmol) was added and the mixture was stirred for 1 h to generate [α-(ethoxycarbonyl)-vinyl]diisobutylaluminum (**14**). Paraformaldehyde (10 g) was heated at 180 °C and the condensing anhydrous formaldehyde was transferred to the reaction mixture (warmed to 50 °C) through a short cannula. The reaction was stirred for 0.5 h at 50 °C, cooled to 0 °C, and quenched with HCl (10% in H_2O; 5 mL). The product was extracted with Et_2O (3 × 50 mL), solvents were evaporated under reduced pressure, and the residue was filtered through silica gel to furnish ethyl 2-(hydroxymethyl)acrylate (**13**; 0.7 g, 5.7 mmol, 51% yield). To the obtained **13**, diluted with CH_2Cl_2 (40 mL) and cooled to 0 °C, were added pyridine (0.6 mL, 7.4 mmol) and acetyl chloride (0.7 mL, 9.8 mmol). The reaction was stirred for 1 h at room temperature (RT), followed by quenching of the excess pyridine with HCl (10% in H_2O; 5 mL). The product was extracted with CH_2Cl_2 (1 × 20 mL) and Et_2O (2 × 30 mL), the solvents were evaporated, and the residue was purified on silica gel (95:5 hexanes/ethyl acetate) to yield **12** (1.0 g, 5.7 mmol, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.30 (t, J = 7.1 Hz, 3H), 2.09 (s, 3H), 4.23 (q, J = 7.1 Hz, 2H), 4.79 (s, 2H), 5.82 (d, J = 1.0 Hz, 1H), 6.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 14.1, 20.8, 60.9, 62.5, 127.1, 135.6, 165.1, 170.3.

Preparation of (1*S*)-1-Phenylbut-3-en-1-amine (16a). To a solution of benzonitrile (**15a**; 0.52 mL, 5.05 mmol) in Et_2O (5 mL) cooled to 0 °C was added DIBAL-H (0.89 mL, 5.0 mmol), and the mixture was stirred for 1 h to provide the intermediate *N*-aluminoimine. For the spectroscopic analysis, the solvent was removed under reduced pressure. ^{1}H NMR (300 MHz, $CDCl_3$, δ) 0.14−0.19 (m, 3H), 0.76−1.07 (m, 12H), 1.79 (m qn, J = 6.6 Hz, 3H), 7.48−7.80 (m, 5H), 9.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 22.7, 22.8, 26.3, 26.5, 28.2, 28.3, 28.5, 28.7, 129.4, 129.5, 132.4, 132.8, 133.0, 137.1, 174.5, 175.0. The obtained *N*-aluminoimine was transferred via cannula to a solution of **8** (1 M in pentane; 6 mL, 6 mmol) diluted with Et_2O (7 mL) and cooled to −100 °C, followed by a slow addition of methanol (0.20 mL, 5.0 mmol). The mixture was stirred for 1 h, while it was allowed to slowly warm from −100 to −78 °C and it was oxidized with NaOH (3 M in H_2O; 2 mL) and (slowly!) H_2O_2 (30% in H_2O; 1.2 mL) and was left stirring under positive N_2 pressure while it slowly warmed to RT. The product was then extracted with Et_2O (3 × 50 mL), treated with HCl (20% in H_2O; 5 mL), and stirred for 0.2 h. To the mixture was added water (50 mL) to extract the product. After removal of the organic layer, the aqueous solution of amine hydrochloride was neutralized with NaOH until pH ∼ 8. The resulting amine was extracted with Et_2O (3 × 50 mL), the solvent was removed under reduced pressure, and the residue was purified on silica gel (hexanes/ethyl acetate/triethylamine 84.5:15:0.5) to afford **16a** (0.66 g, 4.5 mmol, 90% yield) with 88% ee. ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.69 (br s, 2H), 2.32−2.50 (m, 2H), 4.00 (d, J = 8.0 Hz, 1H), 5.07−5.15 (m, 2H), 5.69−5.82 (m, 1H), 7.22−

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7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 44.2, 55.4, 117.7, 126.4, 127.0, 128.5, 135.5, 145.8. MS (EI) *m/z* 128, 106 (Ph-CH-NH_2), 79; MS (CI) *m/z* 148 (M + H), 131 (M − NH_3); high-resolution mass spectrometry (HRMS) 148.1126 (calcd), 148.1129 (actual). $[\alpha]_D^{20}$ = +39 ($CHCl_3$, *c* = 0.10) [lit.[26] +42 ($CHCl_3$, *c* = 0.5)].

Preparation of (1*R*)-1-(3,3-Diphenylpropyl)but-3-enylamine (16b). To a solution of 3,3-diphenylpropionitrile (**15b**; 1.03 g, 5.0 mmol) in Et_2O (10 mL), cooled to 0 °C, was added DIBAL-H (0.89 mL, 5.0 mmol), and the mixture was stirred for 1 h. The obtained intermediate *N*-aluminoimine was transferred via a cannula to a solution of **8** (1 M in pentane; 7.0 mL, 7.0 mmol) in Et_2O (7 mL), cooled to −78 °C, followed by a slow addition of methanol (0.20 mL, 5.0 mmol). The mixture was stirred for 6 h and it was oxidized with NaOH (3 M in H_2O; 2 mL) and (slowly!) H_2O_2 (30% in H_2O; 1.2 mL), and was left stirring under positive N_2 pressure while it slowly warmed to RT. The product was extracted with Et_2O (3 × 30 mL), the solvent was removed under reduced pressure, and the residue was purified on silica gel (hexanes/ethyl acetate/triethylamine 84.5:15:0.5) to afford **16b** (0.8 g, 3.2 mmol, 64% yield) with 68% ee. ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.25−1.48 (m, 2H), 1.92−2.27 (m, 4H), 2.78−2.87 (m, 3H), 3.89 (t, *J* = 7.8 Hz, 1H), 5.01−5.11 (m, 2H), 5.67−5.81 (m, 1H), 7.16−7.32 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 32.6, 36.2, 42.5, 50.9, 51.8, 117.9, 126.4, 128.0, 128.8, 135.8, 145.1, 145.3. MS (EI) *m/z* 265 (M^+), 224 (M − C_3H_5), 91 ($C_7H_7^+$); MS (CI) *m/z* 266 (M + H), 224 (M − C_3H_4), 188. $[\alpha]_D^{20}$ = +8 ($CDCl_3$, *c* = 0.6).

(1*S*)-1-Cyclohexylbut-3-en-1-amine (16c). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 0.94−1.30 (m, 6H), 1.37 (br s, 2H), 1.67−1.78 (m, 5H), 1.93−2.01 (m, 1H), 2.25−2.31 (m, 1H), 2.56 (q, *J* = 4.2 Hz, 1H), 5.06−5.12 (m, 2H), 5.73−5.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 26.5, 26.6, 26.7, 28.4, 29.8, 39.5, 43.5, 55.4, 117.2, 136.7. MS (EI) *m/z* 152 (M − H), 112 (M − C_3H_5), 95, 70; MS (CI) *m/z* 154 (M + H), 112; HRMS 154.1596 (calcd), 154.1599 (actual). $[\alpha]_D^{20}$ = +9 ($CHCl_3$, *c* = 0.37).

Ethyl 2-({[(1*S*)-1-Phenylbut-3-enyl]amino}methyl)-acrylate (17a). To **16a** (0.6 g, 4.0 mmol) diluted with CH_2Cl_2 (10 mL) was added **12** (0.7 g, 4.0 mmol), and the mixture was stirred for 12 h at RT. The solvent was evaporated under reduced pressure and the residue was purified on silica gel (flash; 95:5 hexanes/ethyl acetate) to yield **17a** (1.0 g, 3.9 mmol, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.31 (t, *J* = 7.0 Hz, 3H), 1.96 (br s, 1H), 2.34−2.42 (m, 2H), 3.19 (d, *J* = 14.6 Hz, 1H), 3.39 (d, *J* = 14.6 Hz, 1H), 3.67 (dd, *J* = 8.8 and 11.5 Hz, 1H), 4.21 (q, *J* = 10.7 Hz, 2H), 5.03−5.13 (m, 2H), 5.58 (s, 1H), 5.63−5.81 (m, 1H), 6.22 (s, 1H), 7.19−7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 14.5, 43.5, 48.4, 60.9, 61.2, 117.9, 126.5, 127.4, 127.6, 128.7, 135.7, 138.9, 143.8, 167.0.

Ethyl2-{[(1*R*)-1-(3,3-Diphenylpropyl)but-3-enylamino]-methyl}acrylate (17b). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.30 (t, *J* = 7.1 Hz, 3H), 1.37−1.45 (m, 2H), 2.07−2.25 (m, 5H), 2.63 (qn, *J* = 5.9 Hz, 1H), 3.39 (br s, 2H), 3.89 (t, *J* = 7.7 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 5.05−5.10 (m, 2H), 5.63 (s, 1H), 5.69−5.78 (m, 1H), 6.23 (s, 1H), 7.16−7.32 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 14.5, 43.5, 48.4, 60.9, 61.2, 117.9, 126.5, 127.4, 127.6, 128.7, 135.7, 138.9, 143.8, 167.0.

Ethyl 2-({[(1*S*)-1-Cyclohexylbut-3-enyl]amino}methyl)-acrylate (17c). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.00−1.53 (m, 11H), 1.75−1.84 (m, 4H), 2.09−2.19 (m, 1H), 2.27−2.46 (m, 2H), 3.50 (s, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 5.10−5.17 (m, 2H), 5.77 (s, 1H), 5.82−5.91 (m, 1H), 6.29 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 14.2, 26.7, 26.8, 28.9, 29.3, 35.4, 40.5, 48.4, 60.7, 136.7, 139.3, 166.9.

Preparation of Ethyl 2-({Methyl[(1*S*)-1-phenylbut-3-enyl]amino}methyl)acrylate (20a′). To a solution of **17a** (0.08 g, 0.3 mmol) in CH_3CN (60 mL) cooled to 0 °C was added formaldehyde (37% in H_2O; 0.15 mL, 2.0 mmol), followed by $NaBH_3CN$ (1 M in THF; 0.6 mL, 0.6 mmol), and the mixture was stirred for 14 h at RT. The solvent was removed under reduced pressure and the residue was purified on silica gel (flash; 97:3 hexanes/ethyl acetate) to yield **20a′** (0.07 g, 0.3 mmol, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.38 (t, *J* = 7.1 Hz, 3H), 2.22 (s, 3H), 2.58−2.82 (m, 2H), 3.14 (d, *J* = 14.7 Hz, 1H), 3.36 (d, *J* = 14.4 Hz, 1H), 3.70 (t, *J* = 6.9 Hz, 1H), 4.28 (q, *J* = 7.0 Hz, 2H), 4.99−5.10 (m, 2H), 5.71−5.79 (m, 1H), 5.84 (s, 1H), 6.28 (s, 1H), 7.31−7.42 (m, 5H).

Preparation of Ethyl (6*S*)-6-Phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (21a). To **17a** (0.05 g, 0.2 mmol), diluted with Et_2O (2 mL), was added HCl (1 M in Et_2O; 0.3 mL, 0.3 mmol), and the mixture was stirred for 0.5 h at RT to generate **20a**, followed by the addition of chloroform (250 mL), warming to 60 °C, and addition of **18** (0.02 g, 0.02 mmol, 0.1 equiv) and stirring for 14 h at 60 °C. The mixture was concentrated to approximately 20 mL, when it was neutralized with $NaHCO_3$ (saturated aqueous; 3 mL) and vigorously stirred for 1 h at RT. The product was extracted with Et_2O (3 × 20 mL), the solvents were removed under reduced pressure, and the residue was purified on silica gel (flash; hexanes/ethyl acetate 2:1) to furnish **21a** (0.03 g, 0.14 mmol, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.38 (t, *J* = 7.1 Hz, 3H), 3.76−3.95 (m, 3H), 4.30 (q, *J* = 7.1 Hz, 2H), 7.18 (br s, 1H), 7.34−7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 14.6, 34.6, 45.5, 57.1, 60.7, 126.9, 127.9, 129.0, 130.1, 138.1, 166.2. MS (EI) *m/z* 231 (M^+), 202 (M − C_2H_5), 158, 104; MS (CI) *m/z* 232 (M + H), 155; HRMS (EI) 231.1259 (calcd), 231.1257 (actual). $[\alpha]^{20}_D$ = +68 ($CHCl_3$, *c* = 0.1).

Ethyl (6*S*)-1-Methyl-6-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (21a′). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.31 (t, *J* = 7.1 Hz, 3H), 2.12 (s, 3H), 2.48−2.56 (m, 2H), 3.08 (dq, *J* = 3.2 and 18.0 Hz, 1H), 3.21 (dd, *J* = 5.1 and 8.5 Hz, 1H), 3.70 (dd, *J* = 1.3 and 16.9 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 7.06 (d, *J* = 2.2 Hz, 1H), 7.35−7.27 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, δ) 14.6, 36.0, 43.5, 54.4, 60.7, 65.0, 127.9, 128.2, 128.9, 129.3, 137.6, 142.5, 166.0. MS (EI) *m/z* 245 (M^+), 118; MS (CI) *m/z* 246 (M + H); HRMS (EI) 245.1416 (calcd), 245.1417 (actual). $[\alpha]_D^{20}$ = −59 ($CHCl_3$, *c* = 1.1).

Preparation of 1-*tert*-Butyl 3-Ethyl (6*S*)-6-Phenyl-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (21a″). To a solution of **17a** (0.08 g, 0.3 mmol) in Et_2O (10 mL) was added di-*tert*-butyl dicarbonate (0.07 g, 0.3 mmol), and the mixture was stirred for 14 h at RT. Filtration through silica gel furnished the desired *N*-Boc protected amine **20a″** (0.10 g, 0.3 mmol, 99% yield). The obtained **20a″** was diluted with chloroform (250 mL) and heated to 60 °C, and **18** (0.03 g, 0.03 mmol) was added. The solution was refluxed for 14 h, when the solvent was evaporated and the residue was purified on silica gel (flash; 95:5 hexanes/ethyl acetate) to yield **21a″** (0.07 g, 0.2 mmol, 71% yield from **17a**). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.27 (t, *J* = 7.1 Hz, 3H), 1.51 (s, 9H), 2.78−2.81 (m, 2H), 3.41 (dd, *J* = 2.4 Hz and 18.5 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.55 (d, *J* = 18.7 Hz, 1H), 5.61−5.62 (m, 1H), 7.17−7.31 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 14.5, 28.3, 28.8, 39.4, 50.1, 60.9, 80.7, 127.0, 127.6, 128.6, 128.6, 136.1, 140.2, 155.2, 165.4. MS (EI) *m/z* 331 (M^+), 57 ($C_4H_9^+$); MS (CI) *m/z* 332 (M + H), 276 (M + H − C_6H_8); HRMS (EI) 331.1784 (calcd), 331.1782 (actual). $[\alpha]_D^{20}$ = −5 ($CHCl_3$, *c* = 0.08).

Ethyl (6*R*)-6-(3,3-Diphenylpropyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (21b). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.28 (t, *J* = 7.0 Hz, 3H), 1.95−2.23 (m, 6H), 2.66−2.82 (m, 2H), 3.49 (d, *J* = 17.1 Hz, 1H), 3.68 (d, *J* = 17.0 Hz, 1H), 3.88 (t, *J* = 7.6 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 6.98 (br s, 1H), 7.15−7.31 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 14.6, 32.6, 35.1, 36.4, 42.8, 44.8, 51.8, 60.6, 117.7, 126.5, 128.1, 128.7, 128.8, 136.1, 138.0, 145.1, 166.4. MS (EI) *m/z* 349 (M^+), 167, 154, 80; (CI) *m/z* 350 (M + H), 155; HRMS (EI) 349.2042 (calcd), 349.2045 (actual). $[\alpha]_D^{20}$ = +9 ($CDCl_3$, *c* = 0.2).

Ethyl (6*S*)-6-Cyclohexyl-1,2,5,6-tetrahydropyridine-3-carboxylate (21c). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.05−1.32 (m, 9H), 1.76−3.18 (m, 8H), 2.42−2.51 (m, 1H), 3.49 (d, *J* = 24.0 Hz, 1H), 3.75 (d, *J* = 24.0 Hz, 1H), 4.19 (q, *J* = 10.6 Hz,

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2H), 7.01 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 15.6, 27.5, 27.7, 29.9, 30.5, 43.4, 45.9, 57.8, 61.2, 116.8, 138.5, 144.0, 170.3. MS (EI) *m/z* 237 (M^+), 154 (M − C_6H_{11}), 80; MS (CI) *m/z* 238 (M + H), 192, 155; HRMS 237.1729 (calcd), 237.1725 (actual). $[\alpha]_D^{20}$ = +104 ($CDCl_3$, *c* =1.0).

Preparation of (1*S*,2*S*)-2-Methyl-1-phenylbut-3-en-1-amine (22a). To potassium *tert*-butoxide (1 M in THF; 6 mL, 6 mmol) diluted with THF (6 mL) and cooled to −78 °C was added *trans*-butene (1 mL, 11 mmol) and *n*-butyllithium (2.5 M in hexanes; 2.4 mL, 6.0 mmol). The mixture was stirred for 0.1 h at −78 °C, followed by 0.3 h at −55 °C, and cooled again to −78 °C, when a solution of (−)-*B*-methoxydiisopinocampheylborane (2.28 g, 7.2 mmol) in THF (5 mL) was added, and the reaction was stirred for 1 h at −78 °C. To thus generated **9** was added via cannula *N*-aluminoimine [prepared as follows: to **15a** (0.52 mL, 5.05 mmol) diluted with THF (5 mL) and cooled to 0 °C was added DIBAL-H (0.89 mL, 5.0 mmol), and the mixture was stirred for 1 h], followed by methanol (0.20 mL, 5.0 mmol), and the mixture was stirred for 3 h at −78 °C, when it was oxidized with NaOH (3 M in H_2O; 2 mL) and (slowly!) H_2O_2 (30% in H_2O; 1.2 mL); and the reaction was left stirring under positive N_2 pressure while it slowly warmed to RT. The product was extracted with Et_2O (3 × 50 mL) after the acid−base manipulation, the solvent was removed under reduced pressure, and the crude material was purified on silica gel (hexanes/ethyl acetate/triethylamine 84.5:15:0.5) to afford **22a** (0.64 g, 4.0 mmol, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 0.83 (d, *J* = 6.7 Hz, 3H), 1.53 (br s, 2H), 2.37 (q, *J* = 7.4 Hz, 1H), 3.65 (d, *J* = 8.5 Hz, 1H), 5.10−5.20 (m, 2H), 5.69−5.81 (m, 1H), 7.26−7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 17.7, 46.4, 60.7, 115.9, 127.1, 127.3, 128.3, 141.8, 144.7. MS (EI) *m/z* 160 (M − H), 106, 79; MS (CI) *m/z* 162, 145, 106. $[\alpha]_D^{20}$ = +76 ($CHCl_3$, *c* = 0.92).

Preparation of (1*R*,2*S*)-1-(3,3-Diphenylpropyl)-2-methylbut-3-enylamine (22b). To potassium *tert*-butoxide (1 M in THF; 6 mL, 6 mmol), diluted with pentane (12 mL) and cooled to −78 °C was added *trans*-butene (1 mL, 11 mmol) and *n*-butyllithium (2.5 M in hexanes; 2.4 mL, 6.0 mmol). The mixture was stirred for 0.1 h at −78 °C, followed by 0.3 h at −55 °C, and cooled again to −78 °C, when a solution of (−)-*B*-methoxydiisopinocampheylborane (2.28 g, 7.2 mmol) in pentane (5 mL) was added, and the reaction was stirred for 1 h at −78 °C. To thus generated reagent **9** was added via a cannula the *N*-aluminoimine [prepared as follows: to **15b** (1.03 g, 5.0 mmol) diluted with pentane (10 mL) and cooled to 0 °C was added DIBAL-H (1 M in hexanes; 5.0 mL, 5.0 mmol), and the mixture was stirred for 1 h], followed by methanol (0.20 mL, 5.0 mmol); the mixture was stirred for 3 h at −78 °C, when it was oxidized with NaOH (3 M in H_2O; 2 mL) and (slowly!) H_2O_2 (30% in H_2O; 1.2 mL) and was left stirring under positive N_2 pressure while it slowly warmed to RT. The product was extracted with Et_2O (3 × 50 mL), the volatiles were removed under reduced pressure, and the residue was purified on silica gel (hexanes/ethyl acetate/triethylamine 84.5:15:0.5) to afford **22b** (0.9 g, 3.4 mmol, 64% yield) with 89% ee, >98% de. ^{1}H NMR (300 MHz, $CDCl_3$, δ) 0.97 (d, *J* = 6.8 Hz, 3H), 1.16−1.31 (m, 3H), 2.06−2.33 (m, 3H), 2.58−2.63 (m, 1H), 3.90 (t, *J* = 7.7 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 1H), 5.00−5.06 (m, 2H), 5.63−5.75 (m, 1H), 7.20−7.30 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 17.1, 25.6, 32.6, 33.7, 44.0, 51.8, 55.6, 115.7, 126.3, 128.0, 128.4, 128.7, 141.0, 145.4. MS (EI) *m/z* 279 (M^+), 224, 129, 91; MS (CI) *m/z* 280 (M + H), 224, 202. $[\alpha]_D^{20}$ = +11 ($CHCl_3$, *c* = 0.05).

(1*S*,2*R*)-2-Methyl-1-phenylbut-3-en-1-amine (23a). Obtained similarly to **22a**, however, the reagent **10** was used: ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.06 (d, *J* = 7.2 Hz, 3H), 1.65 (br s, 2H), 2.57 (q, *J* = 8.6 Hz, 1H), 3.96 (d, *J* = 5.1 Hz, 1H), 5.08−5.11 (m, 2H), 5.70−5.76 (m, 1H), 7.28−7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 15.3, 45.0, 60.2, 115.3, 127.1, 127.4, 128.3, 141.3, 144.5. $[\alpha]_D^{20}$ = −27 ($CDCl_3$, *c* = 2.46).

Preparation of (1*R*,2*R*)-2-Ethoxy-1-phenylbut-3-en-1-amine (24a). To a solution of allyl ethyl ether (0.57 mL, 5.0 mmol) in THF (5 mL) cooled to −78 °C was added *sec*-butyllithium (1.4 M in cyclohexane; 3.6 mL, 5.0 mmol), and the mixture was stirred for 1 h at −78 °C. To the generated anion was added (−)-*B*-methoxydiisopinocampheylborane (2.28 g, 7.2 mmol) in THF (5 mL), and the mixture was stirred for 1 h at −78 °C. To thus generated "ate" complex **11** was added via a cannula the *N*-aluminoimine [prepared as follows: to **15a** (0.52 mL, 5.0 mmol) diluted with THF (5 mL) and cooled to 0 °C was added DIBAL-H (0.89 mL, 5.0 mmol), and the mixture was stirred for 1 h] at −78 °C, followed by a dropwise addition of methanol (0.20 mL, 5.0 mmol). The reaction was stirred for 8 h at −78 °C and was oxidized with NaOH (3 M in H_2O; 2 mL) and H_2O_2 (30% in H_2O; 1.2 mL) and was allowed to warm to RT under positive N_2 pressure. The product was extracted with Et_2O (3 × 30 mL), the solvents were evaporated, and the residue was purified on silica gel (ethyl acetate/hexanes/triethylamine 20:79:1) to furnish **24a** (0.58 g, 3.6 mmol, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.21 (t, *J* = 7.0 Hz, 3H), 1.84 (br s, 2H), 3.31−3.41 (m, 1H), 3.56−3.64 (m, 1H), 3.72 (t, *J* = 7.2 Hz, 1H), 3.90 (d, *J* = 7.5 Hz, 1H), 5.01−5.10 (m, 2H), 5.49−5.58 (m, 1H), 7.24−7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 15.6, 60.7, 64.9, 86.4, 118.1, 127.7, 128.2, 128.3, 128.5, 136.4. MS (EI) *m/z* 144 (M − OEt), 106, 79; MS (CI) 192 (M + H), 175 (M + H − NH_3), 146 (M + H − HOEt), 129, 106. $[\alpha]_D^{20}$ = −8 ($CHCl_3$, *c* = 0.7).

Ethyl 2-({[(1*S*,2*S*)-2-Methyl-1-phenylbut-3-enyl]amino}-methyl)acrylate (25a). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.04 (d, *J* = 6.6 Hz, 3H), 1.37 (t, *J* = 7.4 Hz, 3H), 1.91 (br s, 1H), 2.51−2.60 (m, 1H), 3.21 (d, *J* = 14.7 Hz, 1H), 3.48 (d, *J* = 15.0 Hz, 1H), 3.67 (d, *J* = 5.1 Hz, 1H), 4.28 (q, *J* = 7.0 Hz, 2H), 5.03−5.08 (m, 2H), 5.65 (s, 1H), 5.73−5.84 (m, 1H), 6.28 (s, 1H), 7.27−7.41 (m, 5H).

Ethyl 2-({[(1*R*,2*S*)-1-(3,3-Diphenylpropyl)-2-methylbut-3-enyl]amino}methyl)acrylate (25b). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 0.92 (d, *J* = 6.5 Hz, 3H), 1.26−1.44 (m, 5H), 2.03−2.10 (m, 2H), 2.28−2.38 (m, 2H), 3.27 (d, *J* = 14.7 Hz, 1H), 3.40 (d, *J* = 14.0 Hz, 1H), 3.85 (t, *J* = 7.6 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 4.98−5.03 (m, 2H), 5.58 (s, 1H), 5.56−5.65 (m, 1H), 6.19 (s, 1H), 7.16−7.30 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 14.5, 16.4, 28.7, 31.2, 40.8, 48.4, 51.9, 60.3, 60.8, 61.0, 115.3, 126.1, 126.4, 128.1, 128.7, 139.3, 142.1, 145.5, 167.1.

Ethyl 2-({[(1*S*,2*R*)-2-Methyl-1-phenylbut-3-enyl]amino}-methyl)acrylate (26a). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 0.74 (d, *J* = 6.8 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 2.10 (br s, 1H), 2.29−2.37 (m, 1H), 3.06 (d, *J* = 14.7 Hz, 1H), 3.27 (d, *J* = 8.8 Hz, 1H), 3.35 (d, *J* = 14.6 Hz, 1H), 4.20 (q, *J* = 6.9 Hz, 2H), 5.07−5.19 (m, 2H), 5.50 (s, 1H), 5.59−5.68 (m, 1H), 6.20 (s, 1H), 7.24−7.35 (m, 5H).

Ethyl 2-({[(1*R*,2*R*)-2-Ethoxy-1-phenylbut-3-enyl]amino}-methyl)acrylate (27a). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.20 (t, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 2.68 (br s, 1H), 3.11−3.39 (m, 3H), 3.54−3.62 (m, 1H), 3.69 (q, *J* = 8.6 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.89−5.01 (m, 2H), 5.41−5.52 (m, 1H), 5.56 (s, 1H), 6.22 (s, 1H), 7.23−7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 14.5, 15.6, 48.8, 60.9, 64.7, 66.2, 85.6, 118.2, 126.3, 127.7, 128.4, 129.1, 136.1, 138.9, 140.2, 167.0.

Ethyl 2-({[(1*S*,2*S*)-2-Methyl-1-phenylbut-3-enyl]amino}-methyl)acrylate (28a′). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.12 (d, *J* = 6.6 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 2.10 (s, 3H), 2.85−2.92 (m, 1H), 3.05 (d, *J* = 15.0 Hz, 1H), 3.14 (d, *J* = 15.0 Hz, 1H), 3.30 (d, *J* = 9.9 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.79−4.90 (m, 2H), 5.52−5.63 (m, 1H), 5.73 (s, 1H), 6.18 (s, 1H), 7.13−7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 14.5, 18.3, 30.0, 37.5, 38.8, 55.2, 60.9, 73.5, 114.6, 125.6, 127.2, 127.9, 129.8, 137.3, 139.0, 142.0, 167.7.

Ethyl 2-({[(1*S*,2*R*)-2-Methyl-1-phenylbut-3-enyl]amino}-methyl)acrylate (29a′). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 0.80 (d, *J* = 6.6 Hz, 3H), 1.30 (t, *J* = 7.3 Hz, 3H), 2.09 (s, 3H), 2.84−2.97 (m, 1H), 3.15 (s, 2H), 3.41 (d, *J* = 9.9 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 5.01−5.12 (m, 2H), 5.84 (d, *J* = 1.5 Hz, 1H), 5.90−6.01 (m, 1H), 6.25 (s, 1H), 7.22−7.42 (m, 5H); ^{13}C NMR

(75 MHz, $CDCl_3$, δ) 14.6, 17.9, 37.2, 39.2, 55.1, 60.8, 73.7, 113.0, 125.7, 127.3, 128.1, 129.4, 137.3, 138.8, 143.5, 167.7.

Ethyl (5*S*,6*S*)-1,5-Dimethyl-6-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (31a′). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 0.97 (d, J = 7.5 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H), 2.31 (s, 3H), 2.92−3.00 (m, 1H), 3.38 (s, 2H), 3.76 (d, J = 4.5 Hz, 1H), 4.32 (q, J = 7.0 Hz, 2H), 7.23−7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 14.6, 16.4, 36.0, 43.5, 50.9, 60.8, 67.9, 100.3, 127.8, 128.3, 128.7, 129.9, 143.2, 166.0. MS (EI) *m/z* 259 (M^+), 244 (M − CH_3), 230 (M − CH_2CH_3), 118; MS (CI) *m/z* 260 (M + H), 214, 169; HRMS (EI) 259.1572 (calcd), 259.1576 (actual). $[\alpha]_D^{20}$ = +59 ($CDCl_3$, *c* = 0.23).

Ethyl (5*S*,6*R*)-6-(3,3-Diphenylpropyl)-5-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (31b). ^{1}H NMR (300 MHz, $CDCl_3$, δ) 0.95 (d, J = 7.1 Hz, 3H), 1.21−1.37 (m, 5H), 1.56−1.68 (m, 2H), 2.04−2.30 (m, 3H), 3.43 (d, J = 17.3 Hz, 1H), 3.64 (d, J = 17.3 Hz, 1H), 3.89 (t, J = 7.5 Hz, 1H), 4.19 (q, J = 7.0 Hz, 2H), 6.76 (s, 1H), 7.17−7.28 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 15.1, 30.5, 32.6, 36.4, 44.5, 52.1, 60.8, 67.1, 126.0, 127.6, 128.3, 134.5, 139.9, 143.3, 162.1. MS (EI) *m/z* 363 (M^+), 179, 168, 94, 56; MS (CI) *m/z* 364 (M + H), 169; HRMS (EI) 363.2198 (calcd), 363.2797 (actual). $[\alpha]_D^{20}$ = +86 ($CDCl_3$, *c* = 1.2).

Ethyl (5*R*,6*S*)-1,5-Dimethyl-6-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (32a′). ^{1}H NMR (200 MHz, $CDCl_3$, δ) 0.87 (d, J = 6.8 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 2.06 (s, 3H), 2.28−2.30 (m, 1H), 2.66−2.67 (m, 1H), 2.97 (d, J = 25.2 Hz, 1H), 3.73 (d, J = 26.1 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 6.89 (br s, 1H), 7.25−7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, δ) 15.6, 18.8, 30.9, 40.4, 44.6, 55.5, 61.4, 73.8, 127.8, 128.8, 143.1, 163.1. MS (EI) *m/z* 259 (M^+), 230 (M − C_2H_5), 118 ($C_9H_{10}^+$); MS (CI) *m/z* 260 (M + H), 169; HRMS (EI) 259.1572 (calcd), 259.1576 (actual). $[\alpha]_D^{20}$ = +10 ($CDCl_3$, *c* = 1.0).

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Supporting Information Available: All ^{1}H and ^{13}C NMR spectra of the compounds described (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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