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Organocatalytic asymmetric remote aziridination of 2,4-dienals†

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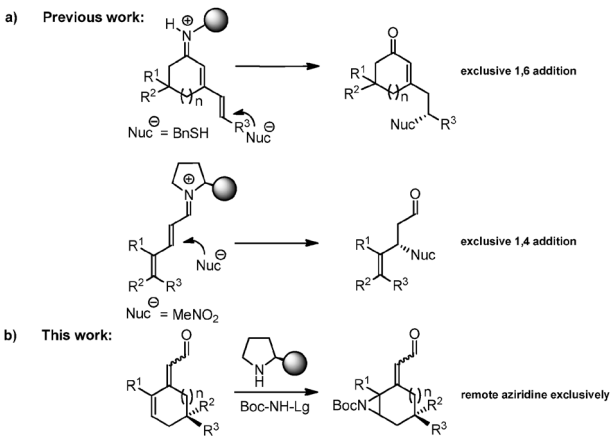
Highly regio- and stereoselective remote aziridination of 2,4-dienals has been developed, based on a vinylogous iminium-ion–dienamine catalytic cascade reaction. Transformations of the aziridine products into enantio-enriched motifs are also demonstrated. Furthermore, the reaction concept is extended to include enantioselective 1,6-addition of thiols.

The ability to perform selective transformations is an important task in organic synthesis. In this regard, chiral amines have been reported as excellent catalysts for stereoselective transformations of carbonyl compounds.[1] Recently, dienamine[2] and trienamine[3] catalysis reactions have emerged as new HOMO-raising strategies for the enantioselective functionalization of enals and 2,4-dienals by the principle of vinylogy.[4] Since the dienamine and trienamine intermediates contain several reactive olefinic sites, the control of the regioselectivity of reactions involving such intermediates remains a challenge.[5]

Although the HOMO-raising strategy has been applied to extended vinylogous systems (di- and trienamine intermediates),[2,3] the LUMO-lowering strategy of vinylogous iminium-ion activation has not achieved the same progress.[6,7] Enantioselective reactions which are based on vinylogous iminium-ion activation remain relatively unexplored. For cyclic 2,4-dienones, Melchiorre *et al.* have demonstrated the 1,6-addition of thiols,[8] while Hayashi *et al.* showed that exclusive β-functionalization *via* 1,4-addition was observed when the same concept was applied to acyclic 2,4-dienals (Scheme 1a).[9]

We envisioned that a novel regio- and stereoselective remote functionalization could be achieved by the employment of 2,4-dienals, which could potentially participate in tandem vinylogous iminium-ion–dienamine catalysis, resulting in functionalization of the remote γ- and δ-positions.[10] This reaction concept thus merges the LUMO-lowering strategy of the vinylogous iminium-ion and the HOMO-raising strategy of the dienamine intermediate in one combined process for the remote enantioselective aziridination of 2,4-dienals (Scheme 1b).



Scheme 1 (a) Previous 1,6- and 1,4-additions to cyclic 2,4-dienones and acyclic 2,4-dienals applying primary and secondary aminocatalyst, respectively. (b) Proposed novel aminocatalytic remote aziridination of 2,4-dienals.

Aziridines are important scaffolds due to their presence in biologically active compounds[11] and as valuable building blocks in organic synthesis.[12] Their role in synthesis is highlighted by their application as chiral synthons, which can selectively *e.g.* be converted into amine derivatives. As a consequence of their importance, development of methods for the asymmetric aziridination of olefins represents an ongoing challenge.[13] In recent years, several organocatalytic procedures for the enantioselective aziridination on enals and enones have emerged.[14] Aziridine aldehydes are very useful reagents, since they exhibit interesting reactivities due to their amphoteric nature.[15] Furthermore, organocatalytically formed aziridines have found application in one-pot reactions providing facile entries into a broad range of useful compounds.[16]

In the following we present the first remote enantioselective aziridination of 2,4-dienals (Scheme 1b). Our initial studies revealed that remote regio- and stereoselective aziridination of 2,4-dienals was possible. However, a key feature of the reaction was the employment of γ-substituted cyclic dienals. A series of experiments were performed to develop the optimal reaction conditions (see ESI†). We found that the employment of 0.1 mmol of a mixture of (*E*)- and (*Z*)-2-(2-methylcyclohex-2-en-1-ylidene)acetaldehyde **1a**, 2 eq.

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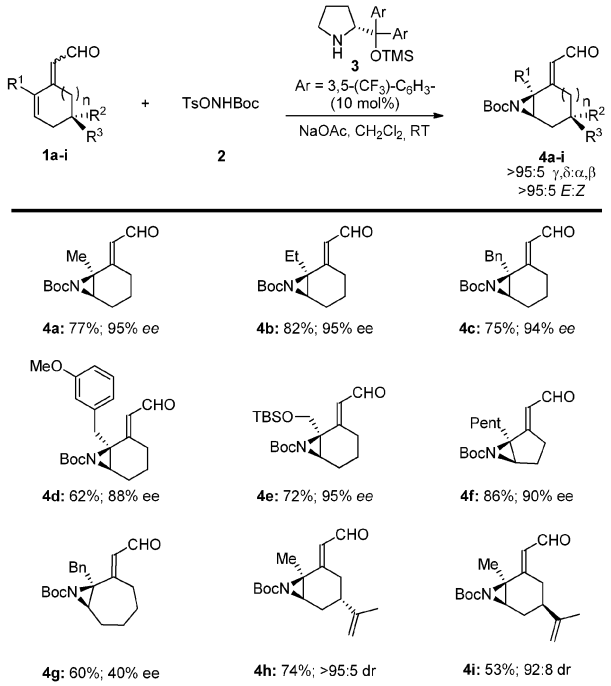


Reactions were performed on a 0.1 mmol scale. See Supporting Information for further details. Isolated yields by FC. For compounds **4h** and **4i** yields refer to the diastereomerically pure products. Enantiomeric excess was determined by chiral stationary phase UPC[2].

Scheme 2 Scope of the organocatalyzed asymmetric remote aziridination of 2,4-dienals **1**.

of TsONHBoc **2**, 10 mol% of the TMS protected prolinol catalyst **3** and 4 eq. of NaOAc in CH_2Cl_2 (0.3 mL) provided aziridine product **4a** in 77% yield and 95% ee.

These results encouraged us to investigate the generality of the organocatalytic asymmetric remote aziridination reaction as presented in Scheme 2. The reaction proceeded with high yields and an excellent enantioselectivity of 95% ee for cyclic 2,4-dienals containing simple aliphatic substituents at the γ-position (**4a,b**). Aromatic functionalities in the side chain were also tolerated (**4c,d**) as well as heteroatoms (**4e**) which all provided similar results. The ring-system is not restricted to 6-membered rings, as the 5-membered cyclic 2,4-dienals performed equally well in the reaction, although a slightly lower enantioselectivity was observed (**4f**), however, a decrease to 40% ee was observed for the 7-membered aziridine aldehyde **4g**. Next, we decided to test the ability of the catalyst to override the steric bias from substituents on the cyclic moiety. 2,4-dienals **1h** and **1i** were obtained from enantiopure *R*- and *S*-carvones, respectively. In both cases, the catalyst demonstrated a high degree of facial selectivity for the remote aziridination, yielding the epimers **4h** and **4i**. Compound **4h** is formed exclusively as one epimer, whereas **4i** is formed in a 92 : 8 ratio. As a result, there is a matched (**4h**) and a mis-matched (**4i**) situation, respectively, between the catalyst and the chiral substituent. It must be noted that the employment of unsubstituted or acyclic analogues of substrate **1** provided no aziridination products.

The absolute configuration of the optically active aziridines was determined by detailed NOESY NMR analysis of products **4h** and **4i** (see ESI†). Compound **4h** showed no correlation of the hydrogen signal at the already known stereocenter to the newly formed chiral hydrogen indicating an *anti*-relationship between these atoms. In contrast, a correlation of the corresponding hydrogens was observed for compound **4i** indicating a *syn*-relationship. This reveals that the 1,6-addition occurs by a nucleophilic attack of **2** at the *Re*-face of a vinylogous iminium-ion intermediate. The absolute stereochemistry of the remaining products was assigned by analogy.

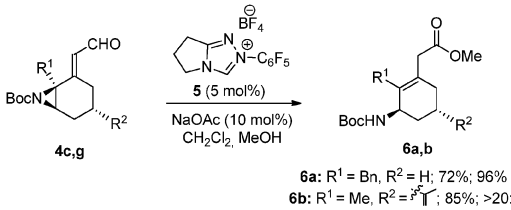
The products of the remote aziridination reaction were utilized in transformations which apply other organocatalytic principles. *N*-Heterocyclic carbenes (NHC) are organocatalysts, which are typically employed in transformations initiated by inducing umpolung reactivity of aldehydes.[17] We were pleased to find that by adding the NHC-catalyst precursor **5**, along with an appropriate base, the optically active aziridine products **4c,g** underwent an allylic aziridine opening to form *N*-protected allylic δ-amino esters **6a,b** (Scheme 3).[18] The transformation was observed to proceed in high yields with no deterioration of the stereocenters established in the preceding reaction.

To further illustrate an advantage of the remotely substituted aziridine, the intramolecular reactivity of the *N*-Boc-protecting group was utilized to form a remote oxazolidinone moiety.[19] Oxazolidinones represent a source of protected vicinal amino alcohols, hence the transformation of *N*-Boc-protected aziridines into oxazolidinones can be viewed as a formal *syn*-amino hydroxylation.[20] Furthermore, oxazolidinones are also interesting in their own right, since optically active oxazolidinones have been found to exhibit *e.g.* biological activity.[21] The *N*-Boc-aziridines can undergo Lewis-acid catalyzed transformation into oxazolidinones.[22] We have found that reduction of aziridine aldehyde **4** followed by treatment with HCl in dioxane furnished oxazolidinone products **7a,b** (Scheme 4). These reactions proceeded in good overall yield and the enantiomeric excess was maintained with a single regioisomer being observed.

Upon further exploration of the concept of vinylogous iminium-ion activation, an expansion of the scope was targeted by the evaluation of other nucleophiles. To our delight, thiols were found to add regio- and enantioselectively in a 1,6-fashion to 2,4-dienals **1** to yield the non-conjugated adducts **9** (Scheme 5).[23,24]

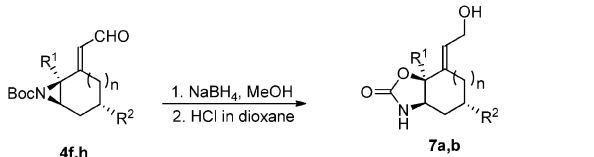
Benzyl mercaptan **8** adds to 2,4-dienals **1a–c** in decent yields and good stereoselectivities up to 87% ee.

In conclusion, we have presented a novel tandem vinylogous iminium-ion–dienamine cascade reaction and demonstrated its potential by the development of a regio- and enantioselective protocol for remote aziridination of cyclic 2,4-dienals. The aziridinations



Reactions were performed on a 0.1 mmol scale. See Supporting Information for further details. Isolated yields by FC. Enantiomeric excess determined by chiral stationary phase UPC[2].

Scheme 3 NHC-catalyzed allylic aziridine opening to form the optically active allylic δ-amino esters **6**.

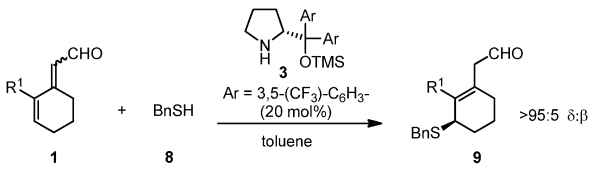


4f,h 7a,b

7a: R^1 = Pentyl, R^2 = H, n = 0; 75%; 90% ee
7b: R^1 = Me, R^2 =  , n = 1; 61%; >20:1 dr

Reactions were performed on a 0.1 mmol scale. See Supporting Information for further details. Isolated yields by FC. Enantiomeric excess determined by chiral stationary phase UPC[2].

Scheme 4 Formation of optically active oxazolidinone products **7**.



1 8 9

E:*Z* mixture

9a: R^1 = Me; 41%; 86% ee
9b: R^1 = Et; 58%; 87% ee
9c: R^1 = Bn; 58%; 80% ee

Scheme 5 Enantioselective 1,6-addition of thiols **8** to 2,4-dienals **1**.

proceed in good to high yields and with excellent regio- and stereoselectivity up to 95% ee. The usefulness of the aziridine aldehyde products was illustrated by their transformation into optically active allylic δ-amino esters and oxazolidinones. Furthermore, we have also demonstrated that the same reaction conditions can also be used for the enantioselective 1,6-addition of thiols to cyclic 2,4-dienals.

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