Highly Diastereoselective and Enantioselective Preparation of Homoallylic Amines: Application for the Synthesis of β-Amino Acids and γ-Lactams

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Dedicated to Professor Ei-ichi Negishi on the occasion of his 70th birthday

Abstract: Reactions of N-silyl- and N-aluminoimines with B-allyldiisopinocampheylborane in the presence of methanol, followed by oxidative workup furnished homoallylic amines in good yields and high *ee*. A ^{11}B NMR spectroscopy study revealed that the reactions do not proceed, even at room temperature, unless a molar equivalent of water or methanol is added. The first reagent-controlled asymmetric crotylboration and alkoxyallylboration of aldimines furnishing β-methyl or β-alkoxy homoallylic amines in very high diastereoselectivity and enantioselectivity are reported herein. Crotylboration and alkoxyallylboration of imines proceed only with the "allyl"-boron "ate" complexes, instead of the "allyl"-dialkylboron reagents used with aldehydes. The addition of methanol is necessary for these reactions as well. Application of this methodology for the conversion of representative nitriles to β-amino acids in two steps has been described. Additionally, a procedure for the preparation of chiral δ-amino alcohols and γ-lactams from nitriles is also reported.

Keywords: allylic compounds · amines · asymmetric synthesis · boranes · imines

Introduction

Preparation of optically pure homoallylic amines is an important task in organic synthesis. Such amines are excellent building blocks for the synthesis of a plethora of nitrogen-containing natural products.[1] Owing to the importance of homoallylic amines, there are abundant literature reports for their preparation using a wide variety of methods.[1d,2] Diastereoselective addition of allyl organometallic compounds to N-substituted imines is a widely recognized procedure for the preparation of homoallylic amines.[3] While the use of substrate-controlled asymmetric additions is a common procedure, the use of reagent control still remains undeveloped.[3] Numerous N-substituted imines have been developed and applied for the syntheses of a variety of molecules, such as amino acids, β-lactams, heterocycles, aziridines, alkaloids, and amines.[3] These aldimines include N-sulfiniyl,[4] N-sulfonyl,[5] N-trialkylsilyl,[6] oximes,[7] and various N-metalloimines.[8] N-silylimines have been first prepared by Rochow and co-workers by reacting aromatic aldehyde with lithium bis(trimethylsilyl)amide.[9] Reactions of such imines with organometallic reagents for the preparation of homoallylic amines was first reported by Hart and co-workers.[10] Enolizable N-silylimines are not stable, but were characterized at very low temperatures (−100 °C).[11] Their preparation and in situ trapping at low temperatures furnished only low yields of the synthesized β-lactam products.[12] This inefficiency of N-silylimines, however, could be alleviated by the use of N-aluminoimines, which were first prepared by Cainelli and co-workers by partial reduction of nitriles with diisobutylaluminum hydride (DIBAL-H).[13] Among the advantages of N-aluminoimines are the ready availability or ease of preparation of the starting nitriles, ease of the imine formation, and relatively high stability of both aromatic and aliphatic imines, even at room temperature. Due to the above advantages of N-aluminoimines and our ongoing interest in organoaluminum chemistry,[14] they became a very interesting substrate for our investigation.

In spite of aldimines being very attractive starting materials for syntheses, the inherent instability of unsubstituted aldimines and the lack of reactivity of the more stable N-substituted ones significantly limit their use.[15] Furthermore, at-

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tempted 1,2-additions to aldimines quite often fail due to the tendency of enolizable compounds to undergo deprotonation instead of addition.[3e] Among the developments in allylations of aldimines, organoboron compounds have found synthetic utility due to the Lewis acidity of boron, which coordinates to nitrogen and improves the electrophilicity of the aldimine. Allylborations and crotylborations of α-optically pure N-substituted aldimines in high diastereoselectivity due to the sterically influenced chirality according to the Cram rules, using B-"allyl"-9-BBN, was described by Yamamoto and co-workers.[16] Reactions of arylimines, oximes and oxime ethers with allyl and crotylboronates were reported to proceed in moderate to good diastereoselectivity.[7] However, use of N-borylimine containing a chiral auxiliary, followed by the addition of alkyllithium reagents gave only poor enantioselectivity.[17]

Asymmetric allylboration, crotylboration, and alkoxyallylboration of aldehydes with reagents **I**–**IV** derived from α-pinene[18] (Figure 1) are well documented and widely used in organic syntheses.[19] In spite of a few reports regarding chiral allylboration of N-masked imines,[20] reactions of these and other boron-based chiral reagents with imines to form homoallylic amines remain significantly underdeveloped. Itsuno and co-workers had reported the preparation of assorted homoallylic amines in moderate to good enantioselectivities from various N-protected imines, such as N-oxime ethers, N-sulfenimines, and N-trimethylsilylimines, by using chiral allylboranes derived from tartrate esters, diols, α-amino alcohols, and α-pinene.[20] They concluded that N-trimethylsilylimines are the most reactive species for such allylations. During our work on the applications of α-pinene-based "allyl"-borating reagents we always obtained homoallylic alcohols in very high *ee* during the allylboration of aldehydes.[19] However, the enantioselectivity reported for the allylboration of N-trimethylsilylbenzaldimine (**1a**) with **I**, complete within 3 h, was only a moderate 73 %.[20a] Since the rate of allylboration of aldehydes with **I** was established as exceptionally fast at −78 °C, and fast even at −100 °C,[21] it appeared desirable to obtain comparable information about the allylboration of imines. The low *ee* value and the slow rate of the reaction prompted us to undertake a project involving "allyl"-boration of N-substituted aldimines. The preliminary results were reported earlier.[22]

Crotylboration and alkoxyallylboration of N-silyl- or N-aluminoimines for the preparation of densely functionalized homoallylic amines have never been reported. In this paper, we describe the results of our investigations on the "allyl"-boration of N-silyl- and N-aluminoimines.

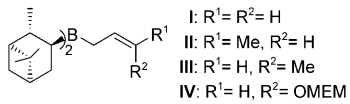
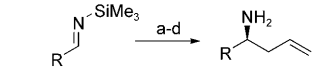


Figure 1. α-Pinene-based reagents for asymmetric allylboration.

Results and Discussion

Allylboration of N-silylimines: N-Trimethylsilylbenzaldimine (**1a**) was mixed with (−)-B-allyldiisopinocampheylborane (**I**) at −78 °C in THF and the reaction was monitored with ^{11}B NMR spectroscopy. The spectrum of an aliquot revealed only unchanged starting materials, even after several hours at room temperature. This was a surprise since allylboration of aldehydes with **I** was previously established as an extremely fast reaction[21] and the previous report[20a] claimed that the reaction was complete within 3 h. However, the desired amine **2a** was obtained in good yield after aqueous workup, which was very exothermic. We rationalized that the reaction must have taken place during the workup when the addition of water resulted in the liberation of the "naked" aldimine intermediate, which rapidly reacted with **I**. We were not able to identify this intermediate spectroscopically, presumably due to the extremely fast rate of the allylboration.[21] Consequently, **1a** was mixed with **I** at −78 °C in THF and upon dropwise addition of 1 equiv of water dissolved in THF to the reaction mixture and workup provided **2a** in 90 % yield and 92 % *ee*, which was considerably better than 70 % yield and 73 % *ee* previously reported (Scheme 1).[20a] Lowering the reaction temperature to −100 °C increased the chiral induction to 94 % *ee*.



1a: R = Ph
1b: R = 2-Thp
1c: R = 4-MeO-(C_6H_4)
1d: R = 2-Cl-(C_6H_4)
1e: R = 2-furyl

2a: R = Ph
2b: R = 2-Thp
2c: R = 4-MeO-(C_6H_4)
2d: R = 2-Cl-(C_6H_4)
2e: R = 2-furyl

Scheme 1. Allylboration of N-silylimines: a) **I**, THF; −100 or −78 °C; b) **1a**–**e**; c) H_2O; 1 h, −100 or −78 °C; d) NaOH, H_2O_2; −78 °C→RT. Thp = thiophene.

After we had standardized the reaction conditions, we examined the allylboration of other N-silylimines prepared from aromatic aldehydes, namely 2-thienyltrimethylsilylimine (**1b**), 4-methoxybenzaldimine (**1c**), 2-chlorobenzaldimine (**1d**), and 2-furfuraldimine (**1e**) (Scheme 1). The above N-silylaldimines upon reaction with **I** in the presence of 1 equiv of water, followed by workup furnished the expected homoallylic amines **2b**–**e** in good yields and high enantioselectivity (Table 1). The yields and enantioselectivities of **2b** and **c** were considerably better than previously reported.[20a] We thus established that N-silylimines were not reactive toward **I** unless a molar equivalent of water was added to the reaction mixture.[22] Later studies revealed that methanol could replace water.[23]

Crotylboration of N-silylimines: Crotylboration of aldehydes with **II** and **III**[18c] is a well-known and highly utilized procedure for the syntheses of numerous complex natural products.[19,24] However, crotylboration of N-substituted imines

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Table 1. Allylboration of N-silylimines.

Entry	Imine		T [°C]	Homoallylic amine		
		R			Yield [%][a]	*ee* [%][b]
1	**1a**	Ph	−78	**2a**	90	92
1	**1a**	Ph	−100	**2a**	87	94
2	**1b**	2-Thp	−78	**2b**	72	81
3	**1c**	4-MeO-(C_6H_4)	−78	**2c**	74	92
4	**1d**	2-Cl-(C_6H_4)	−78	**2d**	69	82
5	**1e**	2-furyl	−78	**2e**	86	86

[a] All yields are of pure isolated products. [b] Enantiomeric excess was determined with HPLC using Chiracel OD-H column and hexanes/isopropanol as the mobile phase.

with these reagents has never been reported. Unlike **I**, which can be prepared and stored for short periods of time, the reagents **II** and **III** are made fresh and used immediately.[18c] The treatment of *cis*- or *trans*-butene with Schlosser's base (equimolar mixture of butyllithium and potassium *tert*-butoxide) at −55 °C furnishes the crotyl anion.[25] Reaction of this anion with *B*-methoxydiisopinocampheylborane furnishes the corresponding boron "ate" complex (**V** or **VI**). In the crotylboration of aldehydes, this "ate" complex is broken by the addition of 1.3 equiv $BF_3{\cdot}OEt_2$ to generate trialkylborane reagents **II** or **III** (Figure 2).[18c,26] However, we found that addition of $BF_3{\cdot}OEt_2$ had detrimental effect on crotylboration of N-silylaldimines and multiple unidentified products were obtained. Indeed, a blank experiment, in which **1a** was mixed with methanol and $BF_3{\cdot}OEt_2$ showed immediate degradation of **1a** (based on a ^{1}H NMR analysis of an aliquot). Therefore, we resorted to crotylboration of the aldimines with the "ate" complexes **V** and **VI** (Figure 2).

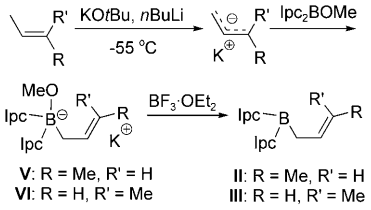
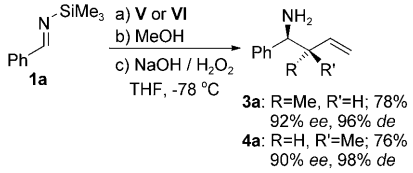


Figure 2. Preparation of reagents for asymmetric crotylboration. Ipc = isopinocampheyl.

To the best of our knowledge, this is the first report of crotylboration with "ate" complexes **V** or **VI**. We had recently reported similar alkoxyallylboration of fluoral with "ate" complex **VII**.[27] We do not know the exact mechanism of the crotylboration with the "ate" complex. The ^{11}B NMR spectrum of the reaction mixture containing **1a** and **V** showed a peak at δ 4, corresponding to the "ate" complex[18c] and in ^{1}H NMR spectrum there was a peak at δ 9.0, corresponding to the unreacted N-silylimine. Upon addition of methanol, we observed an exothermic reaction and ^{11}B NMR spectrum of an aliquot showed the formation of a broad peak at δ 48 and disappearance of the peak at δ 4. Additionally, we observed the disappearance of the peak at δ 9.0 in the crude ^{1}H NMR spectrum. We are currently investigating the mechanism in detail.

The reaction was complete within 3 h and alkaline oxidative workup provided the expected β-methyl homoallylic amine **3a** in 78% yield, 92% *ee* and 96% *de*. The reaction of **VI** with **1a**, after the addition of methanol was also complete within 3 h and alkaline oxidative workup, followed by purification provided the amine **4a** in 76% yield, 90% *ee*, and 98% *de* (Scheme 2).



Scheme 2. Crotylboration of N-silylimines.

Alkoxyallylboration of N-silylimines: Alkoxyallylboration of aldehydes with **IV**[18d] has found many applications in organic syntheses.[19,28] However, there are no literature reports regarding alkoxyallylboration of imines for the preparation of β-alkoxy homoallylic amines. Similar to the reagents **II** and **III**, alkoxyallylboration reagent **IV** is prepared freshly before reaction. Treatment of allyl ether with *sec*-butyllithium furnishes the (*Z*)-allylic anion due to the coordination between the oxygen and lithium.[18d] The allylic anion reacts with *B*-methoxydiisopinocampheylborane to give the corresponding boron "ate" complex **VII**, which upon the addition of $BF_3{\cdot}OEt_2$ gives the reagent **IV** (Figure 3).[18d] However, again, as in the case of crotylboration of N-silylimines, the reactions were not compatible with $BF_3{\cdot}OEt_2$ and the "ate" complex **VII** was used for alkoxyallylboration.

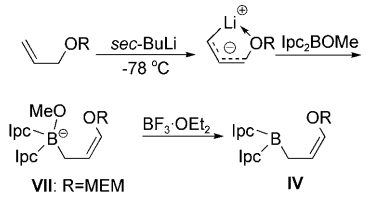


Figure 3. Preparation of alkoxyallylborane reagents.

Our experience in alkoxyallylboration revealed that the best results were obtained with 3-[(2-methoxyethoxy)methoxy]prop-1-ene (allyl-OMEM; R = $CH_2OCH_2CH_2OCH_3$) due to the ease of hydrolysis of the MEM group.[28a] Accordingly, this reagent was evaluated for the preparation of the β-alkoxy homoallylic amine. Thus, when **1a** and **VII** were mixed in THF at −78 °C, followed by the addition of 1 equiv methanol, upon completion of the reaction (3 h, monitored with ^{11}B NMR spectroscopy), oxidative workup furnished

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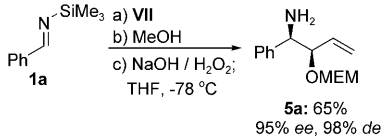


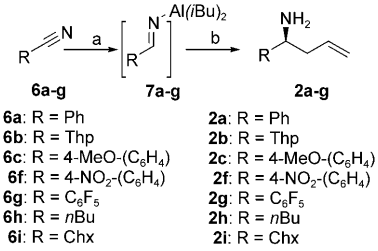
Scheme 3. Alkoxyallylboration of N-silylimines.

the expected amine **5a** in 65% yield, 95% *ee*, and 98% *de* (Scheme 3).

Given the ease of preparation of N-aluminoimines and the possibility of the use of enolizable imines as the starting materials, we chose to use the N-aluminoimines rather than N-silylimines for an expanded study of crotylboration and alkoxyallylboration (see below).

Allylboration of N-aluminoimines: Although we obtained good results from the reaction of the N-silylaldimines with **I** after the addition of water, we could not extend the reaction to the preparation of aliphatic homoallylic amines. We envisaged that the use of N-aluminoimines could alleviate this issue as the stability of the N-aluminoimines is considerably higher.[13] Itsuno and co-workers have reported the allylboration of N-aluminoimines.[29] However, the importance of methanol or water is not recognized in their account. Moreover, the yields of the amine products were low and the % *ee* were inconsistent with the reaction temperature. For example, N-aluminobenzaldimine **7a** provided the homoallylic amine **2a** in 59% yield and 33% *ee* at −78 °C and 67% yield and 69% *ee* at 25 °C.[29] This suggested that the reaction could be taking place during the workup. We speculated that the addition of methanol or water might be equally important in the allylboration of N-aluminoimines as well.

Partial reduction of benzonitrile (**6a**) with DIBAL-H in Et_2O at 0 °C furnished the corresponding N-aluminoimine **7a**, which was added to a solution of **I** in Et_2O/pentane at −100 °C. After several hours, the ^{11}B NMR spectrum of an aliquot revealed a peak at δ 78 corresponding to unchanged **I** and ^1H NMR showed the presence of unreacted N-aluminoimine (δ 9.0), supporting our intuition. Again, addition of methanol initiated an exothermic reaction and within minutes the ^{11}B NMR spectrum of an aliquot showed a peak at δ 47, corresponding to an amino dialkylborane species,[30] while the δ 9.0 peak observed in ^1H NMR disappeared. Upon completion of the reaction (within 3 h, based on ^{11}B NMR analysis), oxidative workup furnished the expected amine **2a** in 90% yield and 88% *ee*, which is considerably better than the 59% yield and 33% *ee* reported previously at −78 °C (Scheme 4; Table 2, entry 1).[29] Thus, we confirmed that methanol is a critical additive in the allylboration of N-aluminoimines as well. This finding and the spectrometric data support the postulated mechanism (Figure 4).



Scheme 4. Allylboration of N-aluminoimines: a) DIBAL-H; Et_2O, 1 h, 0 °C. b) 1) **4a–c**, **f–i** added to **I**, Et_2O, −100→−55 °C; 2) MeOH; 3 h, −100→−55 °C; 3) NaOH, H_2O_2; −78 °C→RT.

Table 2. Allylboration of N-aluminoimines.

Entry	N-Aluminoimine	R	*T* [°C]	Homoallylic amine	Yield [%][a]	*ee* [%][b]
1	**7a**	Ph	−100	**2a**	90 (87)[c]	88 (94)[c]
2	**7b**	2-Thp	−78	**2b**	74 (72)[c]	81 (81)[c]
3	**7c**	4-MeO-(C_6H_4)	−100	**2c**	89 (74)[c]	91 (92)[c]
4	**7f**	4-NO_2-(C_6H_4)	−100	**2f**	85	86
4	**7g**	C_6F_5	−78	**2g**	61	79
6	**7h**	*n*Bu	−100	**2h**	12	78[d]
7	**7h**	*n*Bu	−55	**2h**	65	60[d]
8	**7i**	Chx	−100	**2i**	16	89[d]
9	**7i**	Chx	−55	**2i**	62	68[d]

[a] All yields are of pure isolated products. [b] Enantiomeric excess was determined with HPLC using Chiracel OD-H column and hexanes/isopropanol as the mobile phase. [c] The values in parentheses are for the amines obtained from N-silylimines **1a–c**. [d] Enantiomeric excess determined by ^{19}F NMR spectroscopy after conversion to Mosher amides; results were confirmed using HPLC analysis.

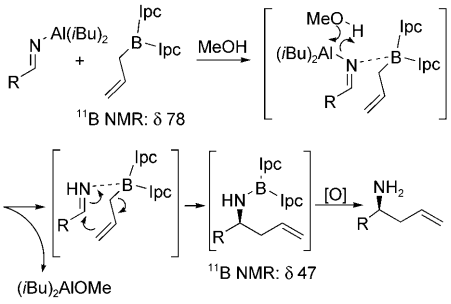


Figure 4. Tentative mechanism for the allylboration of N-aluminoimines.

We believe that the allylboration of imines proceeds analogous to the allylboration of aldehydes, via a six-membered chair-like transition state with the stereochemical outcome determined by the isopinocampheyl auxiliary (Figure 5).[18a,31] In the cases of the crotylboration, there are eight possible transition states, four of which will be predominant, depending on the geometry of the isopinocampheyl group and the butene used.[32] Comparing the optical rotation values of the obtained amine **2a** with those report-

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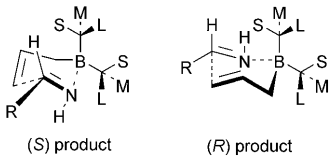

Figure 5. Transition states in allylboration of aldimines.

ed in the literature,[33] we assigned its configuration as *S*. We assigned the configuration of other homoallylic amines based on this analogy as well as on the basis of the configuration of several amino acids prepared from these amines (see below). Configuration of the obtained homoallylic amine supports the mechanism and the postulated transition states.

After we had obtained the homoallylic amine **2a** in high *ee* from benzonitrile (**6a**) via N-aluminoaldimine **7a**, we turned our attention to other classes of nitriles: heteroaromatic (2-thiophenecarbonitrile: **6b**), electron-donating (4-methoxybenzonitrile: **6c**), electron-withdrawing (4-nitrobenzonitrile: **6f**), and perfluorinated (pentafluorobenzonitrile: **6g**). Additionally, we extended the reaction to aliphatic nitriles (valeronitrile: **6h** and cyclohexanecarbonitrile: **6i**) (Scheme 4). Thus, treatment of **6a–c** and **6f–i** with 1 equiv of DIBAL-H furnished the desired N-aluminoimines **7a–c** and **7f–i**, which were transferred to a cooled solution of 1.2 equiv of **I**, followed by the addition of 1 equiv of methanol (Scheme 4). Allylborations of the aromatic substrates **7a–c** and **7f–g** were facile and upon oxidative workup, the corresponding homoallylic amines **2a–c** and **2f–g** were obtained in 61–90% yield and 86–91% *ee* (as determined by HPLC analysis; Table 2; entries 1–5). To our dismay, aliphatic substrates **7h–i** did not provide such good results and amines **2h–i** were obtained only in very poor yields (12–16%) at −100°C, while the enantioselectivity remained good (Table 1, entries 6, 8). Fortunately, reactions run at higher temperatures afforded better yields and we found that at −55°C aliphatic homoallylic amines **2h–i** were obtained in 62–65% yield and 60–79% *ee* (Scheme 4; Table 2, entries 7 and 9). Comparison of the yields, enantioselectivities, and diastereoselectivities of the homoallylic amines obtained by allylboration of N-silyl- and N-aluminoimines revealed marginal advantage of the N-aluminoimines in terms of yields, while the N-silylimines furnished amines in slightly higher *ee* (Table 2). However, because of the ease of preparation of the N-aluminoimines from the nitriles, we recommend utilization of this protocol for the preparation of homoallylic amines via allylboration.

Crotylboration and alkoxyallylboration of N-aluminoimines: Once we had achieved satisfactory crotylboration and alkoxyallylboration of N-silylimine **1a** with the "ate" complexes **V–VII**, we initiated a project involving the crotylboration of N-aluminoimines. Similar to the N-silylimines, the reactions proceeded only with **V** or **VI**. Repeating the blank experiment of mixing **7a** with $BF_3{\cdot}OEt_2$ and methanol furnished the same results as observed in the case of N-silylimine **1a**.

Imine **7a**, obtained from benzonitrile (**6a**), was thus treated with **V** or **VI** in THF at −78°C and after the addition of 1 equiv of methanol, followed by the workup provided the expected amines **3a** and **4a**, respectively, in good yields and very high *de* and *ee*, similar to the results established from the reaction of **1a** with **V** and **VI** (Scheme 5; Table 4, entries 1 and 5). Crotylboration of another aromatic substrate, N-alumino-2-thiophenecarbaldimine (**7b**) proceeded smoothly in THF furnishing the desired products **3b** and **4b** (Scheme 5; Table 4, entries 2 and 6). Unfortunately, aliphatic imines **7h–i** did not react so readily at −78°C in THF and gave only marginal yields of the desired amines along with several unidentified degradation products. Unlike the reactions of **7h–i** with **I**, increasing the reaction temperature to −55°C did not improve the yields. Attempted use of catalytic $In(OTf)_3$ or use of a bulky proton source or water as the additive did not augment the yield, either. Propitiously, examination of various solvents revealed that the reaction proceeded satisfactorily at −78°C when pentane was used as the solvent for both the preparation of imine **7i** and the crotylboration and the homoallylic amine **3i** was obtained in 74% yield and >98% diastereoselectivity (Table 3).

Table 3. Effects of temperature, Lewis acids, and solvents on crotylboration of aliphatic imine **7i** with **V**.

Solvent	Lewis acid	Additive	*T* [°C]	Yield [%]
THF	none	MeOH	−78	21[a]
THF	none	MeOH	−55	32[a]
THF	none	H_2O	−78	38[a]
THF	none	*t*BuOH	−78→25	27[a]
THF	$In(OTf)_3$ (0.1 equiv)	MeOH	−78	22[a]
Et_2O	none	MeOH	−78	30[a]
Et_2O + pentane[b]	none	MeOH	−78	35[a]
pentane + THF[c]	none	MeOH	−78	38[a]
pentane	none	H_2O	−78	74

[a] Pure material was not obtained (50–90% purity by ^{1}H NMR; the impurities were not identified). [b] A 1:1 mixture was used for the preparation of **7i** and crotylboration. [c] **7i** was prepared in THF and pentane was used as the solvent for crotylboration.

Hence, crotylboration of **7h–i** with **V** and **VI** was carried out in pentane. After the addition of 1 equiv of methanol and completion of the reaction (within 3 h, monitored by ^{11}B NMR spectroscopy), alkaline oxidative workup yielded β-methyl homoallylic amines **3h–i** and **4h–i**, respectively, in good yields (61–78%), excellent diastereoselectivities (>98%), and high enantioselectivities (79–89%) (Scheme 5; Table 4, entries 3–4, 7–8).

Having understood that the alkoxyallylboration of N-silylimine **1a** required the "ate" complex **VII** to proceed; we evaluated this reaction on N-aluminoimines. Accordingly, **7a** was mixed with **VII**, followed by the addition of 1 equiv of methanol and the reaction was monitored with ^{11}B NMR spectroscopy. Upon completion (within 3 h, based on

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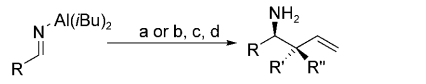
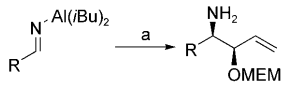


7a: R = Ph
7b: R = 2-Thp
7h: R = *n*Bu
7i: R = Chx

3a: R = Ph, R' = Me, R" = H
4a: R = Ph, R' = H, R" = Me
3b: R = 2-Thp, R' = Me, R" = H
4b: R = 2-Thp, R' = H, R" = Me
3h: R = *n*Bu, R' = Me, R" = H
4h: R = *n*Bu, R' = H, R" = Me
3i: R = Chx, R' = Me, R" = H
4i: R = Chx, R' = H, R" = Me

Scheme 5. Crotylboration of N-aluminoimines: a) 1) **V** or **VI**; THF, −78 °C; 2) **7a–b**; b) 1) **V** or **VI**; pentane, −78 °C; 2) **7h–i**; c) MeOH; 3 h, −78 °C; d) NaOH, H_2O_2; −78 °C→RT.



7a: R = Ph
7b: R = 2-Thp
7h: R = *n*Bu
7i: R = Chx

5a: R = Ph
5b: R = 2-Thp
5h: R = *n*Bu
5i: R = Chx

Scheme 6. Alkoxyallylboration of N-aluminoimines. a) 1) **VII**; THF, −78 °C; 2) **7a–b**, **h–i**; 3) MeOH; 3 h, −78 °C; 4) NaOH, H_2O_2; −78 °C→RT.

Table 4. Crotylboration of N-aluminoimines.

Entry	Reagent	N-Aluminoimine				Homoallylic amine		
		R	R′	R″		Yield [%][a]	*de* [%][b]	*ee* [%][c]
1	**V**	**7a**	Ph	Me	H	**3a**	80 (78)[d]	98 (96)[d]	89 (92)[d]
2	**V**	**7b**	2-Thp	Me	H	**3b**	71	98	89
3	**V**	**7h**	*n*Bu	Me	H	**3h**	64	>98	79[e]
4	**V**	**7i**	Chx	Me	H	**3i**	74	>98	89[e]
5	**VI**	**7a**	Ph	H	H	**4a**	78 (76)[d]	>98 (98)[d]	90 (90)[d]
6	**VI**	**7b**	2-Thp	H	Me	**4b**	76	>98	88
7	**VI**	**7h**	*n*Bu	H	Me	**4h**	61	>98	81[e]
8	**VI**	**7i**	Chx	H	Me	**4i**	78	>98	87[e]

[a] All yields are of pure isolated products. [b] Diastereomeric excess was determined by 1H NMR spectroscopy. [c] Enantiomeric excess was determined with HPLC using Chiracel OD-H column and hexanes/isopropanol as the mobile phase. [d] The values in parentheses were obtained for the N-silylimine **1a**. [e] Enantiomeric excess determined by ^1H and ^{19}F NMR spectroscopy after conversion to Mosher amides.

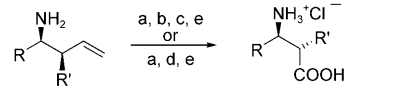
^{11}B NMR analysis), alkaline oxidative workup furnished the β-alkoxy homoallylic amine **5a** with the results (yield, diastereo- and enantioselectivity) comparable with those obtained from N-silylimine (Scheme 6; Table 5, entry 1). Fortunately, unlike in the case of crotylboration, alkoxyallylboration with **VII** proceeded smoothly in THF at −78 °C and after the addition of methanol the reaction was complete within 3 h (^{11}B NMR analysis). After alkaline oxidative workup, the desired β-alkoxy amines **5b**, **h**, and **i** were obtained in good yields (60–71 %), excellent *de* (>98 %), and high *ee* (87–95 %) (Scheme 6; Table 5, entries 2–4).

Table 5. Alkoxyallylboration of N-aluminoimines.

Entry	N-Aluminoimine			Homoallylic amine		
	R			Yield [%][a]	*de* [%][b]	*ee* [%][c]
1	**7a**	Ph	**5a**	65 (65)[d]	>98 (98)[d]	95 (95)[d]
2	**7b**	2-Thp	**5b**	71	>98	87
3	**7h**	*n*Bu	**5h**	60	>98	92[e]
4	**7i**	Chx	**5i**	62	>98	89[e]

[a] All yields are of pure isolated products. [b] Diastereomeric excess was determined by ^1H NMR spectroscopy. [c] Enantiomeric excess was determined with HPLC using Chiracel OD-H column and hexanes/isopropanol as the mobile phase. [d] The values in parentheses were obtained for the alkoxyallylboration of N-silylimine **1a**. [e] Enantiomeric excess was determined by ^{19}F NMR spectroscopy after conversion to Mosher amides.

Conversion of homoallylic amines to β-amino acids: β-Amino acid units are present in many natural products with pharmacological properties and are of utmost importance in medicinal and biochemical research.[34] For example, the (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine moiety is crucial for the biological activity of Taxol.[34,35] Due to their high proteolytic stability, β-amino acids are outstanding substrates for peptidomimetics.[36] To demonstrate the application of our methodology, we converted representative homoallylic amines to β-amino acids. Protection of **2a**, **2g**, **2h**, **4a**, and **5a** with Boc_2O, followed by ozonolysis in CH_2Cl_2 at −78 °C gave the intermediate aldehydes, which upon oxidation with sodium chlorite in 2-methyl-2-propanol in the presence of 2-methyl-2-butene and aqueous NaH_2PO_4 provided the desired N-Boc-protected β-amino acids. The above procedure when applied to **4a** and **5a** resulted in a loss of diastereoselectivity. Fortunately, the diastereoselectivity was retained by a direct oxidation of **4a** and **5a** to acids using $NaIO_4$ in the presence of catalytic $RuCl_3{\cdot}H_2O$. Upon deprotection with ethereal HCl, the desired amino acids were obtained in good yields (71–82 %) as their hydrochloride salts **8a**, **8g**, **8h**, **8a′**, and **8a″** (Scheme 7). Comparison of the optical ro-



2a: R=Ph, R'=H
2g: R=C_6F_5, R'=H
2h: R=*n*Bu, R'=H
4a: R=Ph, R'=Me
5a: R=Ph, R'=OMEM

8a: R=Ph, R'=H (82%)
8g: R=C_6F_5, R'=H (70%)
8h: R=*n*Bu, R'=H (72%)
8a': R=Ph, R'=Me (77%)
8a": R=Ph, R'=OH (71%)

Scheme 7. Prepartion of β-amino acids: a) Boc_2O; Et_2O, 6 h, RT; b) 1) O_3, CH_2Cl_2, 2 h, −78 °C; 2) Me_2S; 1 h, −78 °C→RT; c) $NaClO_2$, NaH_2PO_4; *t*BuOH, 2-methyl-2-butene, H_2O, 0.5 h, RT; d) $NaIO_4$, cat. $RuCl_3{\cdot}H_2O$; CH_3CN/H_2O 1:1, 0.5 h, RT; e) HCl; Et_2O, 0.5 h, RT.

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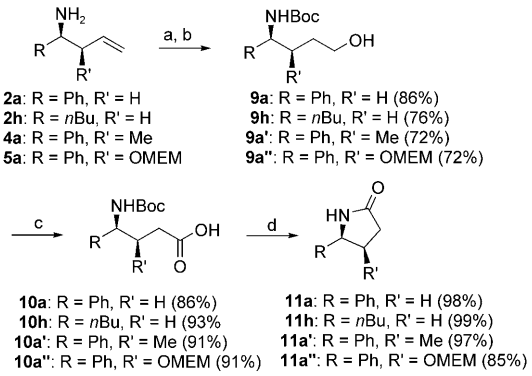
tation of **8a** and **8a′** with the values reported in the literature indicated that our stereochemistry assignments were correct.[37] Thus, the tandem allylboration–oxidation of N-aluminoimines can be used as a general method for the preparation of optically active β-amino acids from aromatic or aliphatic nitriles in two steps.

Preparation of δ-amino alcohols and γ-lactams: To demonstrate further applications of our protocol, we prepared several δ-amino alcohols and converted them to γ-lactams. γ-Amino acids and γ-lactams have found less utility than their β-analogues in medicinal chemistry. However, they are excellent peptidomimetics agents and are important parts of molecules with high biological activity.[38] Hence, we were attracted to their synthesis. Homoallylic amines **2a**, **2h**, **4a**, and **5a** were N-Boc-protected and hydroborated with 9-BBN (Chx_2BH was used for hydroboration of **5a** to simplify the purification) and oxidized under alkaline conditions to furnish the corresponding N-Boc-protected δ-amino alcohols **9a**, **9h**, **9a′**, and **9a″** in 72–86% yields. These alcohols were oxidized to N-Boc protected γ-amino acids **10a**, **10h**, **10a′**, and **10a″** by using PDC in DMF in 86–93% yields. Removal of the Boc protection with CF_3COOH furnished free γ-amino acids, which under the reaction conditions formed the corresponding lactams **11a**, **11h**, **11a′**, and **11a″** in essentially quantitative yields (Scheme 8). Comparison of the optical rotation of **11h** with the value reported in the literature[39] served as an additional proof that the assignment of the configuration is accurate.



Scheme 8. Preparation of δ-amino alcohols and γ-lactams: a) Boc_2O; Et_2O, 4 h, RT; b) 1) 9-BBN or Chx_2BH; THF, 24 h, RT; 2) NaOAc or NaOH, H_2O_2; 5 h, RT. c) PDC; DMF, 12 h, RT; d) CF_3COOH; CH_2Cl_2, 0.5 h, RT. Chx = Cyclohexyl.

Conclusion

In conclusion, we have demonstrated the utility of "allyl"-boration of N-silylimines and N-aluminoimines for the preparation of homoallylic amines in high enantiomeric excess. For the first time, we have reported the reagent-controlled crotylboration and alkoxyallylboration of N-masked imines for the synthesis of β-substituted homoallylic amines in excellent *de* and high *ee*. We have demonstrated that the addition of 1 equiv of methanol or water is critical for the "allyl"-boration of both N-silyl- and N-aluminoimines. We observed that crotylboration and alkoxyallylboration reactions proceed with the "ate" boron complexes rather than with "allyl"-dialkylborane reagents. We have employed this methodology for the enantioselective synthesis of representative β-amino acids, δ-amino alcohols, and γ-lactams in 2–3 steps from nitriles. We believe that due to the ready availability or the ease of preparation of nitriles, simplicity of the reactions, and high reliability in achieving both enantiomers of the homoallylic amines in excellent diastereo- and enantioselectivities, this methodology will find wide applications in organic syntheses.

Experimental Section

Representative experimental procedures for the allylboration, crotylboration, alkoxyallylboration, preparation of β-amino acids, and γ-lactams are given below. Additional procedures and spectral data are available in the Supporting Information.

N-Trimethylsilylbenzaldimine (1a): *n*-Butyllithium (2.5 M in hexanes; 22 mL, 55 mmol) was slowly added to a solution of 1,1,1,3,3,3-hexamethyldisilazide (12 mL, 57 mmol) in Et_2O (57 mL) cooled to −50 °C and the reaction was stirred for 0.5 h. Benzaldehyde (5.5 mL, 54 mmol) was subsequently added and the mixture was stirred for 1 h. Removal of Et_2O under reduced pressure followed by vacuum distillation (b.p. 98 °C, 1.6 mmHg) furnished **1a** (7.8 g, 44 mmol, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.29 (s, 9H), 7.45–7.47 (m, 3H), 7.81–7.82 (m, 2H), 9.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −1.1, 128.5, 128.6, 131.3, 139.4, 168.6.

(1*S*)-1-Phenylbut-3-en-1-amine (2a) from N-silylimine: Compound **1a** (0.9 g, 5.1 mmol) was added to a stirred solution of (−)-*B*-allyldiisopinocampheylborane (**I**; 1 M in pentane; 6 mL, 6 mmol) diluted with THF (5 mL) and cooled to −78 °C, followed by a slow addition of water (0.09 mL, 5.0 mmol) in THF (0.5 mL). The mixture was stirred for 1 h at −78 °C and it was oxidised 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 neutralised 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 material was purified on silica gel (hexanes/ethyl acetate/triethylamine 84.5:15:0.5) to afford **2a** (0.66 g, 4.5 mmol, 90%) in 92% *ee* (HPLC: Chiracel OD-H column, hexanes/isopropanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.69 (brs, 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), 7.22–7.37 (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 $[Ph\text{-}CH\text{-}NH_2]^+$, 79; (CI): m/z: 148 $[M+H]^+$, 131 $[M-NH_3]^+$; HRMS: m/z: calcd for: 148.1126, found: 148.1129; $[\alpha]$ = +43 ($CHCl_3$, c = 1.9), lit.:[33] +42, $CHCl_3$, c = 0.5).

(1*S*)-1-Phenylbut-3-en-1-amine (2a) from benzonitrile: DIBAL-H (0.89 mL, 5.0 mmol) was added to a solution of benzonitrile (**6a;** 0.52 mL, 5.05 mmol) in Et_2O (5 mL) cooled to 0 °C and the mixture was stirred for 1 h to obtain **7a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.14–0.19 (m, 3H), 0.76–1.07 (m, 12H), 1.79 (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).

Compound **7a** was transferred via cannula to a solution of **I** (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 3 h, while it was allowed to slowly warm from −100

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to −78 °C and it was oxidised 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 neutralised 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 material was purified on silica gel (hexanes/ethyl acetate/triethylamine 84.5:15:0.5) to afford **2a** (0.66 g, 4.5 mmol, 90 %) in 88 % *ee* as analysed by the HPLC, having identical spectral data to the reported above; $[\alpha]=+39$ ($CHCl_3$, $c=0.10$), lit.:[33] +42 ($CHCl_3$, $c=0.5$).

(1*S*,2*S*)-2-Methyl-1-phenylbut-3-en-1-amine (3a): *trans*-Butene (1 mL, 10 mmol) and *n*-butyllithium (2.5 M in hexanes; 2.4 mL, 6.0 mmol) were added to potassium *tert*-butoxide (1 M in THF; 6 mL, 6 mmol) diluted with THF (6 mL) and cooled to −78 °C. 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 **V** was added via cannula a solution of **7a** [prepared as follows: To **6a** (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 a slow addition of 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 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 **3a** (0.59 g, 3.7 mmol, 74 %). ^{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, $J=8.4$ Hz, 1H), 5.10–5.24 (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; (CI): *m*/*z*: 162, 145, 106; $[\alpha]=+76$ ($CHCl_3$, $c=0.92$), lit:[37b] +1.5 (MeOH, $c=1.0$).

(1*R*,2*S*)-1-Butyl-2-methylbut-3-enylamine (3h): *trans*-Butene (1 mL, 10 mmol) and *n*-butyllithium (2.5 M in hexanes; 2.4 mL, 6.0 mmol) were added to potassium *tert*-butoxide (1 M in THF; 6 mL, 6 mmol) diluted with pentane (6 mL) and cooled to −78 °C. 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 **V** was added via cannula a solution of **7h** [prepared as follows: To a solution of valeronitrile (**6h**) (0.55 mL, 5.2 mmol) in pentane (10 mL) cooled to 0 °C was added DIBAL-H (0.90 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 oxidised 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) after the acid/base manipulations, 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 **3h** (0.4 g, 2.8 mmol, 64 %) in >98 % *de* (^{1}H NMR analysis) and 79 % *ee* (analysis using ^{1}H and ^{19}F NMR spectroscopy after conversion to Mosher amide and confirmation using HPLC with Chiracel OD-H column with hexanes/isopropanol). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.95 (t, $J=$ 4.5 Hz, 3H), 1.06 (d, $J=4.6$ Hz, 3H), 1.27–1.40 (m, 8H), 2.16 (q, $J=$ 4.5 Hz, 1H), 2.57–2.60 (m, 1H), 5.06–5.09 (m, 2H), 5.72–5.84 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.4, 17.0, 23.2, 28.9, 34.9, 44.3, 55.6, 115.4, 141.4. MS (EI): *m*/*z*: 142 $[M+H]^+$, 86 $[M-C_4H_7]^+$; (CI): *m*/*z*: 142 $[M+H]^+$, 86; $[\alpha]=+15$ ($CDCl_3$, $c=1.28$).

(1*R*,2*R*)-2-[(2-Methoxyethoxy)methoxy]-1-phenylbut-3-en-1-amine (5a): *sec*-Butyllithium (1.4 M in cyclohexane; 4.4 mL, 6.1 mmol) was added to 3-[(2-methoxyethoxy)-methoxy]prop-1-ene (0.91 g, 6.2 mmol) diluted with THF (6 mL) and cooled to −78 °C and the mixture was stirred for 0.5 h at −78 °C. Then, a solution of (−)-*B*-methoxydiisopinocampheylborane (2.37 g, 7.5 mmol) in THF (5 mL) was added and the mixture was stirred for 1 h. To thus generated **VII** was added via cannula a solution of **7a** [prepared as follows: To **6a** (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). The reaction was stirred for 3 h at −78 °C and was oxidised with NaOH (3 M in H_2O; 2 mL) and (slowly!) H_2O_2 (30 % in H_2O; 1.2 mL). The material was left stirring under positive N_2 pressure while it slowly warmed to RT. The product was extracted with Et_2O (3×50 mL) and the volatiles were removed under reduced pressure. The obtained material was purified on silica gel (hexanes/ethyl acetate/triethylamine 94.5:5:0.5 to 69.5:30:0.5) to furnish **5a** (0.81 g, 3.2 mmol, 65 %) in >98 % *de* (^{1}H NMR analysis) and 95 % *ee* (HPLC: Chiracel OD-H, hexanes/isopropanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73 (br s, 2H), 3.34 (s, 3H), 3.37–3.49 (m, 4H), 3.96 (d, $J=5.8$ Hz, 1H), 4.18 (t, $J=6.5$ Hz, 1H), 4.67 (dd, $J=6.9$ Hz, 38.7 Hz, 2H), 5.11–5.11 (m, 2H), 5.58–5.69 (m, 1H), 7.21–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 59.0, 59.8, 67.0, 71.7, 81.7, 93.0, 118.7, 127.2, 127.5, 128.2, 135.5, 142.6; MS (EI): *m*/*z*: 176 $[M-OCH_2CH_2OCH_3]^+$, 106, 79, 59; (CI): *m*/*z*: 252 $[M+H]^+$, 176 $[M+H-CH_3OCH_2CH_2OH]^+$, 106, 79; HRMS: *m*/*z*: calcd for 252.1600, found: 252.1604; $[\alpha]=+103$ ($CHCl_3$, $c=4.22$).

(2*R*,3*S*)-3-Amino-2-methyl-3-phenylpropanoic acid hydrochloride (8a′): Di-*tert*-butyl dicarbonate (0.3 g, 1.4 mmol) was added to **4a** (0.2 g, 1.2 mmol) dissolved in Et_2O (12 mL) and the reaction was stirred for 6 h at RT, after which time the solvent was removed under reduced pressure. To the crude material dissolved in CH_3CN (40 mL) was added $RuCl_3{\cdot}H_2O$ (0.02 g, 0.1 mmol) and the mixture was cooled to 0 °C. After addition of $NaIO_4$ (0.8 g, 3.7 mmol) dissolved in water (40 mL), the mixture was stirred for 0.5 h, followed by extraction with EtOAc (3×30 mL) and filtration through silica gel (Et_2O). After evaporation of the solvents, the residue was diluted with Et_2O (5 mL) and treated with HCl (1 M in Et_2O; 2 mL, 2 mmol) for 0.5 h. The obtained solid was filtered and dried to afford **8a′** (0.2 g, 0.9 mmol, 77 %). ^{1}H NMR (200 MHz, D_2O): δ = 0.91 (d, $J=7.2$ Hz, 3H), 2.97–3.09 (m, 1H), 4.36 (d, $J=9.4$ Hz, 1H), 7.29–7.31 (m, 5H); ^{13}C NMR (50 MHz, D_2O): δ = 15.4, 43.9, 57.8, 127.4, 127.6, 129.6, 129.8, 134.5, 177.3; $[\alpha]=+19$ (D_2O, $c=1.19$).

(5*S*)-5-Phenylpyrrolidin-2-one (11a): Di-*tert*-butyl dicarbonate (0.6 g, 3.1 mmol) was added to **2a** (0.43 g, 2.9 mmol) dissolved in Et_2O (30 mL) and the reaction was stirred for 6 h at RT, after which time the solvent was removed under reduced pressure. The crude material was dissolved in THF (7 mL) and treated with 9-BBN (0.5 M in THF; 13 mL, 6.5 mmol) for 24 h at RT, followed by oxidation with sodium acetate (20 % in H_2O, 20 mL) and H_2O_2 (30 % in H_2O; 6 mL) for 5 h at RT. The product was extracted with Et_2O (3×30 mL), and after evaporation of the solvents purified on silica gel (hexanes/ethyl acetate 2:1) to furnish *tert*-butyl (1*S*)-4-hydroxy-1-phenylbutylcarbamate (**9a**) (0.66 g, 2.5 mmol, 86 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9H), 1.53–1.88 (m, 4H), 2.55 (br s, 1H), 3.67 (t, $J=5.9$ Hz, 2H), 4.67 (br s, 1H), 5.12 (br s, 1H), 7.29–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 29.1, 33.2, 54.6, 62.1, 79.5, 126.3, 127.2, 128.5, 142.7, 155.5.

The N-Boc protected alcohol **9a** (0.22 g, 0.8 mmol) in DMF (10 mL) was added to a stirring solution of pyridinium dichromate (1.13 g, 3.0 mmol) in DMF (20 mL) and the mixture was stirred for 18 h at RT. The reaction was quenched with H_2O (5 mL), the product was extracted with Et_2O (3×50 mL), the combined ether layers were washed with H_2O (3×50 mL), the solvent was removed and the obtained material was purified on silica gel (flash; hexanes/ethyl acetate 2:1) to afford (4*S*)-4-[(*tert*-butoxycarbonyl)amino]-4-phenylbutanoic acid (**10a**) (0.192 g, 0.7 mmol, 86 %). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.22 (s, 9H), 1.78–2.01 (m, 1H), 2.35–2.71 (m, 3H), 5.07–5.13 (m, 1H), 7.15–7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.0, 28.3, 31.9, 61.9, 82.9, 124.8, 127.3, 128.4, 142.1, 149.0, 174.1.

The N-Boc protected γ-amino acid **10a** (0.13 g, 0.5 mmol) dissolved in CH_2Cl_2 (3 mL) was treated with CF_3COOH (0.1 mL) for 0.5 h at RT. After evaporation, the obtained material was purified on silica gel (flash; hexanes/ethyl acetate 1:1) to give **11a** (0.074 g, 0.5 mmol, 98 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.97–2.11 (m, 1H), 2.41–2.70 (m, 3H),

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4.83 (t, $J=7.1$ Hz, 1H), 6.70 (brs, 1H), 7.34–7.46 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.3, 31.3, 58.1, 125.6, 127.8, 128.8, 142.5, 178.7; MS (EI): m/z: 161 $[M]^+$, 117, 104, 77; (CI): m/z: 162 $[M+H]^+$; $[\alpha]=+25$ ($CDCl_3$, $c=3.7$).

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