Asymmetric Synthesis

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Exploiting Organocatalysis: Enantioselective Synthesis of Vinyl Glycines by Allylic Sulfimide [2,3] Sigmatropic Rearrangement**

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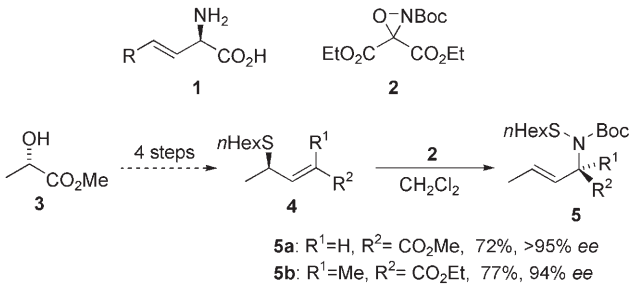
Amino acids—as fundamental building blocks of peptides and proteins—are important targets for enantioselective synthesis. In particular, efficient syntheses of non-proteinogenic amino acids can provide access to modified peptides as valuable biological probes. Several outstanding and versatile techniques exist for the catalytic and enantioselective synthesis of amino acids,[1a] and include the asymmetric hydrogenation of amidoacrylates[1b] and the phase-transfer catalyzed alkylation of glycine enolates.[1c] However, there are several highly interesting types of amino acid to which these methods cannot generally be applied. One such class are the β,γ-unsaturated amino acids (vinyl glycines) **1**. This motif is present in several biologically significant targets, but can be difficult to access, even in racemic form, particularly if the stereocontrolled incorporation of the alkene is desired.[2] Few catalytic asymmetric methods for their synthesis are currently available.[3]

An important current trend in synthesis is the development of transition-metal-free methods, particularly those in which small organic molecules are used as catalysts (organocatalysis).[4] As well as avoiding the use of costly and potentially toxic metal catalysts, these transformations often have the practical benefits that they do not require rigorously anhydrous or anaerobic reaction conditions.

In a continuation of our studies on transition-metal-free reagents for heteroatom transfer, we have developed the novel oxaziridine **2**, which acts as an efficient source of electrophilic nitrogen bearing a synthetically useful protecting group (Boc).[5] Recently, we used this reagent to extend the scope of the amination/[2,3] sigmatropic rearrangement of allylic sulfides,[6] and showed for the first time (two examples) that this transformation can be effected efficiently on α,β-unsaturated esters (Scheme 1).[7] Essentially complete 1,3-chirality transfer was observed in the rearrangement process. These findings were important since earlier attempts to effect amination/rearrangement on these esters had afforded products with low yield and *ee* values.[6g] However, a major limitation with this approach is that in all cases from our studies and of others,[6g,8] the chiral α-branched sulfides required for the rearrangement have been prepared from a precursor from the chiral pool, (*S*)-methyl lactate **3**. As well as making one enantiomer of the amino acid product far more accessible than the other, this has the severe limitation in that the terminal alkene substituent is inevitably methyl.



Scheme 1. Chirality transfer in the allylic sulfimide rearrangement.[7] Boc = *tert*-butoxycarbonyl, *n*Hex = *n*-hexyl.

An alternative approach for the synthesis of the allylic sulfide precursors would greatly expand the scope of the process. Recently, Jorgensen and co-workers reported a highly enantioselective α sulfenylation of aldehydes using the proline-derived organocatalyst **7** and the triazole sulfide **8a** as the electrophile.[9] The sensitive α-sulfenyl aldehyde **9** was reduced in situ to give the alcohol **10** with excellent enantioselectivity (Scheme 1). We reasoned that, if the intermediate aldehyde could be trapped by an in situ olefination,[10] this chemistry could potentially offer a one-pot, organocatalytic route to a range of chiral α-branched allylic sulfides **11** (Scheme 2). Herein we report that this concept can indeed be realized, which led to a concise transition-metal-free catalytic enantioselective synthesis of Boc-protected vinyl glycines.

Exploratory experiments revealed that allylic sulfides **11** with $R^2 = Bn$, as would be generated using **8a**, reacted with oxaziridine **2** to give mixtures of sulfoxidation and sulfimidation. In line with our earlier studies,[7] we were pleased to find that chemoselective nitrogen transfer could be restored when the less sterically demanding S–*n*Hex reagent **8b** was employed. Use of **8b** in the α-sulfenylation/in situ reduction was found to proceed with comparable enantiomeric excess to the reported values with **8a**. We therefore carried out an in situ olefination of the aldehyde **9** ($R^2 = n$Hex). After screening several sets of conditions (see the Supporting

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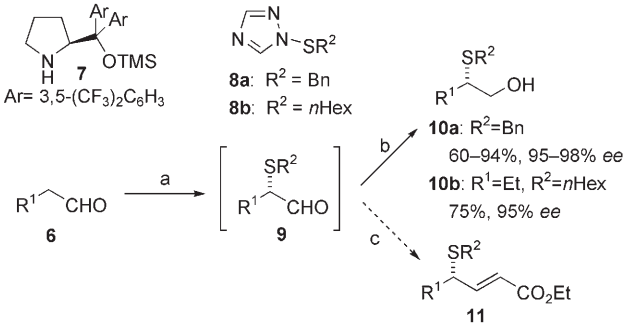
Supporting information (including experimental procedures and compound characterization) for this article is available on the WWW under http://www.angewandte.org or from the author.

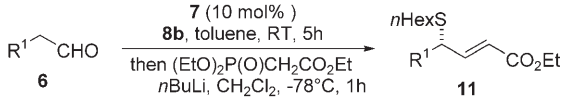


Scheme 2. Asymmetric α sulfenylation/reduction of aldehydes. a) 10 mol% **7**, **8**, toluene, RT, 3 h; b) $NaBH_4$, MeOH; c) olefination. Bn = benzyl, TMS = trimethylsilyl.

Information), we were able to effect the formation of **11** with high *E*/*Z* selectivity and minimal racemization; use of a low reaction temperature, CH_2Cl_2 as the solvent, and a phosphonate anion, generated with *n*BuLi, proved optimal.

With a successful one-pot synthesis of an enantiomerically enriched allylic sulfide accomplished, we explored the scope of the reaction by employing several commercially available aldehydes (Table 1). The reaction was completely tolerant of

Table 1: One-pot asymmetric α sulfenylation/olefination of aldehydes **6a–g**.



Entry	R^1	*E*/*Z*[a]	(*E*)-**11** Yield [%][b]	*ee* [%][c]
1	Me (**a**)	>95:5	52	93
2	Et (**b**)	>95:5	79	93
3	*i*Pr (**c**)	>95:5	70	91
4	*t*Bu (**d**)	>95:5	61	89
5	Bn (**e**)	>95:5	64	88
6	Allyl (**f**)	>95:5	73	90
7	$(CH_2)_2$OTBS (**g**)[d]	>95:5	62	91

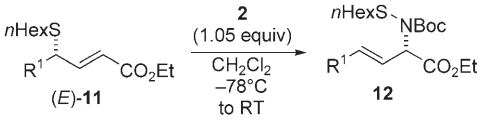
[a] Determined by inspection of the ^{1}H NMR spectrum of the crude reaction mixture. [b] Yield of the isolated *E* alkene after flash chromatography. [c] Determined by HPLC on a chiral stationary phase. [d] TBS = *tert*-butyldimethylsilyl.

the size of the β substituent on the aldehyde (Table 1, entries 1–4), with even a *tert*-butyl group giving excellent results (entry 4). Several other functional groups (such as benzyl, allyl, and OTBS) also participated effectively with consistently high asymmetric induction being obtained (Table 1, entries 5–7), which demonstrates the robustness of the method.

With a versatile route to a range of enantioenriched *E* allylic sulfides **11** in hand, we next tested them in the amination/rearrangement reaction. Pleasingly, all examples reacted with **2** to give **12** with essentially complete chirality transfer and only the *E* product was observed (Table 2).

The stereochemical outcome of these rearrangements may be rationalized by considering the transition-state (TS)

Table 2: [2,3] Sigmatropic rearrangement of enantioenriched *E* allylic sulfides.



Entry	R^1	*ee* of (*E*)-**11** [%][a]	Yield of **12** [%][b]	*ee* of **12** [%][a]
1	Me	93	79	93
2	Et	93	79	93
3	*i*Pr	91	81	91
4	Bn	88	85	87
5	Allyl	90	87	89
6	$(CH_2)_2$OTBS	91	81	91

[a] Determined by HPLC on a chiral stationary phase [b] Yield of isolated product after flash chromatography.

structures shown in Figure 1.[11] If we assume a concerted suprafacial [2,3] sigmatropic rearrangement, the reaction can occur via **TS1**, which would lead to (*E*)-**12**, or by **TS2**, which

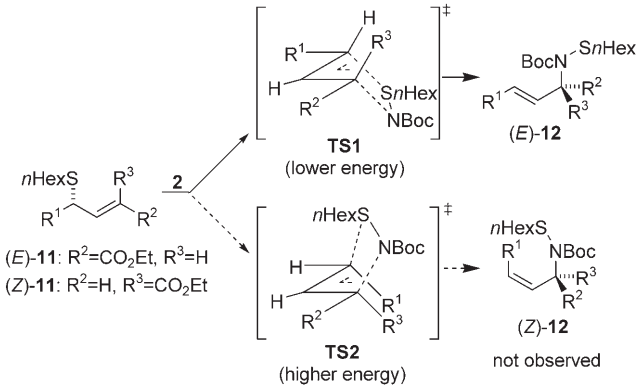


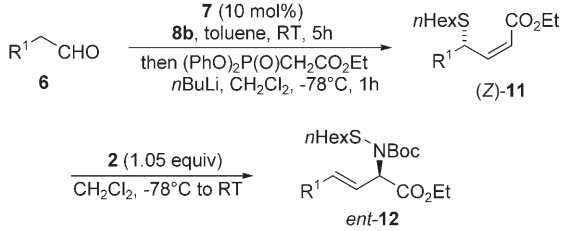
Figure 1. Rationale for the stereochemical control observed in the [2,3] sigmatropic rearrangement of allylic sulfimides.

would lead to the product with Z-alkene geometry and the opposite configuration at the newly formed stereocenter. The essentially exclusive formation of the *E* product in the rearrangement of (*E*)-**11** suggests that **TS1** is significantly lower in energy than **TS2**, probably because of a destabilizing allylic interaction between R^1 and R^3 in **TS2**. It is also worth noting that the sulfimidation process produces a stereogenic center at the sulfur atom. Generally, reaction of branched (non-allylic) sulfides with **2** proceeds with low levels of stereocontrol at the sulfur atom.[12] If we assume this is also the case for the sulfimide intermediates here, the high yields and *E* selectivity in the final product suggest that the sulfimide configuration does not exert a significant influence on the stereochemical outcome of the rearrangement.

An efficient entry into products with the opposite absolute configuration is a valuable requirement for any enantioselective synthetic method. Rather than employing the opposite enantiomer of catalyst **7**, which would be derived from more expensive D-proline, the TS analysis in Figure 1

suggested a more attractive alternative. With **TS1** expected to again be preferred to avoid R^1–R^3 interactions, the substrate (*Z*)-**11** should afford the opposite configuration at the newly generated stereocenter in (*E*)-**12** (R^2 and R^3 interchanged). To explore this approach we required in situ olefination conditions that would afford the Z allylic sulfide selectively. Again, following optimization to prevent racemization, we were able to accomplish this by using the diphenylphosphonate reagent reported by Ando et al.[13] with a good level of *Z*/*E* selectivity (ca. 5:1; Table 3). As predicted, the *Z* isomer cleanly underwent amination/rearrangement with **2**, to give the opposite enantiomeric series, again with very high *E* selectivity and essentially complete chirality transfer.

Table 3: Asymmetric synthesis and [2,3] sigmatropic rearrangement of enantioenriched *Z* allylic sulfides.

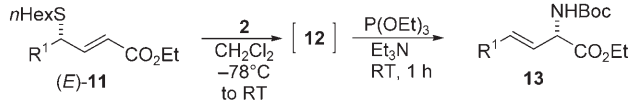


Entry	R^1	*E*/*Z*[a]	Yield of (*Z*)-**11** [%][b]	*ee* of (*Z*)-**11** [%][c]	Yield of *ent*-**12** [%][d]	*ee* of *ent*-**12** [%][c]
1	Et	1:5	64	93	82	93
2	Allyl	1:5	73	92	82	92

[a] Determined by inspection of the ^{1}H NMR spectrum of the crude reaction mixture [b] Isolated yield of (*Z*)-alkene after flash chromatography [c] Determined by HPLC on a chiral stationary phase [d] Isolated yield after flash chromatography.

For most synthetic applications, it is probable that cleavage of the N–S bond will be required; the presence of the alkene, allylic C–N bond and acidic α proton render this transformation potentially problematic. We were able to accomplish the desired desulfurization rapidly and cleanly on stirring with triethylphosphite and triethylamine at room temperature (Table 4). These mild conditions also allowed us to develop a one-pot amination/rearrangement/N–S bond cleavage sequence, which offered improved practicality and overall yields (Table 4). Importantly, migration of the alkene into conjugation was not observed, and HPLC analysis on a chiral stationary phase in one example confirmed that racemization had not taken place (Table 4, entry 4).

Table 4: Asymmetric synthesis of *N*-Boc-protected *E* vinyl glycine derivatives.



Entry	R^1	Yield of **13** from **12** [%][a]	Yield of **13** from **11** [%][b]
1	Me	88	85
2	*i*Pr	94	78
3	Bn	94	81
4	Allyl	92	74[c]
5	$(CH_2)_2$OTBS	93	84

[a] Yield of isolated **13** using a purified sample of **12** as starting material. [b] Yield of isolated product from a one-pot reaction. [c] HPLC on a chiral stationary phase indicated no racemization.

In conclusion, we have developed a novel concise transition-metal-free catalytic enantioselective synthesis of vinyl glycines, biologically important targets that are difficult to access by using current synthetic technology. The procedure combines an organocatalytic α sulfenylation of an aldehyde with a stereospecific [2,3] sigmatropic rearrangement. Either enantiomeric product series can be obtained from the same chiral catalyst through the choice of *E*- or *Z*-selective olefination. In principle, this strategy will also be applicable to the enantioselective synthesis of a wide range of other important nitrogen-containing building blocks by varying the olefination partner. Efforts to exploit this concept further along these lines are currently underway.

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