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# Catalytic Asymmetric Aziridination of α,β-Unsaturated Aldehydes

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**Abstract:** The development, scope, and application of the highly enantioselective organocatalytic aziridination of α,β-unsaturated aldehydes is presented. The aminocatalytic azirdination of α,β-unsaturated aldehydes enables the asymmetric formation of β-formyl aziridines with up to >19:1 d.r. and 99% *ee*. The aminocatalytic aziridination of α-monosubstituted enals gives access to terminal α-substituted-α-formyl aziridines in high yields and up to 99% *ee*. In the case of the organocatalytic aziridination of disubstituted α,β-unsaturated aldehydes, the transformations were highly diastereo- and enantioselective and give nearly enantiomerically pure β-formyl-functionalized aziridine products (99% *ee*). A highly enantioselective one-pot cascade sequence based on the combination of asymmetric amine and N-heterocyclic carbene catalysis (AHCC) is also disclosed. This one-pot three-component co-catalytic transformation between α,β-unsaturated aldehydes, hydroxylamine derivatives, and alcohols gives the corresponding *N*-*tert*-butoxycarbonyl and *N*-carbobenzyloxy-protected β-amino acid esters with *ee* values ranging from 92–99%. The mechanisms and stereochemistry of all these catalytic transformations are also discussed.

**Keywords:** asymmetric catalysis · aziridines · domino reactions · hydroxylamines · unsaturated aldehydes

## Introduction

Since Gabriel's first report on the synthesis of the smallest N-hetrocycle in 1888,[1a] azirdines have been the target of synthetic chemists.[1] The intrinsic ring-strain of these three-membered cyclic compounds makes them versatile chiral building blocks in organic synthesis. For example, aziridines are useful starting materials for nucleophilic ring-opening and -expansion reactions as well as 1,3-dipolar cycloadditions.[1d–l] They can also serve as useful chiral ligands, chiral catalysts, and auxiliaries for asymmetric synthesis.[1d–h] Optically active azirdines are also present in nature (e.g., natural products, such as azirdine carboxylic acid, mitomycin, porfiromycin, and mitiromycin) and exhibit important biologically activities.[2] Thus, an intense research effort has been made for the development of asymmetric methods for the enantioselective synthesis of aziridines. The first asymmetric protocols for the synthesis of chiral aziridines were based on the use of chiral substrates or chiral auxiliaries.[3] The research of finding catalytic asymmetric methods by using organometallic catalysts (e.g., Cu,[4] Rh,[5] Ru,[6] Mn,[7] or Ag[8]) for the enantioselective synthesis of aziridines began in the early 1990s.[1c,9] In this context, Evans and co-workers reported the first catalytic asymmetric aziridination of olefins with [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane by using a [bis(oxazoline]Cu complex as the catalyst.[4a–c] Jacobsen and co-workers developed the Cu-catalyzed enantioselective aziridination of *cis* olefins and imines.[4f] Wulff and co-workers disclosed an elegant catalytic enantioselective aziridination reaction by starting from imines and diazoacetates catalyzed by chiral borate complexes (VAPOL with borane–THF complexes or aryl borate–VAPOL).[10] In pioneering work, Aggarwal and co-workers developed the Rh-catalyzed asymmetric generation of aziridines from sulfur ylides and imines by diazo decomposition.[11] Recently, chiral Brønsted acids, such as dicarboxylic acids[12] and phosphoric acid derivatives,[13] were employed as catalysts for the aza-Darzen reactions between imines and diazoacetamides to give optically active aziridines. Quaternery ammonium salts[14] have also been introduced as catalysts for the aziridination of cycloalkenones and electron-deficient olefins. The catalytic asymmetric formation of terminal aziridines represent a challenging and attractive target, since these compounds readily un-

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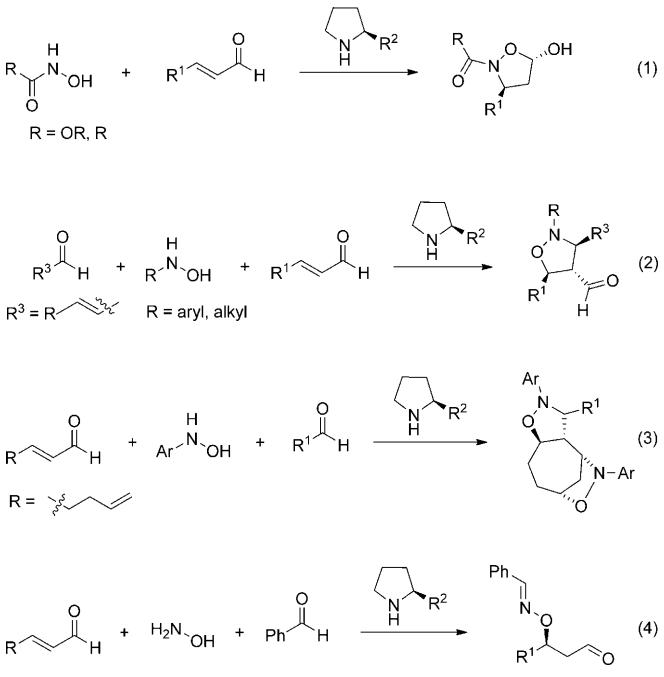
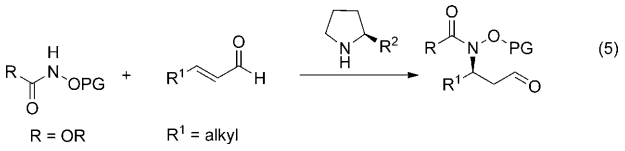
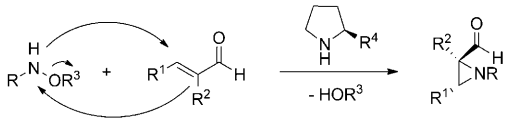
dergo regioselective ring-opening with various nucleophiles.[1b] In addition, there is no general catalytic enantioselective method for the synthesis of highly enantioenriched 2-alkyl-substituted terminal aziridines.[15–16] Katsuki and coworkers reported the catalytic enantioselective aziridination of terminal alkenes catalyzed by new Ru–(Salen)(CO) complexes.[17] However, they are not yet applicable to the catalytic enantioselective aziridination of α,α-disubstituted alkenes, which are important precursors for the synthesis of quaternary α-amino acid derivatives.[18]

Based on our research interest in asymmetric catalysis and green chemistry,[19] we have explored aminocatalytic one-pot asymmetric tandem and multicomponent transformations[20–21] between hydroxylamines and α,β-unsaturated aldehydes.[22–24] We found that the transformations exhibit completely different chemoselectivity depending on the substituent at the N atom of the hydroxyl amine derivative, which affects its p$K_a$ [Eqs. (1–4)].[22–24a] For example, compounds containing an electron-withdrawing substituent (e.g., carbamate or acyl group) at the N atom leads to a tandem aza-Michael/hemiacetal sequence to furnish 5-hydroxyoxazolidine derivatives [Eq. (1)].[22] In contrast, employing an *N*-aryl- or *N*-alkyl-substituted hydroxylamine as the substrate leads to enantioselective intra- or intermolecular 1,3-dipolar cycloadditions [Eqs. (2–3)].[23] The one-pot three-component reaction between hydroxylamine, benzaldehyde, and aliphatic enals leads to an asymmetric oxy-Michael reaction [Eq. (4)].[23a] It is noteworthy, that having a protective group on the O atom (e.g., trimethylsilyl (TMS), *tert*-butyldimethylsilyl (TBS), Me, or Bn) of an *N*-carbamate-protected hydroxylamine leads to aza-conjugate addition if the enal is aliphatic [Eq. (5)].[24] However, reacting an O-protected *N*-aryl- or -alkyl-substituted hydroxylamine with an enal leads to iminium formation.




With this information in our hands, we were able to predict a "retrocatalytic" analysis for a possible novel chiral amine-catalyzed route to enantioenriched β-formyl aziridines (Scheme 1). Thus, by selecting suitable substituents on




Scheme 1. Planned enantioselective synthesis of β-formyl aziridines.

the hydroxyl amine (e.g., carbamate groups at the N atom and acyl or tosyl groups at the O atom) a domino sequence should be possible involving: 1) Initial aminocatalytic enantioselective aza-conjugate addition of the hydroxylamine derivative to an enal. 2) Subsequent irreversible amine-catalyzed stereoselective intramolecular nucleophilic substitution at the now electrophilic N atom of the in situ generated trisubstituted hydroxyl amine. 3) Leaving-group expulsion and aziridine product formation.

In 2006, we disclosed the first chiral amine-catalyzed asymmetric aziridination of simple linear enals based on the vide supra explained retrocatalytic analysis.[25] This has led to the development of aminocatalytic aziridinations of α,β-unsaturated aldehydes and ketones.[26–27] Herein, we report the development, the substrate scope, and one-pot applications of the amine-catalyzed enantioselective aziridination of α,β-unsaturated aldehydes. This catalytic reaction allows for the stereoselective aziridination of linear, α-monosubstituted, and disubstituted α,β-unsaturated aldehydes and the corresponding β-formyl aldehyde products were formed with high d.r. and *ee* values. A highly enantioselective one-pot three-component reaction based on the combination of asymmetric amine and N-heterocyclic carbene catalysis (AHCC) is also disclosed. This cascade catalysis sequence enabled the asymmetric synthesis of β-amino acid esters (92–99% *ee*) by starting from linear enals, hydroxylamine derivatives, and alcohols. The mechanism and the stereochemistry of the reactions are also discussed.

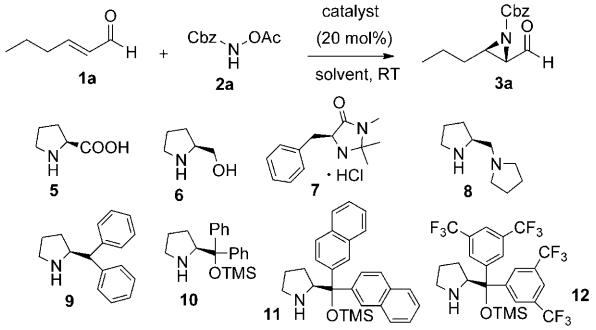
## Results and Discussion

**Catalyst screen**: After extensive screening of different suitable nitrogen atom sources for the asymmetric aziridination of *trans*-2-hexenal (**1a**), we found that acylated hydroxycarbamates **2** had the right properties to give the aziridination product **3a**.[28] We, therefore, began screening the reaction

between **1a** (0.25 mmol) and benzyl *N*-acetoxycarbamate **2a** (0.3 mmol) in the presence of chiral amine catalysts **5**–**12**. We found that proline **5** and imidazolidinone **7** did not give any products under our reaction conditions (Table 1, entries 1 and 3). However, chiral pyrrolidine **6** formed trace amounts of product **3a** (entry 2). It was encouraging to find that chiral pyrrolidines **8** and **9** produced more products in 4 h but with no diastereoselectivity (Table 1, entries 4–5). To our delight, the TMS-protected dipenylprolinol **10**[29] catalyzed the enantioselective formation of 2-formyl-aziridine **3a** in 86% conversion after 3 h with 9:1 d.r. and 99% *ee* (entry 6). The TMS-protected dinaphthylprolinol **11** did also catalyze the asymmetric azirdination of **1a** with high enantioselectivity (entry 7). Jørgensen's diarylprolinol **12** bearing two more bulky and electron-withdrawing 3,5-$(CF_3)_2C_6H_3$ moieties catalyzed the azirdination of **1a** with excellent diastereoselectivity and high enantioselectivity (>19:1 d.r., 98% *ee*), but the conversion was only 20% after 24 h (entry 8). It is important to note that when increasing the temperature to 40°C the reaction rate also increased without significantly decreasing the stereoselectivity (entry 9). Based on these results, we decided to select the TMS-protected dipenylprolinol **10** as the catalyst for the enantioselective azirdination of enals.

Table 1. Catalyst screen for the aziridination between **1a** and **2a**.[a]




| Entry | Catalyst | Solvent | *t* [h] | Conv. [%][b] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|
| 1 | **5** | $CHCl_3$ | 24 | 0 | – | – |
| 2 | **6** | $CHCl_3$ | 16 | <5 | n.d. | n.d. |
| 3 | **7** | $CHCl_3$ | 24 | 0 | – | – |
| 4 | **8** | $CHCl_3$ | 4 | 15 | 1:1 | n.d. |
| 5 | **9** | $CHCl_3$ | 4 | 45 | 1:1 | 57 |
| 6 | **10** | $CHCl_3$ | 3 | 86 | 9:1 | 99 |
| 7 | **11** | $CHCl_3$ | 4 | 76 | 5:1 | 90 |
| 8 | **12** | $CHCl_3$ | 24 | 20 | >19:1 | 98 |
| 9[e] | **10** | $CHCl_3$ | 0.5 | 100 | 5:1 | 96 |

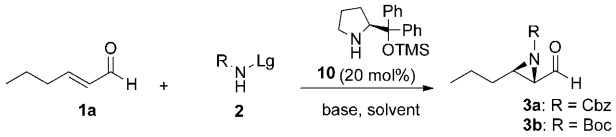
[a] Experimental conditions: A mixture of **2a** (0.30 mmol), aldehyde **1a** (0.25 mmol), and catalyst (20 mol%) in 1.0 mL solvent was stirred for the time shown in the table. [b] Conversion into product **3a** as determined by $^1$H NMR spectroscopic analysis. [c] Determined by $^1$H NMR spectroscopic analysis. [d] Determined by chiral-phase HPLC analysis after reduction to the corresponding alcohol **3′**. [e] The reaction was performed at 40°C. n.d. = not determined.

**Leaving-group and condition screen**: We next screened different substituents on the O atom of *N*-carbobenzyloxy (Cbz)-protected hydroxylamines **2** employing **10** as the organocatalyst. Representative examples are shown in Table 2. We found that the aziridination of **1a** with benzyl acetoxycarbamate **2a** provided the product **3a** in full conversion with 5:1 d.r. and 96% *ee* after 0.5 h at 40°C (Table 2, entry 2). It is noteworthy that when changing **2a** to benzyl *N*-tosyloxycarbamate **2b** as the "nitrene equivalent" the reaction became highly diastereoselective both at room temperature and at 40°C, whereas the conversion decreased (entries 3–4). The addition of base was subsequently investigated. We found that when the more base-stable benzyl *N*-tosyloxycarbamate **2b** was used as the nitrogen nucleophile together with NaOAc as the additive the reaction formed product **3a** in full conversion with excellent diastereo- and enantioselectivity under the same reaction conditions (entry 6). The catalytic aziridination of **1a** with benzyl *N*-methylsulfonyloxy carbamate **2c** as the "nitrene equivalent" was also highly enantioselective (20:1 d.r., 95% *ee*); however, the conversion was lower relative to the transformation with **2b** (entry 7). Based on these results, the aziridination reaction was further investigated employing benzyl *N*-tosyloxycarbamate **2b** as the nitrogen source. We found that high stereoselectivety was achieved in toluene and $CH_2Cl_2$ (entries 8–9). The screening of different base additives (entries 10–12) revealed that the employment of inorganic bases, such as $Na_2CO_3$ and $K_2CO_3$, was also possible (entries 11–12). Different catalyst loading was also employed (entries 15–17). The reaction rate decreased at lower catalyst loading without significantly affecting the stereoselectivity. It is noteworthy that product **2a** could be isolated in moderate yield with 10:1 d.r. and 97% *ee* when only 2.5 mol% of catalyst **10** was employed (entry 17). In fact, the reaction could not be run more than 16–17 h since it stopped due to hydrolysis of Cbz-NHOTs (**2b**) by the base additive NaOAc (entries 16–17). The reaction between *trans*-2-hexenal (**1a**) and *tert*-butoxycarbonyl (Boc)-NHOTs (**2e**) was also investigated with different catalyst loading. The transformations gave the corresponding product **3b** in good conversion with excellent d.r. and *ee* (entries 18–20).[30] We also investigated the reaction between acetylated 9-fluorenylmethoxycarbonyl (Fmoc)-protected hydroxylamine and 2-hexenal (**1a**), which gave the corresponding Fmoc-protected 2-formylaziridine **3j** in 63% yield with 5:1 d.r. but only 46% *ee*.

**Substrate scope**: The release of acetate is more atom-economic and environmentally friendly relative to the release of tosylate. We therefore decided to investigate the aziridination reaction of linear enals **1** with both *N*-acetoxycarbamates (**2a** and **2d**) and *N*-tosyloxycarbamates (**2b** and **2e**). The results are summarized in Table 3. The organocatalytic asymmetric aziridination reactions when using **2a** and **2d** as the reactants were highly chemo- and enantioselective and the corresponding Cbz- and Boc-protected 2-formylaziridines **3** were obtained in good to high yields with 4:1–10:1 d.r. and 84–99% *ee*. Simple linear α,β-unsaturated aldehydes gave the corresponding products in high yields with excel-

Table 2. Leaving-group and condition screen for the aziridination between **1a** and **2**.[a]




| Entry | R | LG | Base | Solvent | $T$ [°C] | $t$ [h] | Conv. [%][b] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Cbz | OAc (**2a**) | – | $CHCl_3$ | RT | 3 | 86 | 9:1 | 99 |
| 2 | Cbz | OAc (**2a**) | – | $CHCl_3$ | 40 | 0.5 | 100 | 5:1 | 96 |
| 3 | Cbz | OTs (**2b**) | – | $CHCl_3$ | RT | 3 | 11 | 20:1 | n.d. |
| 4 | Cbz | OTs (**2b**) | – | $CHCl_3$ | 40 | 1.5 | 32 | 20:1 | n.d. |
| 5 | Cbz | OAc (**2a**) | NaOAc | $CHCl_3$ | RT | 0.5 | 48 | 3:1 | 98 |
| 6 | Cbz | OTs (**2b**) | NaOAc | $CHCl_3$ | RT | 0.5 | 100 (78) | 15:1 | 97 |
| 7 | Cbz | OMs (**2c**) | NaOAc | $CHCl_3$ | RT | 0.5 | 58 | 20:1 | 95 |
| 8 | Cbz | OTs (**2b**) | NaOAc | toluene | Rt | 0.5 | 78 | 7:1 | 97 |
| 9 | Cbz | OTs (**2b**) | NaOAc | $CH_2Cl_2$ | Rt | 0.5 | 100 | 8:1 | 94 |
| 10 | Cbz | OTs (**2b**) | $Et_3N$ | $CHCl_3$ | Rt | 0.5 | 40 | 5:1 | 94 |
| 11 | Cbz | OTs (**2b**) | $Na_2CO_3$ | $CHCl_3$ | RT | 0.5 | 61 | 15:1 | 96 |
| 12 | Cbz | OTs (**2b**) | $K_2CO_3$ | $CHCl_3$ | RT | 0.5 | 90 | 11:1 | 99 |
| 13[e] | Cbz | OTs (**2b**) | NaOAc | $CHCl_3$ | RT | 0.5 | 64 | 10:1 | 96 |
| 14[f] | Cbz | OTs (**2b**) | NaOAc | $CHCl_3$ | RT | 1.6 | 100(67) | 7:1 | 96 |
| 15[g] | Cbz | OTs (**2b**) | NaOAc | $CHCl_3$ | RT | 5 | 84(58) | 10:1 | 98 |
| 16[h] | Cbz | OTs (**2b**) | NaOAc | $CHCl_3$ | RT | 16 | 63(45) | 10:1 | 97 |
| 17[i] | Cbz | OTs (**2b**) | NaOAc | $CHCl_3$ | RT | 16 | 60(41) | 10:1 | 97 |
| 18[j] | Boc | OTs (**2e**) | NaOAc | $CHCl_3$ | RT | 0.67 | 100(84) | 10:1 | 99 |
| 19[k] | Boc | OTs (**2e**) | NaOAc | $CHCl_3$ | RT | 5 | 96(74) | 7:1 | 99 |
| 20[l] | Boc | OTs (**2e**) | NaOAc | $CHCl_3$ | RT | 8 | 88(69) | 8:1 | 98 |

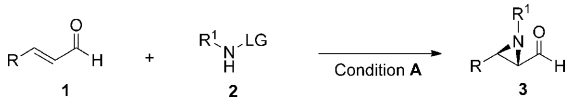
[a] Experimental conditions: A mixture of **2** (0.30 mmol), aldehyde **1a** (0.25 mmol), catalyst **10** (20 mol%), and base (3 equiv) in 1.0 mL $CHCl_3$ was stirred for the time shown in the table. [b] Conversion into product **3a** as determined by $^1$H NMR spectroscopic analysis and the value in parentheses is the isolated yield. [c] Determined by $^1$H NMR spectroscopic analysis. [d] Determined by chiral-phase HPLC analysis after reduction to the corresponding alcohol **3′**. [e] Base (NaOAc; 1 equiv) was used. [f] Base (NaOAc; 1.5 equiv) was used. [g] 10 mol% catalyst **10** was used. [h] 5 mol% catalyst **10** was used. [i] 2.5 mol% catalyst **10** was used. [j] Boc-NHOTs (**2e**) was used and the catalyst (**10**) loading was 20 mol%. [k] Boc-NHOTs (**2e**) was used and the catalyst (**10**) loading was 10 mol%. [l] Boc-NHOTs (**2e**) was used and the catalyst (**10**) loading was 5 mol%.

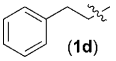
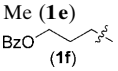
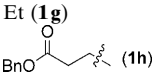
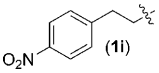
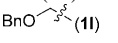
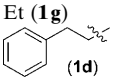
lent *ee* values (Table 3, entries 1–3, 6, 8). The reaction tolerated several enals **1** with different functional groups (entries 4–5, 7, 9–10). For example, highly chemoselective aziridination of aldehyde **1c** at its less electron-rich olefin can be accomplished by using our methodology to give the corresponding product **3d** in 68% yield with 6:1 d.r. and 96% *ee* (entry 4). The reaction performed with 10 mol% catalyst loading slightly reduced the yield and *ee* (entry 2). The organocatalytic asymmetric aziridination of enals **1** when using *N*-tosyloxycarbamate **2b** and **2e** as the "nitrene equivalents" were highly chemo- and enantioselective, and the corresponding Cbz- and Boc-protected 2-formylaziridines **3** were obtained in good to high yields with 5:1–19:1 d.r. and 91–99% *ee* (entries 11–18). The azirdination of linear enals **1a**–**b**, **1e**, and enal **1c** with a terminal double bond at the alkyl chain gave the corresponding products **3**, respectively, with high d.r. (10:1–15:1) and *ee* values (94–99%; entries 11–14, 18). The fumaric acid ethyl ester mono aldehyde **1j** reacted with both Cbz- (**2b**) and Boc-NHOTs (**2e**) providing the corresponding aziridine products **3m** and **3n** in good yields with 5:1 to 6:1 d.r. and 91% *ee*, respectively (entries 15–16). The simplest linear aldehyde, acrolein (**1k**), was also investigated and the reaction proceeded smoothly at 4°C to afford the corresponding product **3o** in 77% yield with 91% *ee* (entry 17). When comparing the azirdination reactions employing **2a** and **2d** as the nitrogen source with the use of **2b** and **2e**, it became clear that the corresponding products **3** are assembled with higher diastereomeric ratios (entries 11–14, 18) except when aldehyde **1j** was employed as the substrate (entries 15–16).

The aminocatalytic azirdidination of cinnamic aldehyde derivatives were also investigated by using **2a–e** as "nitrene equivalents" and amine **10** as the catalyst. To our delight, the reaction was productive when benzyl *N*-tosyloxycarbamate **2b** or *tert*-butyl *N*-tosyloxycarbamate **2e** were umployed as the "nitrene equivalents". In fact, the corresponding formyl aldehydes **3** with an aryl moiety were isolated in moderate to high yields with high d.r. and *ee* values ranging from 95–99% (Table 4). The ratio between products **3**/**4** was also high. For example, substrates bearing an electron-withdrawing group at the aryl moiety gave the corresponding products **3** with 99% *ee* (Table 4, entries 2–3, 5–6, and 10). The aminocatalytic aziridination of heteroaromatic enals **1** was also successful (entry 4). For substrates bearing an electron-donating group at the aryl moiety (e.g., **1**), the corresponding products **3** and **4** were formed as determined by $^1$H NMR spectroscopic analysis of the crude reaction mixture; however, we were not able to isolate product **3**. For example, the aziridination of **1** gave aziridine **3x** as determined by NMR spectroscopic analysis. Unfortunately, **3x** decomposed when exposed to silica-gel column chromatography and only **4x** was isolated in 20% yield (entry 7). (*E*)-3-(Naphthalen-2-yl)acrylaldehyde (**1t**) reacted with both reagents **2b** and **2e** forming the corresponding Cbz- and Boc-protected aziridine products **3y** and **3bb**, respectively, according to $^1$H NMR spectroscopic analysis. However, both products **3y** and **3bb** decomposed upon silica gel column chromatography. However, we were able to isolate the corresponding β-amino acid ester after applying our AHCC methodology (entries 8, 11). Moreover, the aziridine reagent, *tert*-butyl *N*-tosyloxycarbamate **2e**, gave the corresponding product **3** with better yields relative to benzyl *N*-tosyloxycarbamate **2b** (entries 9–11 vs. 1, 5, 8). Byproducts **4** are also synthetically useful since they can be readily transformed into the corresponding protected α,β-dehydroamino acids after oxidation. α,β-Dehydroamino acids are present in biologically important natural products

Table 3. Organocatalytic asymmetric aziridination of aliphatic α,β-unsaturated aldehydes **1** with **2**.[a]




| Entry | R | $R^1$ | Prod. | Conditions A | $T$ [°C] | $t$ [h] | Yield [%][b] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | *n*-Pr (**1a**) | Cbz | **3a** | A1 | 40 | 0.5 | 78 | 4:1 | 96[f] |
| 2[e] | *n*-Pr (**1a**) | Cbz | **3a** | A1 | 40 | 0.5 | 68 | 4:1 | 90[f] |
| 3 | *n*Bu (**1b**) | Cbz | **3c** | A1 | 40 | 0.5 | 70 | 5:1 | 96[f] |
| 4 |  (**1c**) | Cbz | **3d** | A1 | 40 | 0.5 | 68 | 6:1 | 96[f] |
| 5 |  (**1d**) | Boc | **3e** | A2 | 40 | 0.4 | 68 | 5:1 | 92[f] |
| 6 | Me (**1e**) | Boc | **3f** | A2 | 18 | 5 | 54 | 5:1 | 90 |
| 7 |  (**1f**) | Boc | **3g** | A2 | 40 | 0.4 | 60 | 5:1 | 98 |
| 8 | Et (**1g**) | Cbz | **3h** | A1 | 40 | 0.6 | 60 | 5:1 | 97[f] |
| 9 |  (**1h**) | Cbz | **3i** | A1 | 40 | 0.5 | 62 | 5:1 | 84 |
| 10 |  (**1i**) | Cbz | **3k** | A1 | 40 | 0.4 | 66 | 7:1 | 92 |
| 11 | *n*-Pr (**1a**) | Cbz | **3a** | A3 | 18 | 0.5 | 72 | 15:1 | 97[f] |
| 12 | *n*Bu (**1b**) | Cbz | **3c** | A3 | 18 | 1 | 65 | 15:1 | 97[f] |
| 13 | Me (**1e**) | Cbz | **3l** | A3 | 18 | 0.5 | 65 | 15:1 | 95 |
| 14 |  (**1c**) | Cbz | **3d** | A3 | 18 | 0.5 | 84 | 10:1 | 94[f] |
| 15 | $CO_2$Et (**1j**) | Cbz | **3m** | A3 | 18 | 0.67 | 57 | 5:1 | 91[f] |
| 16 | $CO_2$Et (**1j**) | Boc | **3n** | A4 | 18 | 0.67 | 67 | 6:1 | 91[g] |
| 17 | H (**1k**) | Cbz | **3o** | A3 | 4 | 0.5 | 77 | – | 91 |
| 18 | *n*Pr (**1a**) | Boc | **3b** | A4 | 18 | 0.67 | 84 | 10:1 | 99[g] |
| 19[h] |  (**1l**) | Boc | **3p** | A4 | 18 | 5.5 | 73 | 7:1 | 99 |
| 20 | Et (**1g**) | Cbz | **3h** | A3 | 18 | 0.4 | 74 | 13:1 | 98[f] |
| 21 |  (**1d**) | Boc | **3e** | A4 | 18 | 0.4 | 68 | 10:1 | 97 |
| 22[i] | *n*Pr (**1a**) | Cbz | **3a** | A3 | 18 | 0.5 | 70 | 19:1 | 97[f] |

[a] Experimental conditions: A1: A mixture of Cbz-NHOAc (**2a**) (0.30 mmol), aldehyde **1a** (0.25 mmol), and catalyst **10** (20 mol%) in 1.0 mL $CHCl_3$ was stirred for the time shown in the table. A2: A mixture of Boc-NHOAc (**2d**) (0.30 mmol), aldehyde **1a** (0.25 mmol), and catalyst **10** (20 mol%) in 1.0 mL $CHCl_3$ was stirred for the time shown in the table. A3: A mixture of Cbz-NHOTs (**2b**) (0.25 mmol), aldehyde **1** (0.30 mmol), catalyst **10** (20 mol%), and NaOAc (3 equiv) in 1.0 mL $CHCl_3$ was stirred for the time shown in the table. A4: A mixture of Boc-NHOTs (**2e**) (0.25 mmol), aldehyde **1** (0.30 mmol), catalyst **10** (20 mol%), and NaOAc (3 equiv) in 1.0 mL $CHCl_3$ was stirred for the time shown in the table. [b] Isolated yield of pure product **3** after silica-gel column chromatography. [c] Determined by $^1$H NMR spectroscopic analysis. [d] Determined by chiral-phase HPLC analysis. [e] 10 mol% of catalyst **10** was used. [f] Determined by chiral-phase HPLC analysis after reduction to the corresponding alcohol **3′** (see the Experimental Section). [g] Determined by chiral-phase HPLC analysis after reduction and benzoylation of **3n** and **3b** to the corresponding product **3n″** and **3b″**, respectively (see the Experimental Section). [h] 5 mol% catalyst **10** was used. [i] Reaction performed at 1 mmol scale of enal **1**.

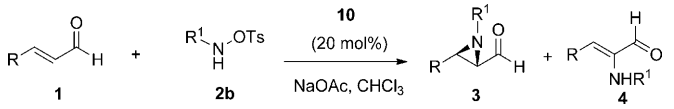
(e.g., peptides, antibiotics and enzymes) and useful compounds for synthetic peptide design.[31]

**Organocatalytic asymmetric aziridination of α-substituted α,β-unsaturated aldehydes**: Encouraged by the above success, we became intrigued as to whether functionalized aziridines containing an α-tertiary amine stereocenter could be synthesized by a chiral amine-catalyzed reaction between α-substituted α,β-unsaturated aldehydes **1**[32–33] and a suitable nitrogen source **2**. To our delight, when using **2b** as the reagent, the aziridination of **1u** proceeded smoothly in the presence of chiral pyrrolidine catalysts (**10**, **12**, and **14**) together with a base additive affording the corresponding product **3cc** in high conversion (Table 5). Different base additives and solvents were screened (Table 5, entries 1–7) and we found that NaOAc in toluene were the best conditions (entry 5). Increasing the concertration of **1u** from 0.25 to 0.5 M gave the product **3cc** in higher yield (entry 8). It is important to note that the reaction did not produce any product if the amine catalyst is not present (entry 9). Other diarylprolinol silyl ethers **12**–**14** were probed and catalyst **13** with a TES group gave a similiar result (full conversion and 93% *ee*) relative to catalyst **10** (entry 10). However, the enantioselectivity of the reaction decreased when catalysts **12** and **14** were employed (entries 11–12). Performing the aminocatalytic reaction at a lower temperature (4°C) and reducing the amount of base additive (1.5 equiv) gave **3cc** in 88% yield and 94% *ee* (entry 13). With these results in hand, we decided to investigate the scope of the aziridination of α-substituted-α,β-unsaturated aldehydes **1** when using amine catalyst **10** and NaOAc as the additive in toluene at 4°C (Table 6).

The aminocatalytic aziridination with Cbz- (**2b**) and Boc-NHOTs (**2e**) were efficient, highly enantioselective, and proceeded smoothly to give the corresponding Cbz- and Boc-protected terminal aziridine products **3cc**–**ll** in good yields with 91–96% *ee* (Table 6, entries 1–10). The chiral amine **10**-catalyzed aziridination was successful for several α-methylene aldehydes **1** with different functional groups (entries 6–9). For example, the highly enantioselective aziridination of aldehyde **1x** at its electron-deficient olefin was accomplished and gave the corresponding terminal aziridines **3hh** and **3ii** in 65 and 73% yields with 91 and 92% *ee*, respectively (entries 6–7). Asymmetric aminocatalytic aziridination of enal **1y** with a Bz-protected terminal hydroxy group at the α-alkyl substituent (**1y**) furnished products **3jj** and **3kk** in 75 and 90% yields with 92 and 94% *ee*, respectively (entries 8–9). Moreover, the aziridinating reagent TsNHOTs (**2f**) was also employed under the same reaction conditions

Table 4. Organocatalytic asymmetric aziridination of aromatic α,β-unsaturated aldehydes **1** with benzyl *N*-toluenesulfonyloxycarbamate **2b**.[a]

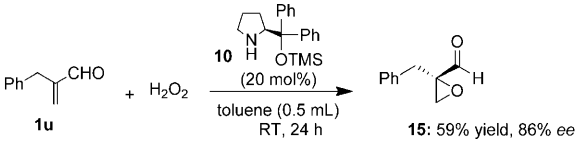



| Entry | R | $R^1$ | Prod. | *t* [h] | Ratio **3**/**4**[b] | Yield [%][b] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|---|---|
| 1 | (1m) | Cbz | **3r** | 0.5 | 10:1 | 52 | 19:1 | 99[g] |
| 2[f] | (1n) | Cbz | **3s** | 2 | >20:1 | 60 | 18:1 | 99[g] |
| 3 | (1o) | Cbz | **3t** | 0.5 | >20:1 | 40 | 19:1 | 97[g] |
| 4 | (1p) | Cbz | **3u** | 0.5 | 4:1 | 64 | 15:1 | 95 |
| 5 | (1q) | Cbz | **3v** | 0.5 | 6:1 | 64 | 15:1 | 99 |
| 6 | (1r) | Cbz | **3w** | 0.5 | 4:1 | 44 | 10:1 | 99[g] |
| 7 | (1s) | Cbz | **3x** | 0.67 | 3:1 | 55[h] | 12:1 | n.d. |
| 8 | (1t) | Cbz | **3y** | 0.67 | 4:1 | 25[i] | 19:1 | 95[i] |
| 9 | (1m) | Boc | **3z** | 1 | 25:1 | 63 | 15:1 | 99 |
| 10 | (1q) | Boc | **3aa** | 1 | 20:1 | 72 | 19:1 | 99[g] |
| 11 | (1t) | Boc | **3bb** | 1.5 | 9:1 | 38[i] | 19:1 | 99[i] |
| 12[j] | (1m) | Cbz | **3r** | 0.5 | 10:1 | 69 | 19:1 | 99[g] |

[a] Experimental conditions: A mixture of **2b** (0.30 mmol), aldehyde **1** (0.25 mmol), catalyst **10** (20 mol%), and NaOAc (3 equiv) in 1.0 mL $CHCl_3$ was stirred at 18 °C for the time shown in the table. [b] The ratio of **3** to **4** was determined by $^1$H NMR spectroscopic analysis. [c] Isolated yield of pure product **3** after silica-gel column chromatography. [d] Determined by $^1$H NMR spectroscopic analysis. [e] Determined by chiral-phase HPLC analysis. [f] Reaction was run at 4 °C. [g] Determined by chiral-phase HPLC analysis after reduction to the corresponding alcohol **3′** (see the Experimental Section). [h] Conversion into product **3x** as determined by $^1$H NMR spectroscopic analysis and 20% of compound **4x** was isolated. [i] Yield and *ee* were obtained after converting into the corresponding protected β-amino acid ester derivative **16** in the presence of carbene catalyst (**NHC-2**, the structure can be seen from below, in Table 8). [j] Reaction performed at a 1 mmol scale of enal **1**.

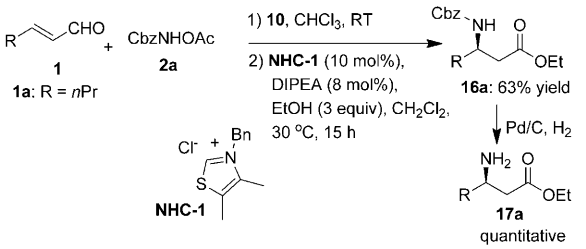
tioselective azirdination of disubstituted-α,β-unsaturated aldehydes **1**. If successful, this type of reaction would generate aziridines with adjacent tertiary and quaternary stereocenters a challenging task in organic synthesis. Initially we investigated the chiral amine **10**-catalyzed azirdination reaction between aldehyde **1aa** and *N*-Boc-hydroxylamine derivative **2e**. The reaction gave the corresponding product in high yield and good d.r. but low *ee*.[35] To our delight, we found that the reaction with TsNHOTs (**2f**) as the "nitrene equivalent" gave the corresponding aziridines **3nn** in 61% yield with 8:1 d.r. and 99% *ee* (Table 7, entry 1). Thus, the exploration of the reaction for a set of aliphatic disubstituted enals **1** was performed. The reaction was highly enantioselective and gave the corresponding aziridines **3oo–rr** with adjacent tertiary and quaternary stereocenters in high yields with 10:1–25:1 d.r. and 99% *ee* (entries 2–5). For example, the aldehyde **1bb** with three double bonds was enantioselectively aziridinated to give aziridine **3oo** with two terminal double bonds in 77% yield with 10:1 d.r. and 99% *ee* (entry 2). The asymmetric aziridination of aldehyde **1dd** gave the corresponding nearly enantiomerically pure aziridine **3qq** in 79% yield (>25:1 d.r. and 99% *ee*, entry 4). The reaction was also highly enantioselective for the catalytic azirdination of α-methyl-cinamic aldehyde **1ff** (entry 6). Thus, both mono- and disubstituted α,β-

and the corresponding product **3mm** was obtained in 92% yield with 84% *ee* (entry 11). Based on the above results, we also investigated if protected diaryl prolinols could catalyze the catalytic epoxidation of α-monosubstituted enals.[33c] Thus, similar conditions as described in Table 6 were investigated for the enantioselective epoxidation of α-substituted enal **1u** with $H_2O_2$ (Scheme 2).[34] The chiral amine **10**-catalyzed reaction was successful and the corresponding epoxide **15** was isolated in 59% yield with 86% *ee* [Eq. (6)].




(6)

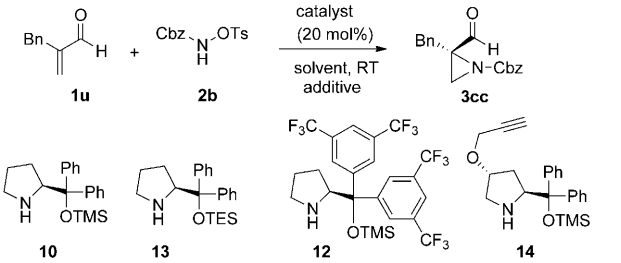
With the experience gathered until now, we decide to undertake the challenge of developing an aminocatalytic enan-




Scheme 2. Two-step one-pot asymmetric synthesis of protected β-amino acid ester derivative **16a**. DIPEA = *N*,*N*′-diisopropylethylamine.

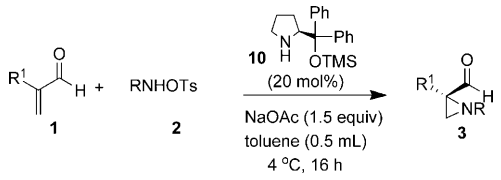
Table 5. Condition screening of the asymmetric aziridination of α-substituted α,β-unsaturated aldehydes **1u** with benzyl *N*-toluenesulfonyloxycarbamate **2b**.[a]

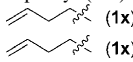
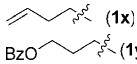
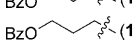
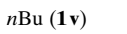



| Entry | Catalyst | Solvent | Additive | *t* [h] | Conv. [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | **10** | $CHCl_3$ | NaOAc | 17 | 69 | 88 |
| 2 | **10** | $CHCl_3$ | $K_2CO_3$ | 17 | 69 | 7 |
| 3 | **10** | $CHCl_3$ | $Et_3N$ | 16 | 66 | 25 |
| 4 | **10** | $CHCl_3$ | $Na_2CO_3$ | 16 | 46 | 14 |
| 5 | **10** | toluene | NaOAc | 17 | 100 (49)[d] | 94 |
| 6 | **10** | $CH_2Cl_2$ | NaOAc | 19 | 54 | 84 |
| 7 | **10** | EtOH | NaOAc | 17 | 100 | 59 |
| 8[e] | **10** | toluene | NaOAc | 17 | 100 (68)[d] | 92 |
| 9 | – | toluene | NaOAc | 17 | 0 | – |
| 10 | **13** | toluene | NaOAc | 16 | 100 | 93 |
| 11 | **12** | toluene | NaOAc | 16 | 43 | 72 |
| 12[f] | **14** | toluene | NaOAc | 20 | 100 | 76 |
| 13[e,g] | **10** | toluene | NaOAc | 16 | 100 (88)[d] | 94 |

[a] Experimental conditions: A mixture of **2b** (0.30 mmol), aldehyde **1u** (0.25 mmol), additive (0.75 mmol), and catalyst (20 mol%) in 1.0 mL solvent was stirred for the time shown in the table. [b] Conversion of **1u** as determined by $^1$H NMR spectroscopic analysis. [c] Determined by chiral-phase HPLC analysis. [d] Isolated yield in parenthesis. [e] Reaction was run in 0.5 mL solvent. [f] Catalyst **20** (10 mol%) was used. [g] Reaction run at 4 °C.

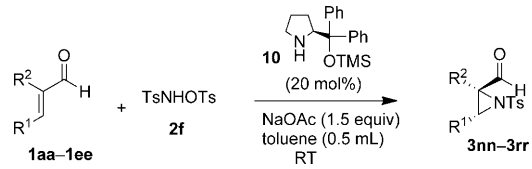
Table 6. The asymmetric aziridination of α-substituted-α,β-unsaturated aldehydes **1** with **2b** (Cbz-NHOTs) and **2e** (Boc-NHOTs).[a]

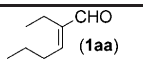
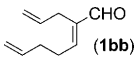
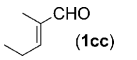
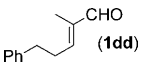
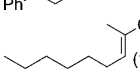
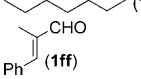
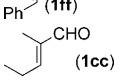



| Entry | $R^1$ | R | Product | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | Bn (**1u**) | Cbz | **3cc** | 88 | 94 |
| 2 | Bn (**1u**) | Boc | **3dd** | 89 | 96 |
| 3 | *n*-hexyl (**1v**) | Cbz | **3ee** | 69 | 95 |
| 4 | *n*-pentyl (**1w**) | Cbz | **3ff** | 64 | 95 |
| 5 | *n*-pentyl (**1w**) | Boc | **3gg** | 67 | 95 |
| 6 |  (**1x**) | Cbz | **3hh** | 65 | 91 |
| 7 |  (**1x**) | Boc | **3ii** | 73 | 92 |
| 8[d] |  (**1y**) | Cbz | **3jj** | 75 | 92 |
| 9 |  (**1y**) | Boc | **3kk** | 90 | 94 |
| 10 | *n*Bu (**1v**) | Boc | **3ll** | 81 | 96 |
| 11 | *n*-pentyl (**1w**) | Ts | **3mm** | 92 | 84 |
| 12[e] | *n*-hexyl (**1v**) | Cbz | **3ee** | 60 | 95 |

[a] Experimental conditions: A mixture of aldehyde **1** (0.25 mmol), **2** (0.30 mmol), NaOAc (0.375 mmol), and catalyst **10** (20 mol%) in toluene (0.5 mL) was stirred at 4 °C for 16 h. The product **3** was purified by column chromatography. [b] Isolated yield of pure product **3** after silica-gel column chromatography. [c] Determined by chiral-phase HPLC analysis. [d] Reaction was run at RT. [e] Reaction performed at a 1 mmol scale of enal **1**.

Table 7. The asymmetric aziridination of α,β-disubstituted-α,β-unsaturated aldehydes **1** with **2f** (TsNHOTs).[a]




| Entry | **1** | *t* [h] | Prod. | Yield [%][b] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|
| 1 |  (**1aa**) | 74 | **3nn** | 61 | 8:1 | 99 |
| 2 |  (**1bb**) | 68 | **3oo** | 77 | 10:1 | 99 |
| 3 |  (**1cc**) | 66 | **3pp** | 84 | >25:1 | 99 |
| 4 |  (**1dd**) | 72 | **3qq** | 79 | >25:1 | 99 |
| 5 |  (**1ee**) | 66 | **3rr** | 83 | 17:1 | 99 |
| 6 |  (**1ff**) | 65 | **3ss** | 55 | >25:1 | 98 |
| 7[e] |  (**1cc**) | 66 | **3pp** | 78 | >25:1 | 99 |

[a] Experimental conditions: A mixture of aldehyde **1** (0.25 mmol), **2** (0.30 mmol), NaOAc (0.375 mmol), and catalyst **10** (20 mol%) in toluene (0.5 mL) was stirred at 4 °C for the time shown in the table. The product **3** was purified by column chromatography. [b] Isolated yield of pure product **3** after silica-gel column chromatography. [c] Determined by crude $^1$H NMR spectroscopic analysis. [d] Determined by chiral-phase HPLC analysis. [e] The reaction was performed at a 1 mmol scale of enal **1**.

unsaturated aldehydes can be aziridinated in a catalytic asymmetric fashion by our methodology.

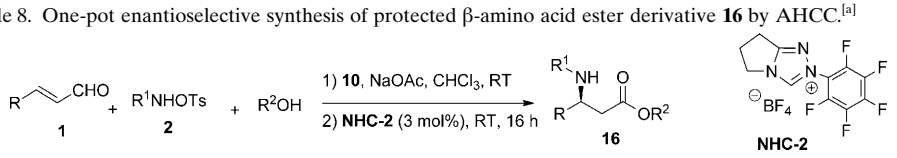
**One-pot enantioselective AHCC and short asymmetric synthesis of amino acid derivatives**: The employment of N-heterocyclic carbene (NHC) catalysis is a powerful method for the ring-opening of three-membered rings as shown by Bode and co-workers (e.g., epoxides, aziridines, and cyclopropanes).[36–37] Recently, we developed the first combination of asymmetric AHCC for the one-pot three-component synthesis of β-hydroxy esters and β-malonate esters with high *ee* values.[38] This was accomplished by first performing aminocatalytic enantioselective epoxidations or cyclopropanations of enals followed by an in situ ring-opening/oxidation/esterification sequence by a N-heterocyclic carbene catalyst. With these results in mind, we embarked on the development of AHCC for the one-pot three-component synthesis of Cbz- or Boc-protected β-amino acid esters (Scheme 2). In initial experiments, we found that the sequential one-pot combination of chiral amine **10** and in situ generated NHC catalyst from thiazolium salt **NHC-1**,[36] gave the corresponding β-amino acid ester **16a** in 63% yield by starting from 2-hexenal **1a**, acetyl carbamate **2a**, and ethanol (3 equiv). Removal of the Cbz group by hydrogenolysis with 10 wt.% Pd/C gave the corresponding β-amino acid ester **17a**. The absolute configuration of the aziridine prod-

uct **3** was assigned to be *R* at C3 by comparison of the optical rotation power of compound **17a** with literature data ($[\alpha]_D^{25} = +10.9$ ($c = 0.5$ in $H_2O$); lit.[39] (*S*)-**17a**: $[\alpha]_D^{25} = -10.7$ ($c = 2.1$ in $H_2O$)).

We next investigated the AHCC protocol by using Rovis NHC catalyst (2-(perfluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,1-c,1,2,4]triazol-2-ium tetrafluoroborate)[40] precursor **NHC-2** (Table 8). The one pot AHCC procedure was highly enantioselective and the corresponding *N*-Boc or *N*-Cbz-protected β-amino acid esters **16** were obtained in moderate to high yields with 92–99% *ee* (Table 8). The NHC catalyst generated in situ from **NHC-2** was efficient and only 3 mol% was needed. When Boc-NHOTs **2e** was used as the nitrogen substrate the catalyst loading of **10** could be reduced to 5 mol%. For example, the one-pot catalytic sequence between aldehydes **1l** or **1d**, **2e**, and MeOH gave the corresponding β-amino acid esters **16l** and **16d** in 73 and 80% yield and 93 and 92% *ee*, respectively (Table 8, entries 3–4). It is noteworthy that the one-pot enantioselective AHCC sequence enabled the synthesis of β-amino acid derivatives even though enals **1** with a β-aryl moiety were used as substrates. For example, β-amino acid esters **16t** and **16tt** were isolated in low yields but with excellent *ee* values (95 and 99%, respectively) when (*E*)-3-(naphthalen-2-yl)acrylaldehyde (**1t**) was employed as the starting material. The alcohol component could also be varied and reduced to three equivalents without affecting the yields and stereoselectivity of the reaction.

Table 8. One-pot enantioselective synthesis of protected β-amino acid ester derivative **16** by AHCC.[a]

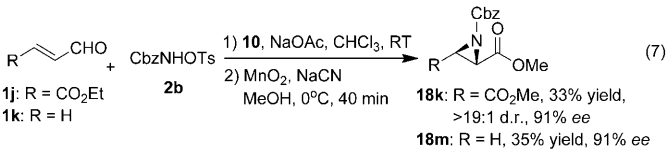



| Entry | R | $R^1$ | $R^2$ | Cat. **10** [mol%] | *t* [h] | Prod. | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|---|---|
| 1 | *n*-Pr (**1a**) | Cbz | Me | 20 | 0.5 | **16b** | 62 | 93 |
| 2 | Ph (**1m**) | Cbz | Me | 20 | 0.5 | **16m** | 54 | 96 |
| 3 | BnO (**1l**) | Boc | Me | 5 | 8 | **16l** | 73 | 93 |
| 4 | Ph (**1d**) | Boc | Me | 5 | 8 | **16d** | 80 | 92 |
| 5 | (**1t**) | Cbz | Me | 20 | 0.7 | **16t** | 25 | 95 |
| 6 | (**1t**) | Boc | Me | 20 | 1 | **16tt** | 38 | 99 |
| 7 | *n*Pr (**1a**) | Cbz | Me[d] | 20 | 0.5 | **16b** | 62 | 95 |
| 8 | *n*Pr (**1a**) | Cbz | Et[d] | 20 | 0.5 | **16a** | 69 | 94 |
| 9 | *n*Pr (**1a**) | Cbz | Bn[d] | 20 | 0.5 | **16c** | 62 | 94 |
| 10 | Ph (**1m**) | Cbz | Me[d] | 20 | 0.5 | **16m** | 46 | 94 |
| 11 | Ph (**1d**) | Boc | Me[d] | 5 | 8 | **16d** | 77 | 92 |
| 12[e] | *n*Pr (**1a**) | Cbz | Me[d] | 20 | 0.5 | **16b** | 64 | 95 |

[a] Experimental conditions: A mixture of aldehyde **1** (0.25 mmol), **2** (0.30 mmol), NaOAc (0.75 mmol), and catalyst **10** (5–20 mol%) in $CHCl_3$ (1.0 mL) was stirred at RT for the time shown in the table. Then, methanol (1.0 mL) and 2-(perfluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,1-*c*,1,2,4]triazol-2-ium tetrafluoroborate (3 mol%) was added to the reaction mixture. The resulting solution was stirred for 16 h at room temperature. After that, the solvent was evaporated and product **16** was purified by flash chromatography. [b] Isolated yield of pure product **16** after silica-gel column chromatography. [c] Determined by chiral-phase HPLC analysis. [d] Alcohol (3 equiv) was used. [e] The reaction was performed at a 1 mmol scale of the enal **1**.

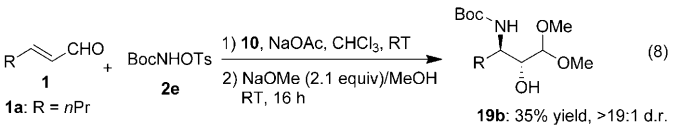
As mentioned before aziridines are present in natural products and useful synthons for total synthesis.[1] Thus, we decided to investigate the short expeditious formal total synthesis of (2*S*,3*S*)-(+)-aziridine-2,3-dicarboxylic acid [Eq. (7)].[41] It was successfully executed by oxidation and in situ esterification of the β-formyl azirdine product, which had been generated by the chiral amine **10**-catalyzed aziridination of (*E*)-ethyl 4-oxobut-2-enoate **1j** in methanol. In fact, this protocol gave the protected natural product (2*S*,3*S*)-(+)-aziridine-2,3-dicarboxylic acid derivative **18k** in 33% yield (two steps) with >19:1 d.r.[41a,b] Interestingly, transesterification occurred during the one-pot oxidation esterification step.

Acid ester **18m**, which is useful in total synthesis,[42] was also expeditiously synthesized in moderate yield by using




(7)

this methodology. Moreover, the possibility of performing a one-pot asymmetric *trans*-aminohydroxylation of enal **1a** was investigated [Eq. (8)].[26c] It was successful in a two-step sequence involving the organocatalytic enantioselective aziridination followed by a Payne-type rearrangement with NaOMe (2.2 equiv) by starting from *trans*-hex-2-enal (**1a**) to give *trans*-3-amino-2-hydroxy aldehydes **19b** in moderate overall yield but excellent stereoselectivity [>19:1 d.r. and 99% *ee*, Eq. (8)].




(8)

**Determination of the absolute configurations**: The absolute configuration of linear aziridines **1** was determined by synthesis of **17a** (Scheme 2). Thus, the aziridine reaction of

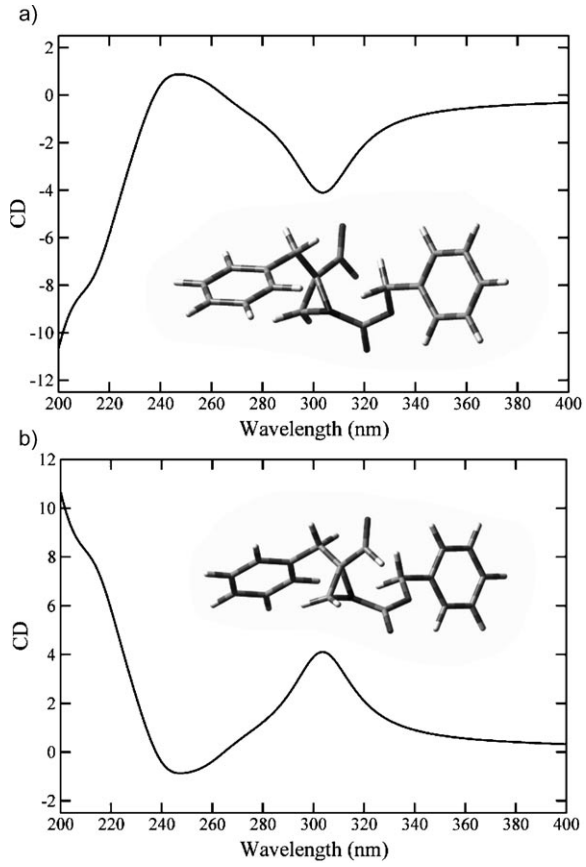



Figure 1. a) ECD spectra calculated for the (2*R*)-**3cc** and the optimized geometry. b) ECD spectra calculated for the (2*S*)-**3cc** and the optimized geometry. c) Experimental (full trace) ECD spectra of compound **3cc**.

linear enals **1** gives access to (2*S*,3*R*)-2-formylaziridines **3** by using amine catalyst (*S*)-**10**. The absolute configuration of terminal aziridines **3** obtained by enantioselective aziridination of monosubstituted α,β-unsaturated aldehydes **1** was assigned by means of TD-DFT calculations of the electronic dichroism (ECD) spectra of **3cc** (Figure 1).[43] The DFT calculations of the *S* enantiomer of **3cc** matched with the experimental CD spectra of **3cc** (Figure 1). Thus, the absolute configuration of **3cc** at C-2 is assigned *S*.

The aboslute configuration of the aziridine products **3** synthesized from disubstituted-α,β-unsaturated aldehydes **1** was determined by X-ray analysis of **3nn**.[44] The absolute configuration of product **3nn** was 2*S*,3*R* (Figure 2). Thus, the aziridine reaction of disubstituted-α,β-unsaturated aldehydes enals **1** by using amine (*S*)-**10** as the catalyst gives access to (2*S*,3*R*)-2-formylaziridines **3**.

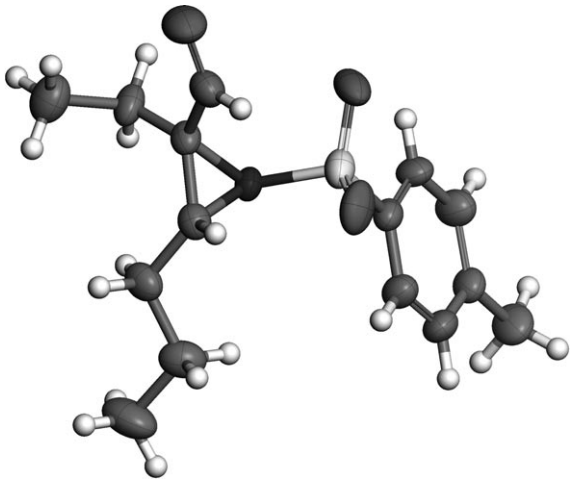
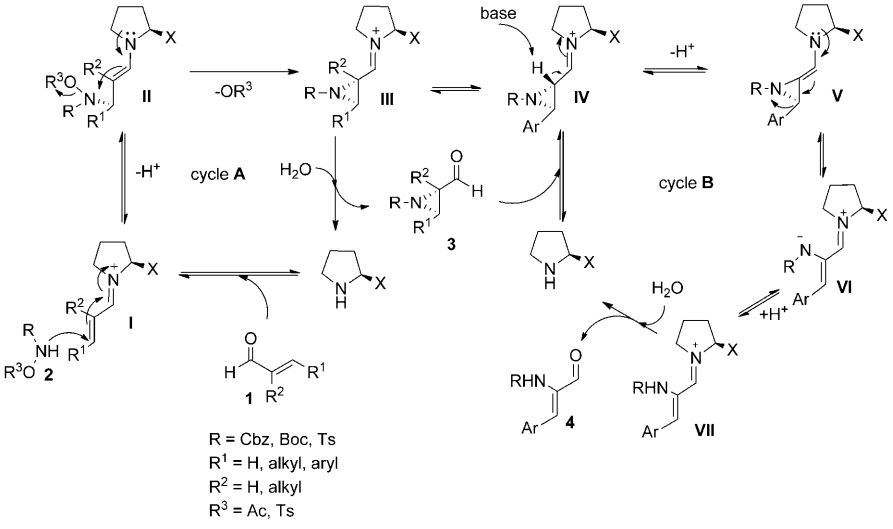


Figure 2. ORTEP picture of (2*S*,3*R*)-2-ethyl-3-propyl-1-tosylaziridine-2-carbaldehyde (**3nn**).

**Mechanism**: Based on the absolute configuration of the aziridine products **3**, synthesized by the aminocatalytic reaction between hydroxyl amines **2** and linear, monosubstituted, and disubstituted-α,β-unsaturated aldehydes **1**, we were able to propose a unified mechanism for their formation (Scheme 3, cycle A). Thus, initial reversible iminium formation between enals **1** and the chiral pyrrolidine derivative gives the iminium intermediate **I**. Efficient shielding of the *Si* face ($R^1$ = alkyl) of the iminium intermediate **I** leads to nucleophilic aza-conjugate addition of **2** to the β-carbon atom at the *Re* face ($R^1$ = alkyl) of iminium intermediate **I** and generates the chiral enamine intermediate **II**. Next, the generated chiral enamine intermediate **II** performs a 3-*exo*-tet nucleophilic attack on the electrophilic nitrogen atom




Scheme 3. Proposed reaction pathway for the enantioselective aziridination of enals **3**.

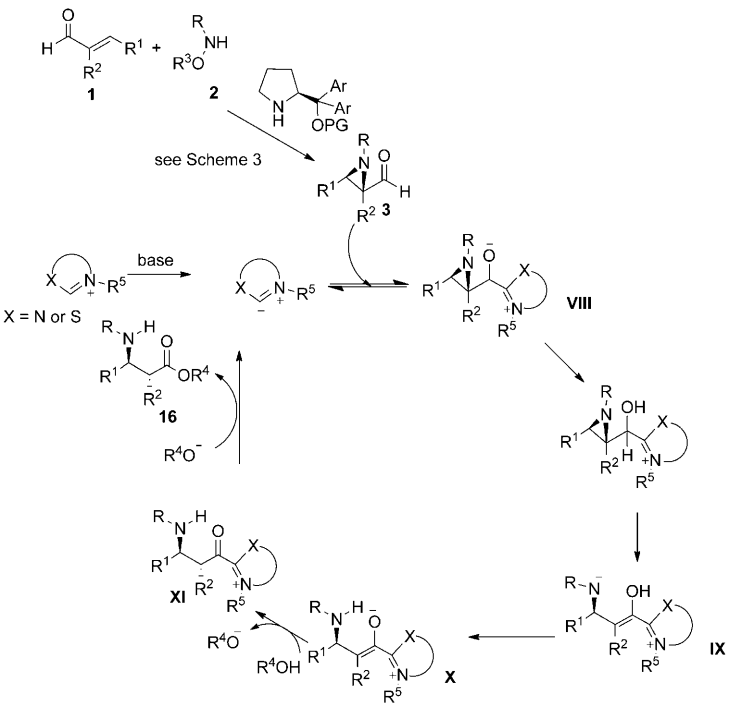
  

from its *Re* face and the leaving group ($R^3OH$) is released. The intramolecular ring closure pushes the equilibrium forward and makes this step irreversible and gives iminium intermediate **III**. It is noteworthy that it is this cyclization step, which dictates the stereoselectivity for the aminocatalytic aziridination of α-substituted enals **1** ($R^1 = H$). Subsequent hydrolysis of the iminium intermediate **III** gives the corresponding aziridine product **3** and releases the amine catalyst. Thus, the protected (*S*)-prolinol derivatives catalyzes the aziridination of linear- and disubstituted-α,β-unsaturated aldehydes **1** with hydroxylamines **2** to give the corresponding (2*S*,3*R*)-2-formylaziridines **3**. The reactions with α-substituted enals ($R^1 = H$, $R^2 =$ alkyl) gave the corresponding (*S*)-aziridines **3**.

In the case of the aminocatalytic enantioselective aziridination of cinnamic aldehyde derivatives **1**, the corresponding aziridine products could also rearrange to form α-amino-α,β-unsaturated aldehydes **4** (Scheme 3, cycle B). In fact, this type of base-catalyzed rearrangement has been previously observed in aminocataytic enantioselective cyclopropanation reactions between enals and bromomalonates.[33a,45] As described vide supra, iminium intermediate **III** is generated by the first catalytic cycle (cycle A). It can next undergo hydrolysis to give the corresponding aziridine product **3** or enter a second catalytic cycle in which a base-promoted formation of enamine intermediate **V** occurs through iminium intermediate **IV** (cycle B). Iminium intermediate **IV** can also be generated by in situ condensation between the chiral amine catalyst and the aziridine product **3**. In fact, mixing the cinnamic aldehyde derived product **3r** together with catalyst **10** in the presence of base gave **4r**. Next, ring-opening of **V** gives iminium intermediate **VI**. Protonation of intermediate **VI** and hydrolysis of iminium **VII** liberates the chiral-amine catalyst **10** and gives the corresponding α-amino-α,β-unsaturated aldehyde **4**. Our experimental results indicate that cinnamic aldehyde derivatives with an electron-donating substituent give more of product **4** relative to the ones with electron-withdrawing groups.

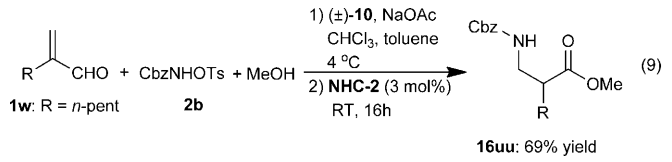
The mechanistic proposal for the one-pot three-component reaction between α,β-unsaturated aldehydes **1**, hydroxylamines **2**, and an alcohol, which gave β-amino acid ester derivatives **16** by AHCC is shown in Scheme 4. The one-pot tandem reaction starts with a chiral amine-catalyzed highly diastereo- and enantioselective aziridinnation of enal **1** to form aziridine **3** (Scheme 3). Next, the in situ generated N-heterocyclic carbene catalyst performs a nucleophilic attack at the aldehyde moiety of β-formyl-azirdine **3** and zwitterionic species **VIII** is formed. Subsequent, C–N bond cleavage/ring opening occurs and intermediate **IX** is generated. Activated intermediate **XI** is formed by keto–enol tautomerization via intermediates **IX** and **X**.[36,38,40b] Final transesterification by the alcohol component gives the corresponding β-amino acid ester **16** and releases the carbene catalyst.

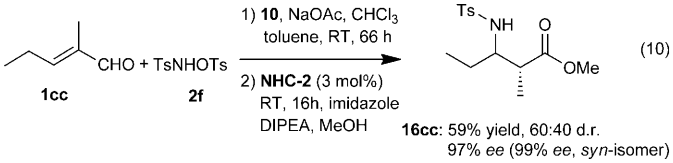
According to the proposed mechanism for the one-pot assembly of β-amino acid esters **16** (Scheme 4). The reaction with α-monosubstituted enals **1** should give $\beta^2$-amino acid derivatives,[46] which are important naturally occurring




Scheme 4. Possible mechanism of the one-pot three-component reaction between an enal **1**, hydroxylamine **2**, and an alcohol.

amino acid residues in peptides, with no enantioselectivity. Thus, we investigated the one-pot cascade reaction sequence by starting with aldehyde **1w** [Eq. (9)]. The transformation with racemic catalyst **10** gave the corresponding $\beta^2$-amino acid ester **16uu** in 69% yield. The same transformation with (*S*)-**10** as the catalyst afforded nearly racemic **16uu** (< 5% *ee*).[47] However, the intermediate aziridine **3ff** was formed with 95% *ee* (Table 6, entry 4). Thus, no stereoselective protonation occurred in cycle C when α-monosubstituted enals **1** were employed as substrates. However, stereoselective protonation occurred when performing the AHCC sequence employing enal **1cc** as the substrate [Eq. (10)].




## Conclusion

In summary, we have disclosed the development, scope, and application of the highly enantioselective aziridination of

α,β-unsaturated aldehydes. The study shows that by carefully designing the substituents of a hydroxylamine derivative it is possible to employ it as a substrate for the highly enantioselective aziridination of α,β-unsaturated aldehydes in the presence of a simple chiral amine catalyst. The aminocatalytic aziridination of linear α,β-unsaturated aldehydes was highly diastereo- and enantioselective and enabled the asymmetric synthesis of the corresponding β-formyl aziridines with up to >19:1 d.r. and 99% *ee*. The aminocatalytic aziridinaton of α-monosubstituted enals gave the corresponding terminal aziridines with a quaternary stereocenter in high yields and up to 99% *ee*. It is noteworthy that aminocatalytic aziridination of disubstituted-α,β-aldehydes was highly stereoselective (8:1–>25:1 d.r., 99% *ee*) and gave the corresponding azirdine products bearing two adjacent tertiary and quaternary stereocenters. A highly enantioselective one-pot three-component asymmetric synthesis of β-amino acid esters was also developed. The reaction was achieved by the one-pot combination of chiral AHCC. We also demonstrated that the catalytic aziridination reaction could be applied to the formal total synthesis of naturally occurring azirdines. The mechanisms and stereochemistry of the reactions are also discussed. Future research will include development of novel one-pot cascade catalysis reactions by using α,β-unsaturated aldehydes and hydroxylamine derivatives as substrates, application of the optically active aziridine products in total- and diversity-oriented synthesis (e.g., metal-catalyzed stereoselective cycloadditions and multicomponet reactions), and further development of related organocatalytic aziridination reactions.

## Experimental Section

**General**: Chemicals and solvents were either purchased from commercial suppliers or purified by standards techniques. The pyrrolidine catalysts were synthesized according to literature procedures.[1] For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of ammoniummolybdate (100 g), $Ce(SO_4)_2$ (2 g) and 10% $H_2SO_4$ (1 L) followed by heating or by treatment with a solution of potassium permanganate (3 g), $K_2CO_3$ (20 g), 5% aq. NaOH (5 mL) and water (300 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm), $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker AM400 or Varian AS400. Chemical shifts are given in $\delta$ relative to tetramethylsilane (TMS), the coupling constants $J$ are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature, TMS served as internal standard ($\delta$ = 0 ppm) for $^1$H NMR and $CDCl_3$ was used as internal standard ($\delta$ = 77.16 ppm) for $^{13}$C NMR. HPLC was carried out using a Waters 2690 Millenium with photodiode array detector. Optical rotations were recorded on a Perkin Elmer 241 Polarimeter ($d$ = 589 nm, 1 dm cell). High-resolution mass (ESI) were obtained with a Bruker Micro-TOF spectrometer. Far-UV CD measurements were made on an Applied photophysics chirascan CD spectropolarimeter (Surrey, United Kingdom) with a quartz cuvette with a path length of 0.1 cm. Wavelengths ranging between 190 and 400 nm were scanned, with a 0.5 nm step resolution and 100 nm per min scan speed. The response time was 4 s, with 50 mdeg sensitivity and a 1 nm band width. Measurements were conducted at 20 °C in acetonitrile and the concentration was $1.43\times10^{-4}$ mol L$^{-1}$. Spectra were collected and averaged over 1–34 scans. The CD spectra were evaluated using Applied photophysics Pro-Data viewer 4.0.17. $\Delta\varepsilon$ values are expressed as L mol$^{-1}$ cm$^{-1}$.

Representative procedure for the aziridination between benzyl *N*-acetoxycarbamate 2a or *tert*-butyl *N*-acetoxycarbamate 2d and α,β-unsaturated aldehyde 1: α,β-Unsaturated aldehyde **1** (1.0 equiv, 0.25 mmol) was added to a stirred solution of catalyst **10** (20 mol%) and benzyl *N*-acetoxycarbamate **2a** or *tert*-butyl *N*-acetoxycarbamate **2d** (1.2 equiv, 0.30 mmol) in $CHCl_3$ (1.0 mL) at 40 °C. The reaction was vigorously stirred for the reported time. Next, the reaction was directly loaded upon a silica gel column and immediate chromatography (pentane/EtOAc or toluene/EtOAc) gave the corresponding aziridine product **3**.

**Representative procedure for the aziridination between benzyl *N*-tosylcarbamate 2b or *tert*-butyl *N*-tosylcarbamate 2e and aliphatic α,β-unsaturated aldehyde 1**: α,β-Unsaturated aldehyde **1** (1.2 equiv, 1.2 mmol) and NaOAc (3.0 mmol, 3 equiv) were added to a stirred solution of catalyst **10** (20 mol%) and benzyl *N*-tosylcarbamate **2b** or *tert*-butyl *N*-tosylcarbamate **2e** (1.0 equiv, 1.0 mmol) in $CHCl_3$ (4.0 mL) at room temperature. The reaction was vigorously stirred for the reported time. Next, the reaction was directly loaded upon a silica gel column and immediate chromatography (pentane/EtOAc or toluene/EtOAc) gave the corresponding aziridine product **3**.

**(2*S*,3*R*)-Benzyl 2-formyl-3-propylaziridine-1-carboxylate (3a)**: Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.13 (d, $J$ = 4.8 Hz, 1H), 7.38–7.34 (m, 5H), 5.19 (d, $J$ = 12.8 Hz, 1H), 5.14 (t, $J$ = 12.8 Hz, 1H), 3.01–2.98 (m, 1H), 2.86–2.78 (m, 1H), 1.67–1.42 (m, 4H), 0.95 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 195.6, 160.1, 135.8, 128.9, 128.8, 128.7, 128.6, 68.8, 47.1, 44.1, 33.0, 20.1, 13.7 ppm; HRMS (ESI): $m/z$: calcd for $C_{14}H_{17}NO_3$: 270.1101 $[M+Na]^+$; found: 270.1104; $[\alpha]_D^{25}$ = −11.7 ($c$ = 1.0 in $CHCl_3$) for an enantiomerically enriched sample of 99% *ee*; the enantiomeric excess was determined by reduction to the corresponding alcohol by HPLC analysis in comparison with authentic racemic material (ODH-column, *n*-hexane/*i*PrOH 95:5, $\lambda$ = 210 nm, 1.0 mL min$^{-1}$): $t_R$ (major enantiomer) = 13.7, $t_R$ (minor enantiomer) = 12.2 min.

**Representative procedure for the aziridination between benzyl *N*-tosylcarbamate 2b or *tert*-butyl *N*-tosylcarbamate 2e and aromatic α,β-unsaturated aldehydes 1**: α,β-Unsaturated aldehyde **1** (1.0 equiv, 1.0 mmol) and NaOAc (3.0 mmol, 3 equiv) were added to a stirred solution of catalyst **10** (20 mol%) and benzyl *N*-tosylcarbamate **2b** or *tert*-butyl *N*-tosylcarbamate **2e** (1.2 equiv, 1.2 mmol) in $CHCl_3$ (4.0 mL) at room temperature. The reaction was vigorously stirred for the reported time. Next, the reaction was directly loaded upon a silica gel column and immediate chromatography (pentane/EtOAc or toluene/EtOAc) gave the corresponding aziridine product **3**.

**(2*S*,3*R*)-Benzyl 2-formyl-3-(pyridin-3-yl)aziridine-1-carboxylate (3u)**: Yellow oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.49 (d, $J$ = 2.8 Hz, 1H), 8.64–8.55 (m, 2H), 7.56 (dt, $J$ = 2.0, 8.0 Hz, 1H), 7.40–7.28 (m, 6H), 5.20 (dd, $J$ = 12.0, 20.0 Hz, 2H), 3.88 (d, $J$ = 2.4 Hz, 1H), 3.38 ppm (t, $J$ = 2.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 193.7, 159.5, 150.3, 148.9, 135.1, 133.9, 130.6, 129.0, 128.9, 128.9, 123.9, 69.3, 49.6, 44.0 ppm; HRMS (ESI): $m/z$: calcd for $C_{16}H_{15}N_2O_3$: 283.1077 $[M+Na]^+$; found: 283.1077; $[\alpha]_D^{25}$ = −56.0 ($c$ = 0.5 in $CHCl_3$) for an enantiomerically enriched sample of 95% *ee*; the enantiomeric excess was determined by chiral HPLC with an AD-column (*n*-hexane/*i*PrOH 85:15, $\lambda$ = 210 nm): 1.0 mL min$^{-1}$, $t_R$ (major enantiomer) = 26.0, $t_R$ (minor enantiomer) = 12.6 min.

**General procedure for the aziridination between benzyl *N*-tosyloxycarbamates 2b or *tert*-butyl *N*-tosyloxycarbamates 2e and α-substituted-α,β-unsaturated aldehyde 1**: α-Substituted α,β-unsaturated aldehyde **1u–aa** (1.0 equiv, 1.0 mmol), benzyl *N*-tosyloxycarbamate **2b** or *tert*-butyl *N*-tosyloxycarbamate **2e** (1.2 equiv, 1.2 mmol) and NaOAc (1.5 mmol, 1.5 equiv) were added to a stirred solution of catalyst **10** (20 mol%) in toluene (2.0 mL) at 0 °C and the resulting reaction mixture was vigorously stirred for the reported time at 4 °C. Next, the reaction was directly loaded upon a silica-gel column and immediate chromatography (pentane/EtOAc) furnished the corresponding aziridine products **3cc–mm**.

**(*S*)-Benzyl-2-benzyl-2-formylaziridine-1-carboxylate (3cc)**: Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.92 (s, 1H), 7.35–7.33 (m, 3H), 7.28–7.23 (m, 7H), 5.15 (d, $J$ = 9.6 Hz, 1H), 5.10 (d, $J$ = 9.6 Hz, 1H), 3.26 (d, $J$ = 12.0 Hz, 1H), 3.16 (d, $J$ = 12.0 Hz, 1H), 2.70 (s, 1H), 2.40 ppm (s,

1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 195.8, 160.2, 135.5, 135.2, 129.9, 128.7, 128.64, 128.58, 128.4, 127.1, 68.8, 50.2, 35.2, 34.2 ppm; HRMS (ESI): *m/z*: calcd for $C_{18}H_{17}NO_3Na$: 318.1101 $[M+Na]^+$; found: 318.1099; $[\alpha]_D^{25}$ = +49.7 (*c* = 1.0 in $CHCl_3$) for an enantiomerically enriched sample of 92% *ee*; the enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ODH column, *n*-hexane/*i*PrOH 95:5, 1.0 mL min$^{-1}$, 210 nm): $t_R$ (major enantiomer) = 21.5, $t_R$ (minor enantiomer) = 25.0 min.

**General procedure for the aziridination reaction between 4-methyl-*N*-(tosyloxy)benzenesulfonamide 2f and α,β-disubstituted enals 1**: α,β-Disubstituted enal **1aa–ee** (1.0 equiv, 0.25 mmol), 4-methyl-*N*-(tosyloxy)benzenesulfonamide **2f** (1.2 equiv, 0.30 mmol), and NaOAc (0.375 mmol, 1.5 equiv) were added to a stirred solution of catalyst **10** (20 mol%) in toluene (0.5 mL) at room temperature and the resulting reaction mixture was vigorously stirred for the reported time. Next, the reaction was directly loaded upon a silica-gel column and immediate chromatography (pentane/EtOAc 10:1) furnished the aziridine product **3nn–rr**.

**(2*S*,3*R*)-2-Ethyl-3-propyl-1-tosylaziridine-2-carbaldehyde (3nn)**: Colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.47 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 3.53 (dd, *J* = 5.6, 2.4 Hz, 1H) 2.45 (s, 3H), 2.07–1.97 (m, 1H), 1.59–1.50 (m, 1H), 1.48–1.30 (m, 4H), 1.01 (t, *J* = 7.2 Hz, 3H), 0.90 ppm (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 195.1, 144.7, 136.6, 129.8, 127.7, 62.7, 52.0, 29.4, 21.8, 20.8, 19.5, 13.7, 10.5 ppm; HRMS (ESI): *m/z*: calcd for $C_{15}H_{21}NO_3SNa$: 318.1134 $[M+Na]^+$; found: 318.1126; $[\alpha]_D^{25}$ = +4.9 (*c* = 1.0 in $CHCl_3$) for an enantiomerically enriched sample of 99% *ee*; the enantiomeric excess was determined by HPLC analysis in comparison with the authentic racemic material (ODH-column, *n*-hexane/*i*PrOH 98:2, 0.5 mL min$^{-1}$, 250 nm): $t_R$ (major enantiomer) = 20.1, $t_R$ (minor enantiomer) = 21.6 min.

**Procedure for the epoxidation of α-substituted enal (1u)**: 2-Benzylacrylaldehyde (**1u**) (0.25 mmol, 1 equiv) and $H_2O_2$ (0.3 mmol, 1.2 equiv) were added to a stirred solution of catalyst **10** (20 mol%) in toluene (0.5 mL). The reaction mixture was vigorously stirred at room temperature for 24 h. The crude reaction mixture was passed through a silica gel column (pentane/EtOAc 10:1) to give the pure product **15** (24 mg, yield: 59%). Compound **15**: $R_f$ = 0.52 (pentane/EtOAc 6:1).

**(*S*)-2-Benzyloxirane-2-carbaldehyde (15)**: Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.97 (s, 1H), 7.34–7.24 (m, 5H), 3.26 (d, *J* = 15.2 Hz, 1H), 3.21 (t, *J* = 15.2 Hz, 1H), 3.03 (d, *J* = 4.8 Hz 1H), 2.88 ppm (d, *J* = 4.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): 198.7, 135.0, 130.1, 128.6, 127.1, 61.5, 49.0, 33.2 ppm; HRMS (ESI): *m/z*: calcd for $C_{10}H_{10}O_2Na$: 185.0570 $[M+Na]^+$; found: 185.0573; $[\alpha]_D^{25}$ = −23.9 (*c* = 1.0 in $CHCl_3$) for an enantiomerically enriched sample of 86% *ee*. The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (OJ-column, *iso*-hexane/*i*PrOH 98:2, 0.5 mL min$^{-1}$, 210 nm): $t_R$ (major enantiomer) = 50.5, $t_R$ (minor enantiomer) = 58.2 min.

**Preparation of (3*R*)-benzyloxycarbonylamino-hexanoic acid ethyl ester (16a)**: Compound **3a** (25 mg, 0.1 mmol, 1.00 equiv) was added to a solution of 3-benzyl-4,5-dimethylthiazolium chloride[36] (3 mg, 0.01 mmol, 10% equiv) in $CH_2Cl_2$ (0.5 mL) at room temperature. EtOH (18 μL, 0.3 mmol, 3.0 equiv) and DIPEA (4 μL, 0.02 mmol, 20 mol%) were added to this suspension. The resulting solution was warmed to 30 °C and stirred for 15 h. The reaction mixture was treated with sat. aq. $NH_4Cl$ (1 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 3:1) to afford ester **16a** (19 mg, 63%). Compound **16a**: $R_f$ = 0.45 (pentane/EtOAc 3:1).

**(*R*)-Ethyl 3-(benzyloxycarbonylamino)hexanoate (16a)**: Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.29–7.37 (m, 5H), 5.17 (br s, 1H), 5.09 (s, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.98–4.02 (m, 1H), 2.51–2.59 (m, 2H), 1.42–1.53 (m, 2H), 1.29–1.38 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.91 ppm (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 156.0, 136.8, 129.0, 128.7, 128.6, 128.2, 66.7, 60.7, 48.1, 39.2, 36.8, 19.5, 14.3, 13.9 ppm; HRMS (ESI): *m/z*: calcd for $C_{16}H_{23}O_4N$: 316.1519 $[M+Na]^+$; found: 316.1524; $[\alpha]_D^{25}$ = +18.1 (*c* = 1.0 in $CHCl_3$) for an enantiomerically enriched sample of 94% *ee*. The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (ODH column, *n*-hexane/*i*PrOH 95:5, 0.5 mL min$^{-1}$): $t_R$ (major enantiomer) = 22.1, $t_R$ (minor enantiomer) = 23.6 min.

**One-pot synthesis of β-amino acid ester derivatives 16**: A mixture of aldehyde **1** (1.0 mmol), **2** (1.2 mmol), NaOAc (3.0 mmol), and catalyst **10** (5–20 mol%) in $CHCl_3$ (4.0 mL) was stirred at room temperation for the time shown in the Table 8. Then, alcohol (3 equiv) and 2-(perfluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,1-*c*,1,2,4]triazol-2-ium tetrafluoroborate (3 mol%) were added to the reaction mixture. The resulting solution was stirred for 16 h at room temperature. After that, the solvent was evaporated and product **16** was purified by flash column chromatography.

**(*R*)-Methyl 3-{[(benzyloxy)carbonyl]amino}hexanoate (16b)**: Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.37–7.31 (m, 5H), 5.18 (d, *J* = 8.8 Hz, 1H), 5.09 (s, 2H), 4.02–3.96 (m, 1H), 3.66 (s, 3H), 2.54 (t, *J* = 6.4 Hz, 2H), 1.53–1.47 (m, 2H), 1.40–1.35 (m, 2H), 0.91 ppm (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.2, 156.0, 136.7, 128.6, 128.2, 127.1, 66.7, 51.8, 48.0, 39.0, 36.7, 19.5, 13.9 ppm; HRMS (ESI): *m/z*: calcd for $C_{15}H_{21}NO_4Na$: 302.1363 $[M+Na]^+$; found: 302.1371; $[\alpha]_D^{25}$ = +7.5 (*c* = 1.0 in $CHCl_3$) for an enantiomerically enriched sample of 93% *ee*; the enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material (Ad-column, *n*-hexane/*i*PrOH 95:5, 1.0 mL min$^{-1}$, 210 nm): $t_R$ (minor enantiomer) = 13.2, $t_R$ (major enantiomer) = 15.0 min.

**Preparation of (*R*)-ethyl 3-aminohexanoate (17a)**: 10% (w/w) of Pd/C (10%) was added to a stirred solution of ester **16a** (15 mg, 0.05 mmol) in MeOH (1 mL). The reaction was stirred under 90 atm. of hydrogen overnight. Then the crude reaction mixture was filtered through a plug of Celite. The solvent was removed under reduced pressure to afford the pure product **17a** (8 mg, quant.).

**(*R*)-Ethyl 3-aminohexanoate (17a)**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.10 (q, *J* = 7.2 Hz, 2H), 3.11–3.15 (m, 1H), 2.41 (dd, *J* = 4.0, 15.6 Hz, 1H), 2.19 (dd, *J* = 8.8, 15.6 Hz, 1H), 1.53 (br s, 2H), 1.29–1.37 (m, 4H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.90 ppm (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.6, 60.2, 47.9, 42.6, 39.7, 19.1, 14.2, 13.9 ppm; $[\alpha]_D^{25}$ = +10.9 (*c* = 0.5 in $H_2O$) (lit. (*S*)-**17a**: $[\alpha]_D^{25}$ = −10.7 (*c* = 2.1 in $H_2O$)).[39]

**General procedure for the oxidation/esterification of aziridine 3**: Activated manganese dioxide (2.4 mmol, 209 mg, 17 equiv) was added to a stirred solution of aldehyde **3** (0.14 mmol, 1 equiv) and sodium cyanide (15 mg, 0.3 mmol, 2 equiv) in methanol (0.73 mL) at 0 °C.[48] After stirring the mixture at 0 °C for 40 min, the reaction mixture was diluted with ethyl acetate and filtered through a pad of Celite. The filtrated was concentrated in vacuo. The residue was diluted with ether, washed with saturated aqueous ammonium chloride and brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (pentane/ethyl acetate 4:1) to give the corresponding ester **18**.

**(2*S*,3*S*)-1-Benzyl 2,3-dimethyl aziridine-1,2,3-tricarboxylate (18k)**: Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.38 (m, 5H), 5.18 (m, 2H), 3.76 (s, 6H), 3.45 (s, 2H), 2.19 ppm (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 166.8, 158.4, 135.2, 128.8, 128.7, 128.7, 69.1, 53.2, 40.3 ppm; HRMS (ESI): *m/z*: calcd for $C_{14}H_{15}O_6N$: 316.0792 $[M+Na]^+$; found: 316.0794; $[\alpha]_D^{25}$ = +5.3 (*c* = 0.2 in $CHCl_3$).

**Typical procedure for the opening of aziridine 3 by NaOMe**: NaOMe (0.78 mmol, 2.1 equiv) in MeOH (1 mL) was added to aldehyde **3b** (79 mg, 0.37 mmol, 1 equiv) and the reaction mixture was stirred for 16 h at room temperature. Then, the reaction was quenched by adding $H_2O$ slowly. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic fractions were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (pentane/ethyl acetate 3:1) to give diester **19b** in 35% yield (36 mg). Compound **19b**: $R_f$ = 0.17 (pentane/EtOAc 3:1).

***tert*-Butyl (2*R*,3*R*)-2-hydroxy-1,1-dimethoxyheptan-3-ylcarbamate (19b)**: Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.73 (br d, *J* = 8.4 Hz, 1H), 4.28 (d, *J* = 6.0 Hz, 1H), 3.77 (br s, 1H), 3.67 (s, 1H), 3.45 (s, 3H), 3.41 (s, 3H), 2.47 (s, 1H), 1.44 (s, 9H), 1.44–1.35 (m, 4H), 0.92 ppm (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 156.1, 104.3, 79.4, 73.5,

55.1, 54.4, 51.8, 31.9, 28.5, 19.4, 14.2 ppm; HRMS (ESI): *m/z*: calcd for $C_{13}H_{27}NO_5$: 300.1787 $[M+Na]^+$; found: 300.1775; $[\alpha]_D^{25} = +12.4$ ($c = 0.5$ in $CHCl_3$).

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