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Asymmetric Formal *trans*-Dihydroxylation and *trans*-Aminohydroxylation of α,β-Unsaturated Aldehydes via an Organocatalytic Reaction Cascade

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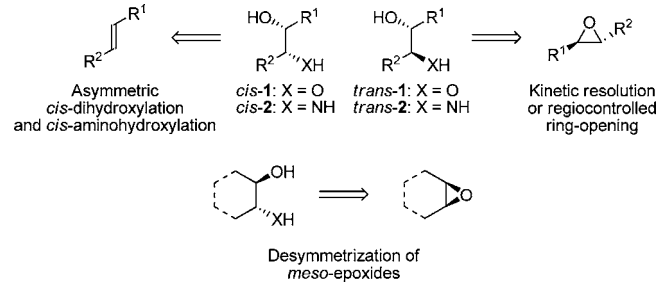
Abstract: This study demonstrates the first formal asymmetric *trans*-dihydroxylation and *trans*-aminohydroxylation of α,β-unsaturated aldehydes in an organocatalytic multibond forming one-pot reaction cascade. This efficient process converts α,β-unsaturated aldehydes into optically active *trans*-2,3-dihydroxyaldehydes and *trans*-3-amino-2-hydroxyaldehydes with the aldehyde moiety protected as an acetal. The elaborated one-pot protocol proceeds via the formation of 2,3-epoxy and 2,3-aziridine aldehyde intermediates, which subsequently participate in a novel NaOMe-initiated rearrangement reaction leading to the formation of acetal protected *trans*-2,3-dihydroxyaldehydes and *trans*-3-amino-2-hydroxyaldehydes in a highly stereoselective manner. Advantageously, this multibond forming reaction cascade can be performed one-pot, thereby minimizing the number of manual operations and purification procedures required to obtain the products. Additionally, for the purpose of *trans*-aminohydroxylation of the α,β-unsaturated aldehydes, a new enantioselective aziridination protocol using 4-methyl-*N*-(tosyloxy)benzenesulfonamide as the nitrogen source has been developed. The mechanism of the formal *trans*-dihydroxylation and *trans*-aminohydroxylation of α,β-unsaturated aldehydes is elucidated by various investigations including isotopic labeling studies. Finally, the products obtained were applied in the synthesis of numerous important molecules.

Introduction

Catalytic enantioselective oxidations of prochiral olefins play a pivotal role in modern organic chemistry, enabling access to various highly valuable synthetic intermediates.[1] Especially, optically active diols and aminoalcohols represent privileged structural motifs that can be found in numerous natural products and other molecules relevant for the life science industry such as sugars, carbasugars, aminosugars, iminosugars, sphingolipids, and sphingoids.[2] Among useful protocols for their formation,[3] the Sharpless *cis*-dihydroxylation[4] and *cis*-aminohydroxylation[5] occupy a prominent position offering direct access to optically active 1,2-diols (*cis*-**1**) and β-aminoalcohols (*cis*-**2**) (Scheme 1, left). The generality and broad substrate scope of these transition-metal-catalyzed transformations make them particularly well-suited for large-scale applications.[4c] However, despite their remarkable usefulness, the toxicity and expense of osmium compounds might be an issue of concern. Additionally, in the case of the aminohydroxylation, achieving high levels of regiocontrol still constitutes a challenging problem.[5,6] The catalytic enantioselective methods for the preparation of *trans*-1,2-diols (*trans*-**1**) and *trans*-β-aminoalcohols (*trans*-**2**) mainly rely on two methodologies: kinetic resolution of racemic epoxides[7] or regioselective ring-opening of chiral, enantioenriched epoxides[8] (Scheme 1, right). The ability of a chiral catalyst to control desymmetrization of *meso*-epoxides has also been demonstrated[9] (Scheme 1, bottom).

Scheme 1. Traditional Approaches to 1,2-Diols **1** and β-Aminoalcohols **2**



Optically active 2,3-dihydroxyaldehydes or 3-amino-2-hydroxyaldehydes serve as versatile chiral building blocks, commonly used in asymmetric total syntheses.[10] However, direct protocols allowing access to these privileged structural motifs are very limited. To the best of our knowledge, no oxidative approach based on asymmetric dihydroxylation or aminohydroxylation of α,β-unsaturated aldehydes has ever been described. Only an indirect synthesis, involving the enantioselective Sharpless *cis*-dihydroxylation of cyclic acetal-protected α,β-unsaturated aldehydes followed by deprotection to the 2,3-dihydroxyaldehydes, has been described (Scheme 2, eq 1).[11] While this protocol gives *cis*-configured products, the asym-

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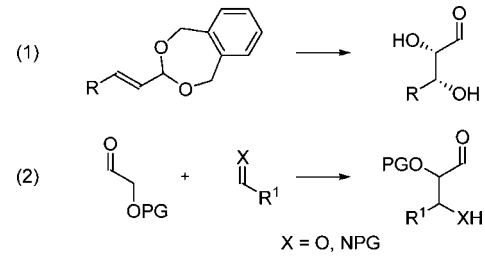
metric syntheses of *trans*-2,3-dihydroxyaldehydes or *trans*-3-amino-2-hydroxyaldehydes via an epoxide or aziridine ring-opening have never been accomplished. Instead, conventional routes to these compounds are based on carbon−carbon bond forming processes rather than oxidative protocols. It has been demonstrated that direct aminocatalytic aldol or Mannich reactions, employing *O*-protected hydroxyacetaldehyde derivatives as donors with aldehydes[12] or imines[13] as acceptors, constitute a facile entry to these compounds (Scheme 2, eq 2). However, problems related to low efficiency, limited substrate

Scheme 2. Classical Approaches to Optically Active 2,3-Dihydroxyaldehydes and 3-Amino-2-hydroxyaldehydes



scope, or moderate diastereoselectivity are encountered. Furthermore, in the case of the Mannich reaction *cis*-diastereoselectivity is generally observed.[13] Therefore, given the remarkable usefulness of these compounds and the lack of general methodologies for their preparation, the development of novel approaches, enabling efficient and stereoselective access to *trans*-2,3-dihydroxyaldehydes and *trans*-3-amino-2-hydroxyaldehydes, is highly desirable. In this context, performing asymmetric *trans*-dihydroxylation and *trans*-aminohydroxylation of easily available α,β-unsaturated aldehydes seems particularly attractive and challenging.

α,β-Unsaturated aldehydes are commonly used reagents in asymmetric synthesis. However, due to their versatile reactivity, mild reaction conditions or the introduction of protecting groups is often demanded to obtain chemoselective transformations. In the past few years, these restrictions have been partially circumvented by the use of asymmetric aminocatalysis.[14] The high condition tolerance of these protocols has also enabled the development of multistep one-pot or domino reactions allowing access to molecules of high complexity in a single manual operation. Within this field, it has been demonstrated that α,β-unsaturated aldehydes may be easily and efficiently converted into various molecules of interest in a highly stereoselective manner by aminocatalytic protocols and using consecutive

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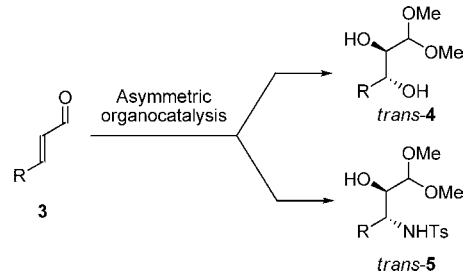
Scheme 3. Formal *trans*-Dihydroxylation and *trans*-Aminohydroxylation of α,β-Unsaturated Aldehydes **3**



reactions at e.g. the carbonyl functionality in combination with the organocatalytically introduced functionality.[15] Encouraged by these results, we envisioned that α,β-unsaturated aldehydes **3** can participate in a multibond forming reaction cascade leading to the formation of *trans*-2,3-dihydroxyaldehydes **4** or *trans*-3-amino-2-hydroxyaldehydes **5** in a highly stereoselective fashion and including an *in situ* protection of the aldehyde moiety as the corresponding dimethyl acetal (Scheme 3).

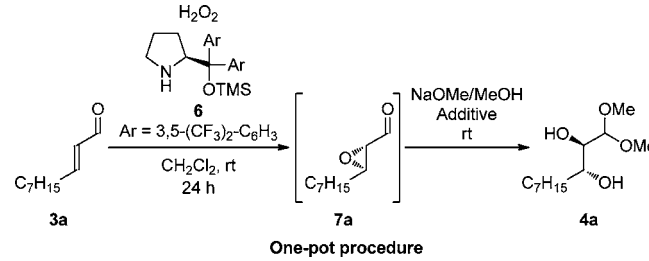
Herein, we report our results on a highly enantio- and diastereoselective, organocatalytic one-pot formal *trans*-dihydroxylation and *trans*-aminohydroxylation of α,β-unsaturated aldehydes **3**. The developed approach benefits from operational simplicity, high stereoselectivity, and low catalyst loading. Furthermore, the *trans*-aminohydroxylation is fully regioselective.

Results and Discussion

Formal *trans*-Dihydroxylation of α,β-Unsaturated Aldehydes. At the outset of our studies, we envisioned that a formal *trans*-dihydroxylation of α,β-unsaturated aldehydes **3** could proceed through the intermediacy of 2,3-epoxy aldehydes **7** (Table 1). It was anticipated that addition of NaOMe to the carbonyl group in **7** should initiate a novel rearrangement reaction of the epoxy aldehydes,[16] leading to the formation of 2,3-dihydroxyaldehydes with the aldehyde functionality protected as the corresponding dimethyl acetal **4** (for details see mechanistic considerations below). Furthermore, the optical purity obtained in the organocatalytic step was expected to be preserved during the reaction cascade. Additionally, the possibility of performing both of the reaction sequences in a one-pot fashion without the necessity to isolate or purify the intermediating 2,3-epoxy aldehydes seemed attractive.

We began our investigations with the goal of finding the suitable conditions for the desired novel epoxidation/NaOMe-initiated rearrangement (ENaMIR) cascade. In the initial studies,

Table 1. Optimization Studies on the Formal Enantioselective Organocatalytic *trans*-Dihydroxylation of *trans*-2-Decenal **3a**[a]



entry	additive	catalyst loading [mol %]	NaOMe initiated rearrangement time [h]	amount of 0.5 M NaOMe [equiv]	yield **4a** (conv) [%][b]	ee [%][c]	dr[d]
1	-	10	24	3	43 (>95)	98	>20:1
2	Na_2SO_4	10	24	3	40 (>95)	98	>20:1
3	MS	10	24	3	47 (>95)	98	>20:1
4	MS	5	24	3	43 (>95)	98	>20:1
5	MS	2.5	24	3	43 (>95)	98	>20:1
6	-	2.5	24	3	45 (>95)	98	>20:1
7[e]	-	2.5	24	3	nd (21)	nd	nd
8[f]	-	2.5	24	3	43 (>95)	98	>20:1
9[g]	-	2.5	24	3	decomposition	nd	nd
10	-	2.5	6	3	nd (53)	nd	nd
11	-	2.5	24	4	46 (>95)	98	>20:1
12	-	2.5	48	4	46 (>95)	98	>20:1
13	-	2.5	24	6	57 (>95)	98	>20:1
14	-	2.5	24	8	63 (>95)	98	>20:1
15	-	2.5	24	10	65 (>95)	98	>20:1
16	-	2.5	24	12	63 (>95)	98	>20:1

[a] Unless otherwise stated, all reactions were performed at 0.2 mmol scale at rt. [b] Overall yield for two steps. [c] Determined by chiral stationary phase GC (see the Supporting Information). [d] Determined by ^{1}H NMR of the crude reaction mixture. [e] NaOMe-initiated rearrangement performed at 0 °C. [f] NaOMe-initiated rearrangement performed at 30 °C. [g] NaOMe-initiated rearrangement performed with 4.3 M NaOMe.

we decided to follow the established procedure for the organocatalytic asymmetric epoxidation of α,β-unsaturated aldehydes **3**,[17a] applying 2-[bis(3,5-bis(trifluoromethyl)phenyl)(trimethylsilyloxy)methyl]pyrrolidine **6**[18] as the catalytic chiral inductor in the multibond forming reaction cascade and hydrogen peroxide as the oxidant (Table 1). *trans*-2-Decenal **3a** was chosen as the model substrate, and to our delight the ENaMIR cascade, applying 3 equiv of NaOMe (0.5 M) in the second step, proceeded smoothly at room temperature (rt), affording the corresponding diol **4a**, albeit in a moderate yield (Table 1, entry 1). Gratifyingly, despite the basic reaction conditions required for the rearrangement to take place, neither racemization nor epimerization of the target product occurred, and diol

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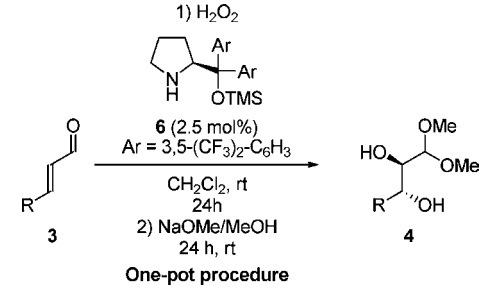
4a was obtained in excellent enantiomeric and diastereomeric excess. Performing the reaction in the presence of various drying agents during the rearrangement step showed no significant improvement of the yield (compare entries 2, 3). Further screening revealed that the catalyst loading in the epoxidation step may easily be decreased to 2.5 mol % without influencing the yield or stereoselectivity of the overall reaction cascade (compare entries 3−6). However, with 1 mol % of the catalyst very low conversion was observed after 24 h. Temperature screening indicated that rt is optimal for the NaOMe-initiated rearrangement (compare entries 6−8). At 0 °C only partial conversion of epoxide **7a** to the diol **4a** was observed after 24 h (entry 7) and elevation of the temperature to 30 °C did not improve the yield (entry 8). A higher concentration of NaOMe (4.3 M) led to decomposition of either the starting material or the product, and the formation of a complex reaction mixture was observed (entry 9). Likewise, modifying the rearrangement time was not beneficial for the yield of the reaction cascade. After 6 h, the reaction was not complete (entry 10), and prolonging the time of rearrangement to 48 h did not affect the outcome (compare entries 11,12). Finally, it was found that the amount of NaOMe is a highly important factor influencing the rearrangement efficacy (compare entries 6, 11, 13−16). Increasing the amount of NaOMe up to 10 equiv with respect to the starting enal **3a** allowed us to improve the yield to 65% (entry 16). Importantly, the optical purity of the product **4a** was fully preserved under these reaction conditions.

With the optimized conditions in hand, we investigated the scope of this methodology. Various α,β-unsaturated aldehydes **3** were subjected to the ENaMIR cascade, and the results are summarized in Table 2. In general, aliphatic as well as aromatic α,β-unsaturated aldehydes **3a**−**k** could be successfully applied in this new one-pot cascade protocol, thereby indicating its high versatility (entries 1−11). In the case of cinnamaldehyde **3i** and its derivatives **3j**,**k** with different substitution patterns on the aromatic ring, the target products **4i**−**k** were formed in lower yield and with slightly reduced stereoselectivity (entries 9−11) when compared to the application of aliphatic α,β-unsaturated aldehydes **3a**−**h**. However, in the case of electron-rich aromatic enals, rapid decomposition of the initially formed 2,3-epoxy aldehydes competed with the desired rearrangement resulting in the formation of complex reaction mixtures. Additionally, no epoxidation occurred in the case of heteroaromatic enals. Further studies on the scope of the ENaMIR cascade revealed that enals **3l**,**o** with additional functionalities in the side chain were well tolerated (entries 12−15). In particular, the use of (*E*)-4-(benzyloxy)but-2-enal **3n** providing direct access to protected D-erythrose **4n** in good yield and excellent stereoselectivity is noteworthy (entry 14). Importantly, this reaction was performed on a 2 mmol scale maintaining its high efficiency and stereoselectivity, thereby indicating the synthetic utility of our approach.

Formal *trans*-Aminohydroxylation of α,β-Unsaturated Aldehydes. Encouraged by the development of the formal enantioselective organocatalytic *trans*-dihydroxylation of α,β-unsaturated aldehydes **3**, we decided to explore the formal *trans*-aminohydroxylation of **3**. We anticipated that replacement of 2,3-epoxy aldehyde intermediates with the corresponding 2,3-aziridine aldehydes would afford *trans*-3-amino-2-hydroxyaldehydes after the NaOMe-initiated rearrangement. There are two procedures for the organocatalytic aziridination of α,β-unsaturated aldehydes described in the literature, enabling the synthesis

Table 2. Formal Enantioselective Organocatalytic *trans*-Dihydroxylation of α,β-Unsaturated Aldehydes **3**[a]



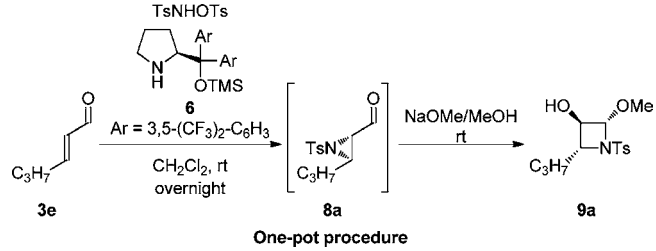
entry	R	yield [%][b]	ee [%][c]	dr[d]
1	Heptyl (**3a**)	**4a** - 65	98	>20:1
2	Hex (**3b**)	**4b** - 63	97	>20:1
3	Pen (**3c**)	**4c** - 61	97	>20:1
4	Bu (**3d**)	**4d** - 60	98	>20:1
5	Pr (**3e**)	**4e** - 60	98	>20:1
6	*i*Pr (**3f**)	**4f** - 46	98	>20:1
7	Et (**3g**)	**4g** - 63	97	>20:1
8[e]	Me (**3h**)	**4h** - 54	96	16:1
9[f]	C_6H_5 (**3i**)	**4i** - 37	96[g]	10:1
10[f]	2-NO_2-C_6H_4 (**3j**)	**4j** - 49	96[h]	>20:1
11[f]	4-Cl-C_6H_4 (**3k**)	**4k** - 40	90[i]	10:1
12	*Z*-Hex-3-enyl (**3l**)	**4l** - 56	95	>20:1
13	*E*-Hex-3-enyl (**3m**)	**4m** - 73	96	>20:1
14[j]	CH_2OBn (**3n**)	**4n** - 70	99	>20:1
15	CH_2CH_2Ph (**3o**)	**4o** - 77	98	>20:1

[a] Unless otherwise stated, all reactions were performed with **3** (0.2 mmol), H_2O_2 (35 wt % in H_2O) (0.26 mmol), and **6** (0.005 mmol) in 0.4 mL of CH_2Cl_2 for 24 h followed by 0.5 M NaOMe (2 mmol). [b] Overall yield for two steps. [c] Determined by chiral stationary phase GC (see the Supporting Information). [d] Determined by ^{1}H NMR of the crude reaction mixture. [e] Epoxidation performed with 10 mol % of the catalyst **6**. [f] Epoxidation performed with 10 mol % of the catalyst **6** for 5 h. [g] Determined by chiral stationary phase GC after derivatization into the corresponding acetonide (see the Supporting Information). [h] Determined by chiral stationary phase HPLC. [i] Determined by chiral stationary phase HPLC after derivatization into the corresponding acetonide (see the Supporting Information). [j] Reaction performed at 2 mmol scale.

of *N*-carbamate protected (Boc or Cbz) 2,3-aziridine aldehydes.[19a,b] However, at the outset of these studies we expected that the presence of a tosyl substituent as a nitrogen atom protecting group should facilitate the NaOMe-initiated rearrangement due to its high electron-withdrawing ability. For this reason, both protocols seemed unsuitable for our investigations. Therefore, we decided to undertake the studies on asymmetric aziridination of α,β-unsaturated aldehydes **3** using TsNHOTs as the aziridinating reagent. CH_2Cl_2 was chosen as the solvent of choice for the aziridination of **3**, since it has been shown to be very efficient in the earlier studies performed by Hamada et al.[19b] To our delight, 2-[bis(3,5-bis(trifluoromethyl)phenyl)(trimethylsilyloxy)methyl]pyrrolidine **6** efficiently catalyzed the aziridination of *trans*-2-hexenal **3e** to give the optically active *N*-tosyl-2,3-aziridine aldehyde **8a**. The reaction was performed in the presence of NaOAc as a basic additive to facilitate the cyclization of the originally formed aza-Michael adduct. Product **8a** was formed as a single diastereoisomer and could be easily isolated in high yield and characterized. However, we were

(19) (a) Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Córdova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 778. (b) Arai, H.; Sugaya, N.; Sasaki, N.; Makino, K.; Lectard, S.; Hamada, Y. *Tetrahedron Lett.* **2009**, *50*, 3329. For a recent review of organocatalytic asymmetric aza-Michael reactions, see: (c) Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058.

Table 3. Optimization Studies on the Formal Enantioselective Organocatalytic *trans*-Aminohydroxylation of *trans*-2-Hexenal **3e**[a]



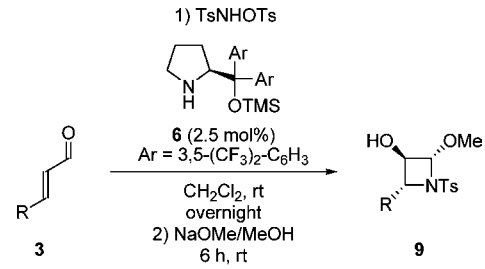
entry	catalyst loading [mol %]	aziridination temp	rearrangement time [h]	amount of 0.5 M NaOMe [equiv]	yield **9a** (conv.) [%][b]	ee [%][c]	dr[d]
1	10	rt	24	1.2	65 (>95)	98	>20:1
2	10	0 °C	24	1.2	67 (>95)	98	>20:1
3	10	40 °C	24	1.2	decomposition	-	-
4	5	rt	24	1.2	76 (>95)	98	>20:1
5	2.5	rt	24	1.2	75 (>95)	98	>20:1
6	2.5	rt	6	1.2	75 (>95)	98	>20:1
7	2.5	rt	6	1.8	82 (>95)	98	>20:1
8	2.5	rt	6	2.4	75 (>95)	98	>20:1
9	2.5	rt	6	3.0	67 (>95)	98	>20:1

[a] All reactions were performed at 0.1 mmol scale. [b] Overall yield for two steps. [c] Determined by chiral stationary phase HPLC (see the Supporting Information). [d] Determined by ^{1}H NMR of the crude reaction mixture.

unable to determine the enantiomeric excess of the aziridination product **8a** at this stage. The attempted derivatization of **8a** into the corresponding alcohol via $NaBH_4$ reduction was not chemoselective. Therefore, we decided to subject the enantiomerically enriched **8a** directly to the NaOMe-initiated rearrangement. To our surprise, the isolated product was not the expected *trans*-*N*-(2-hydroxy-1,1-dimethoxyhexan-3-yl)-4-methylbenzenesulfonamide **5a**. Careful analysis of the NMR data revealed the actual structure to be the corresponding cyclic *N*,*O*-acetal **9a** (Table 3, entry 1). Its formation can be explained by an intramolecular addition of the sulfonamide group to the intermediate oxocarbenium ion (see mechanistic details below), presumably occurring due to the enhanced nucleophilicity of *N*-tosyl amines. Notably, the cyclization proceeded with complete diastereoselectivity, as the corresponding product **9a** was formed as a single diastereoisomer. Additionally, we were pleased to find that the NaOMe-initiated rearrangement reaction was fully compatible with the developed asymmetric organocatalytic aziridination protocol as **9a** was obtained with excellent enantioselectivity. In this manner the enantioselectivity of the aziridination step was also indirectly determined, indicating its high stereoselectivity and efficiency. Further screening of the aziridination conditions revealed that lowering of the temperature to 0 °C did not provide a significant improvement (entry 2). At 40 °C fast decomposition of the aziridinating reagent was observed (entry 3). Gratifyingly, the catalyst loading could be decreased to 2.5 mol % without influence on the reaction cascade outcome (compare entries 1, 4, 5). Having established the optimal conditions for the aziridination of enal **3e** with TsNHOTs as the nitrogen source, we decided to further optimize the NaOMe-initiated rearrangement step (entries 6−9). First, it was found that the NaOMe-initiated rearrangement with 2,3-aziridine aldehyde **8a** was very fast, and the reaction was completed within 6 h (entry 6). Second, the amount of base proved to be of importance again (compare entries 6−9), and the best results were obtained when 1.8 equiv of NaOMe were applied (entry 7). It should be noted that when the amount of NaOMe was lowered below 1 equiv, no rearrangement occurred.

As shown in Table 4, the newly developed aziridination/NaOMe-initiated rearrangement reaction (ANaMIR) cascade provides a general entry to 3-substituted-2-(methoxy)azetidin-3-ols **9**, thereby also confirming the high efficiency of the aziridination protocol. A noteworthy feature of the ANaMIR cascade is its high stereoselectivity, and in all the cases, excellent enantioselectivities were observed. Furthermore, the final products with three new stereogenic centers were formed as single diastereoisomers in good yields (70−82%). The ANaMIR cascade is also very general, as additional functional groups in the alkyl chains can be present (Table 4, entries 6−9). The use of the opposite enantiomer of the catalyst (*R*)-**6** at the aziridination step afforded the enantiomeric product *ent*-**9g** as a single

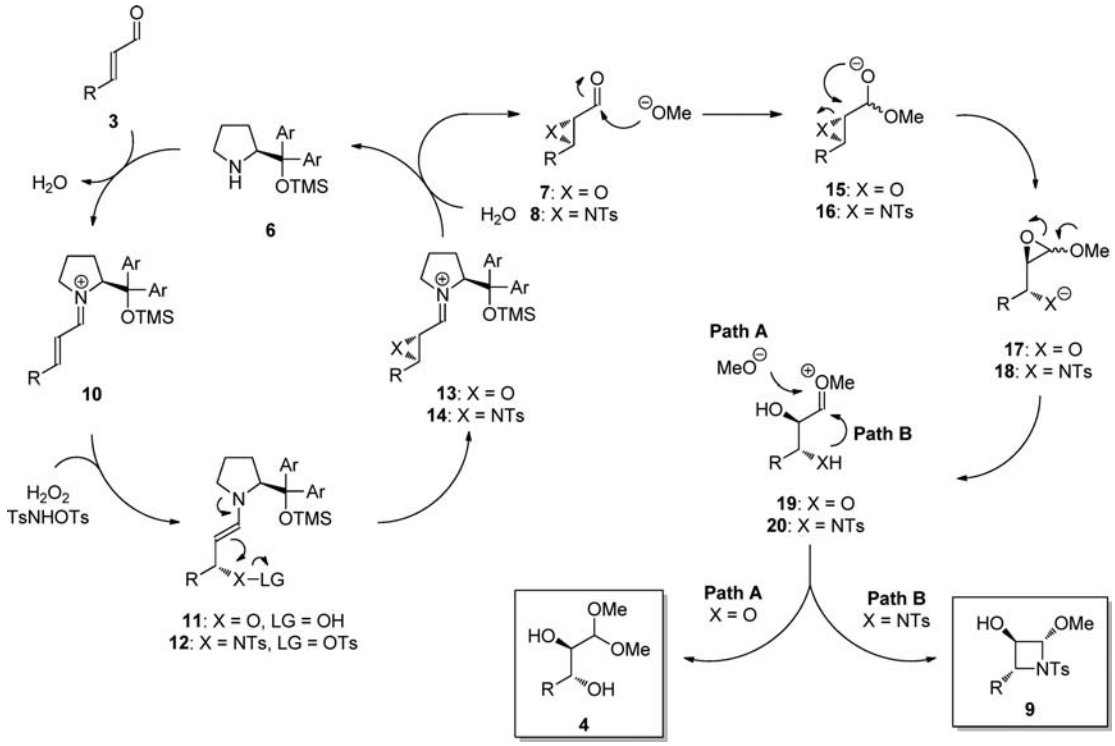
Table 4. Formal Enantioselective Organocatalytic *trans*-Aminohydroxylation of α,β-Unsaturated Aldehydes **3**[a]



entry	R	yield [%][b]	ee [%][c]	dr[d]
1	Pr (**3e**)	**9a** - 82	98	>20:1
2	Heptyl (**3a**)	**9b** - 77	96	>20:1
3	Bu (**3d**)	**9c** - 87	96	>20:1
4	*i*Pr (**3f**)	**9d** - 77	96	>20:1
5	Me (**3h**)	**9e** - 79	98	>20:1
6	*E*-Hex-3-enyl (**3l**)	**9f** - 76	98	>20:1
7	CH_2OBn (**3n**)	**9g** - 70	97	>20:1
8[e,f]	CH_2OBn (**3n**)	*ent*-**9g** - 73	96	>20:1
9	CH_2CH_2Ph (**3o**)	**9h** - 80	98	>20:1

[a] Unless otherwise stated, all reactions were performed with TsNHOTs (0.2 mmol), **3** (0.24 mmol), and **6** (0.005 mmol) in 1 mL of CH_2Cl_2 overnight followed by 0.5 M NaOMe (0.36 mmol). [b] Overall yield for two steps. [c] Determined by chiral stationary phase HPLC (see the Supporting Information). [d] Determined by ^{1}H NMR of the crude reaction mixture. [e] Aziridination performed with the enantiomeric catalyst (*R*)-**6**. [f] Reaction performed at 0.5 mmol scale.

Scheme 4. Mechanistic Proposal for the Formal Enantioselective Organocatalytic *trans*-Dihydroxylation and *trans*-Aminohydroxylation of α,β-Unsaturated Aldehydes



diastereoisomer with 96% ee and comparable yield. Unfortunately, our aziridination protocol turned out to be incompatible with aromatic enals. In these cases, decomposition of the aziridinating reagent was faster than the aziridination reaction. Consequently, only low conversion of the aromatic enals **3** was observed at this step. All attempts to improve these results, either by changing the base applied or by modifying the relative ratio of the aromatic enal and TsNHOTs, failed.

Mechanistic Considerations. The mechanistic proposal for the formal enantioselective organocatalytic *trans*-dihydroxylation and *trans*-aminohydroxylation of α,β-unsaturated aldehydes **3** is outlined in Scheme 4. Initially, the activation of **3** is achieved via formation of iminium ion **10** in the reversible reaction with chiral amine catalyst **6**. Conjugate addition of hydrogen peroxide or TsNHOTs followed by cyclization via intramolecular nucleophilic displacement leads to iminium ions **13** or **14**, respectively. At this stage the stereochemistry of the two new stereogenic centers is established under control of the catalyst **6**. Subsequent hydrolysis of **13** or **14** liberates the catalyst **6** and affords optically active 2,3-epoxy aldehyde **7** or 2,3-aziridine aldehyde **8**. With the organocatalytic cycles being accomplished, aldehydes **7** and **8** are subjected to the NaOMe-initiated rearrangement. Addition of methoxide to the carbonyl group of **7** or **8** leads to the formation of the alkoxides **15** or **16**, which undergo a novel Payne[20] or aza-Payne-like[21] rearrangement to give internal epoxides **17** or **18**.[22] Presumably, this reaction proceeds via an intramolecular S_N2 mechanism, and thereby full inversion of the configuration at the C-2 stereogenic center is observed. Oxocarbenium ions **19** or **20** are formed in the next step of the cascade. At this stage, depending on the nucleophilicity of the β-X substituent two different reaction pathways may occur. For X = O (Scheme 4, Path A) the intermolecular 1,2-addition of methoxide to the oxocarbenium ion **19** is favored leading to the formation of *trans*-2,3-dihydroxyaldehyde dimethyl acetal **4**. Alternatively, when X = NTs (Scheme 4, Path B) an intramolecular cyclization occurs, furnishing 3-substituted-2-(methoxy)azetidin-3-ol **9** in a highly stereoselective manner.

The absolute stereochemistry of the diol **4c** was assigned as (2*R*,3*R*) by the chemical correlation with alcohol **22**[23] (Scheme 5, eq 1). The transformation of **4c** into **22** was accomplished in a reaction sequence including protection of the diol **4c** as

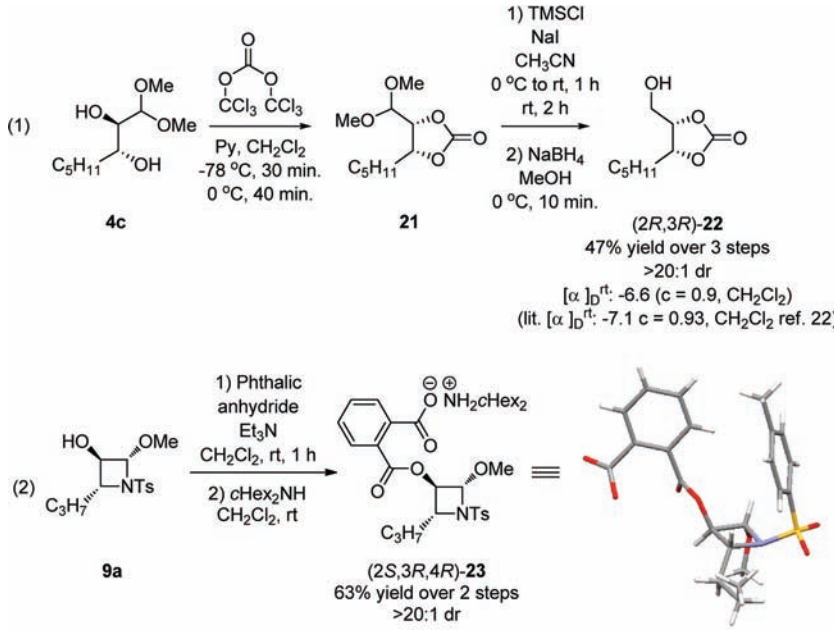
(20) (a) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819. For applications of the Payne rearrangement in 1,2-diol synthesis, see: (b) Wrobel, J. E.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 3761. (c) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687. (d) Schomaker, J. M.; Pulgam, V. R.; Borhan, B. *J. Am. Chem. Soc.* **2004**, *126*, 13600.

(21) For a review on aza-Payne rearrangement, see: (a) Ibuka, T. *Chem. Soc. Rev.* **1998**, *27*, 145. For some selected examples, see: (b) Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Otaka, A.; Tamamura, H.; Fujii, N.; Mimura, N.; Miwa, Y.; Taga, T.; Chounan, Y.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 2044. (c) Bilke, J. L.; Dzuganova, M.; Fröhlich, R.; Würthwein, E.-U. *Org. Lett.* **2005**, *7*, 3267. (d) Schomaker, J. M.; Geiser, A. R.; Huang, R.; Borhan, B. *J. Am. Chem. Soc.* **2007**, *129*, 3794. For application of the aza-Payne rearrangement in the synthesis of β-aminoalcohols, see: (e) Ibuka, T.; Nakai, K.; Habashita, H.; Fujii, N.; Garrido, F.; Mann, A.; Chounan, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1993**, *34*, 7421. (f) Nakai, K.; Ibuka, T.; Otaka, A.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *Tetrahedron Lett.* **1995**, *36*, 6247. (g) Ibuka, T.; Nakai, K.; Akaji, M.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *Tetrahedron* **1996**, *52*, 11739. (h) Schomaker, J. M.; Bhattacharjee, S.; Yan, J.; Borhan, B. *J. Am. Chem. Soc.* **2007**, *129*, 1996.

(22) A referee suggested an alternative reaction mechanism assuming the participation of another 2,3-epoxy aldehyde **7** molecule. This involves the addition of the alkoxide **15** to the aldehyde carbonyl in **7** followed by 5-exo-tet epoxide opening by the oxygen atom originating from the second 2,3-epoxy aldehyde **7** and subsequent oxocarbenium ion formation. However, since the experiments are performed at very low concentrations of the 2,3-epoxy aldehydes **7** in the rearrangement step (ca. 0.045 M) the initially proposed reaction mechanism proceeding via Payne rearrangement seems more likely.

(23) Le Merrer, Y.; Gravier-Pelletier, C.; Dumas, J.; Depezay, J. C. *Tetrahedron Lett.* **1990**, *31*, 1003.

Scheme 5. Assignment of the Absolute Configuration of **4c** and **9a**

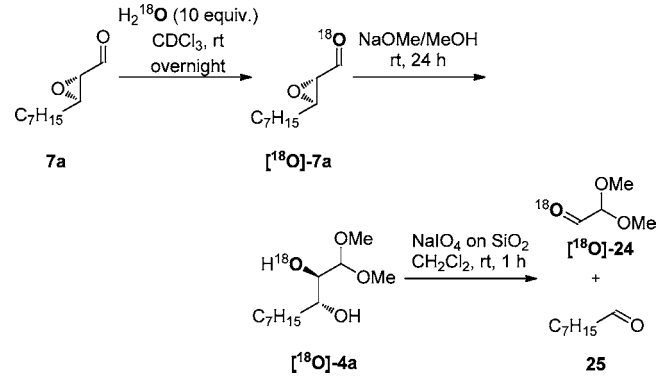


carbonate **21**, followed by TMSI-mediated deprotection of the dimethyl acetal and $NaBH_4$ reduction of the aldehyde functionality. The absolute configuration of the azetidine **9a** was unambiguously established as (2*S*,3*R*,4*R*) by X-ray analysis.[24] However, to obtain a crystal suitable for this analysis, compound **9a** had to be converted into dicyclohexylammonium phthalate **23** obtained by reacting **9a** with phthalic anhydride followed by addition of dicyclohexylamine (Scheme 5, eq 2). The absolute configuration of all remaining diols **4a**,**b**,**d**−**o** and azetidin-3-ols **9b**−**h** was assigned by analogy. In both of the cases the observed stereochemistry of the products **4a**−**o** and **9a**−**h** is in accordance with the mechanistic proposal presented above.

To shed more light on the mechanism of the newly developed rearrangement we decided to perform labeling experiments with $H_2{}^{18}O$. We anticipated that if the above proposed mechanism (Scheme 4) is operative, the migration of ^{18}O from C_1 (sp2) to C_2 (sp3) should be observed (Scheme 6). As it has been demonstrated by Vederas,[24] the isotopic substitution with ^{18}O causes a change in the ^{13}C NMR chemical shift of the carbon atom attached to the labeled oxygen atom. Therefore, this migration should be possible to follow on the basis of this ^{18}O-isotope effect by measuring ^{13}C NMR spectra of the labeled compounds before and after the rearrangement. However, since the magnitude of the ^{18}O-isotope effect is small, we aimed at using partially ^{18}O-enriched compounds for our studies. In this manner it should be possible to observe the signals from both compounds in the same spectra, thereby enabling a direct measurement of the magnitude of the ^{18}O-isotope effect.

To incorporate the ^{18}O-isotope, 2,3-epoxy aldehyde **7a** was stirred in $CDCl_3$ in the presence of a 10-fold excess of ^{18}O-enriched water (97% ^{18}O, Sigma-Aldrich) for 24 h (Scheme 6). To our delight, partial incorporation of the ^{18}O-isotope into 2,3-epoxy aldehyde **7a** was observed under these conditions, as confirmed by ^{13}C NMR spectroscopy (Figure 1). The measured values of the ^{18}O-isotope effect for C_1 (sp2) are given in Table

Scheme 6. ^{18}O-Incorporation Experiment



5. The product obtained was then directly subjected to NaOMe-initiated rearrangement conditions. After isolation by FC, a ^{13}C NMR spectrum of the partially ^{18}O-isotope enriched product **[^{18}O]-4a** was recorded. This measurement unequivocally indicated the presence of an ^{18}O-isotope at C_2 (sp3) in **[^{18}O]-4a**. The chemical shifts of particular carbon and hydrogen atoms were unambiguously assigned by 2D heterocorrelation spectroscopy. It is noteworthy that, in both of the cases, an upfield shift of the carbon atom signal (of the C directly attached to ^{18}O label) was observed (Figure 1), and the values of the ^{18}O-

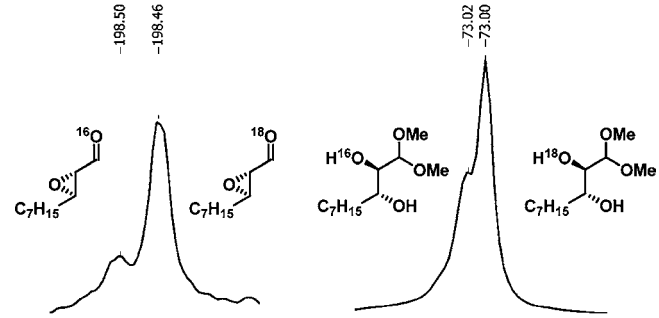


Figure 1. ^{13}C NMR spectra of **7a**, **[^{18}O]-7a**, **4a**, and **[^{18}O]-4a**.

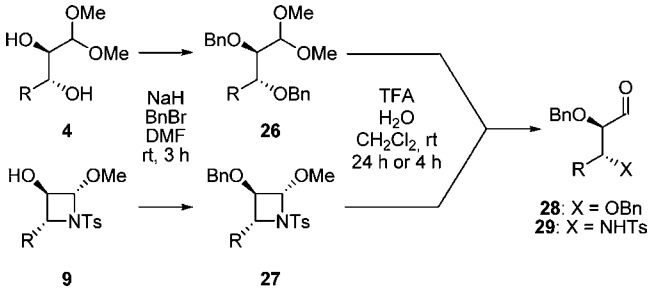
(24) CCDC 772544 contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44(1223)336-033.

Table 5. Comparison of C_1 and C_2 ^{13}C NMR Chemical Shifts (δ) for **7a**, **[^{18}O]-7a**, **4a**, and **[^{18}O]-4a**

compound	δ [ppm][a]	signal shift in [Hz]
7a (C_1)	198.50	3.8
[^{18}O]-7a (C_1)	198.46	
4a (C_2)	73.02	1.4
[^{18}O]-4a (C_2)	73.00	

[a] Data taken from the ^{13}C NMR spectra of the partially ^{18}O-isotope enriched products.

Table 6. Benzylation−Deprotection Strategy for the Synthesis of Aldehydes **28** and **29**[a]



entry	R	X	yield [%][b]	dr[c]
1	Heptyl (**4a**)	OBn	**28a** - 66	>20:1
2[d]	CH_2OBn (**4n**)	OBn	**28b** - 71	>20:1
3	Pr (**9a**)	NHTs	**29a** - 67	>20:1
4	*i*Pr (**9d**)	NHTs	**29b** - 88	>20:1
5[e]	CH_2OBn (**9g**)	NHTs	**29c** - 81	>20:1

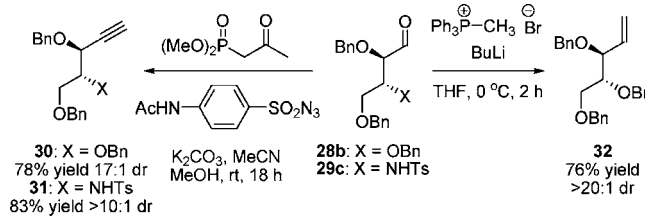
[a] Unless otherwise stated, all reactions were performed with **4** (0.1 mmol) or **9** (0.1 mmol), NaH (0.3 or 0.15 mmol), and BnBr (0.3 or 0.15 mmol) in 1 mL of DMF for 3 h. After aqueous workup crude product **26** or **27** was dissolved in DCM (0.6) and 1:1 mixture of TFA/H_2O (0.6 mL) and left for 24 or 4 h. [b] Overall yield for two steps. [c] Determined by ^1H NMR of the crude reaction mixture. [d] Reaction performed at 3 mmol scale. [e] Reaction performed at 0.5 mmol scale.

isotope effect for C_1 (sp2) and C_2 (sp3) are in accordance with those previously reported by Vederas.[25]

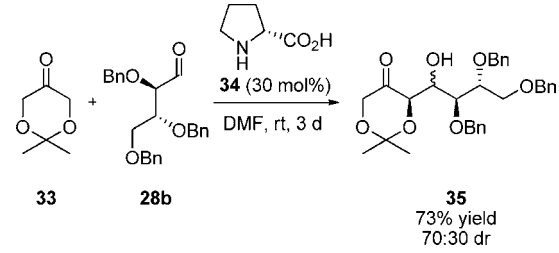
To deliver further evidence for the position of the ^{18}O-isotope in the molecule after the NaOMe-initiated rearrangement, we decided to perform oxidative cleavage of the diol **[^{18}O]-4a** and follow the reaction by GC MS. In general, mass spectroscopy is an analytical technique frequently used for determination of the position of the ^{18}O-isotope in organic compounds in standard ^{18}O-labeling experiments. The corresponding M^+ at 106 (**[^{18}O]-24**) and 128 (**25**) were identified. This result combined with the ^{13}C NMR measurements of the ^{18}O-isotope effect clearly indicate that C_2 (sp3) is attached to the ^{18}O label in **[^{18}O]-4a**, thereby confirming the mechanism of the developed ENaMIR and ANaMIR cascades.

Product Elaborations. Having established a general and efficient strategy for the formal enantioselective organocatalytic *trans*-dihydroxylation and *trans*-aminohydroxylation of α,β-unsaturated aldehydes **3**, we decided to present the usefulness of the products obtained in various stereoselective transformations. Initially, we investigated the possibility to deprotect the aldehyde moiety in compounds **4** and **9**. Preliminary experiments revealed that the hydroxyl groups in **4** and **9** had to be protected prior to the acetal cleavage. The benzyl group was the protection group of choice, since it can be removed under mild hydrogenation conditions. Benzylation of **4** and **9** was performed according to a standard literature procedure (Table 6).[26] Subsequently, the crude products **26** and **27** were subjected to acetal hydrolysis using TFA to afford aldehydes **28** and **29** in good overall yields. Importantly, no epimerization of the starting acetals **4** and **9** occurred in this reaction sequence, and **28** and **29** were formed as single diastereoisomers. It is noteworthy that the synthesis of (2*R*,3*R*)-2,3,4-tris(benzyloxy)butanal **28b** was earlier disclosed in the literature based on a chiral pool approach in five steps with 42% overall yield starting from D-glucose.[27]

Scheme 7. Homologation of Aldehydes **28b** and **29c**



Scheme 8. Transformation of **28b** into Protected Ketoheptose **35**



Further studies were focused on the synthetic utility of the deprotected aldehydes **28b** and **29c**. In the first attempts, their homologation was performed (Scheme 7). Ohira modification[28] of the Seyferth−Gilbert homologation of **28b** and **29c** proved to be particularly well-suited for the construction of propargylic polyols as demonstrated in the synthesis of **30** and **31**. This class of compounds is commonly used as intermediates in total syntheses of natural products.[29] Treatment of aldehyde **28b** with the Ohira−Bestmann reagent prepared *in situ* from commercially available dimethyl 2-oxopropylphosphonate and 4-acetamidobenzenosulfonyl azide afforded **30** with good yield. In a similar manner, compound **31** was synthesized by homologation of **29c**. Despite basic reaction conditions and the high acidity of the α-carbonyl proton only slight epimerization of the starting aldehydes **28b** and **29c** took place. Alternatively, the reaction of **28b** with a Wittig reagent enabled the introduction of a terminal double bond into the target molecule yielding **32** without epimerization.

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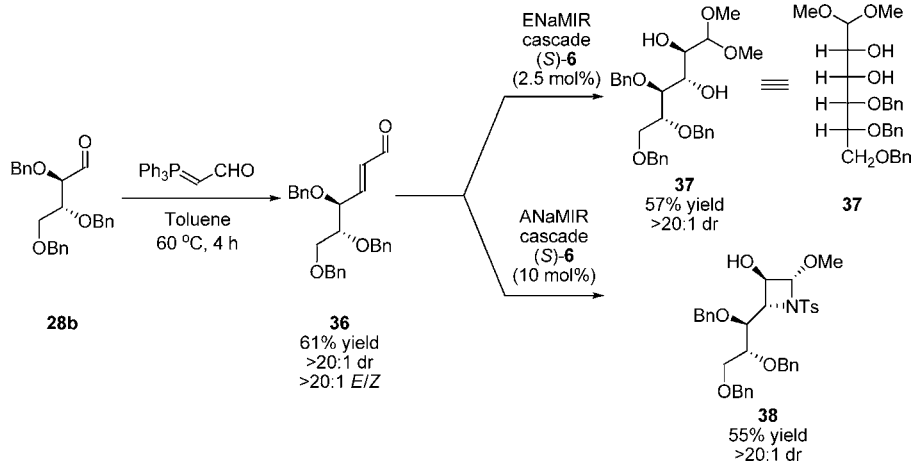
(26) Kratzer, B.; Mayer, T. G.; Schmidt, R. R. *Eur. J. Org. Chem.* **1998**, 291.

(27) Storz, T.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 2380.

(28) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521. (c) Roth, G. J.; Liepold, B.; Müller, S.; Bestmann, H. J. *Synthesis* **2004**, 59.

(29) For selected examples regarding application of propargylic diols in total syntheses, see: (a) Nicolaou, K. C.; Tang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3449. (b) Scheidt, K. A.; Bannister, T. D.; Tasaka, A.; Wendt, M. D.; Savall, B. M.; Fegley, G. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 6981. (c) Alami, M.; Crousse, B.; Linstrumelle, G.; Mambu, L.; Larchevéque, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2949. (d) Ren, F.; Hogan, P. C.; Andersen, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381. For selected examples regarding application of propargylic triols in total syntheses, see: (e) Hamajima, A.; Isobe, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2941. (f) Pandey, G.; Dumbre, S. G.; Khan, M. I.; Shabab, M. *J. Org. Chem.* **2006**, *71*, 8481. (g) Kagawa, N.; Ihara, M.; Toyota, M. *Org. Lett.* **2006**, *8*, 875.

Scheme 9. Synthesis of Protected D-Allose **37** and D-3-Aminoallose Derivative **38**



Studies on organocatalytic asymmetric synthesis of carbohydrates and their derivatives using aldehyde **28b** as a chiral building block were undertaken in the next part of the project. The usefulness of the aminocatalytic intermolecular aldol reactions for the construction of carbohydrate skeletons has been recognized by different research groups.[10,30] We found that the D-proline-catalyzed aldol reaction between 2,2-dimethyl-1,3-dioxan-5-one **33** and aldehyde **28b** proceeded efficiently at rt affording a facile entry to the protected ketoheptose **35** in good yield (Scheme 8). Unfortunately, the diastereoselectivity of the reaction was only moderate. Importantly, the reaction using L-proline proceeded with lower diastereoselectivity clearly indicating a mismatched interaction between the chiral substrate and the chiral catalyst.

Bearing in mind the low diastereoselectivity attained in the aldol reaction between **28b** and **33**, we envisioned an alternative approach to carbohydrate derivatives relying on a second ENaMIR or ANaMIR cascade using compound **36** as the starting material (Scheme 9). The synthesis of **36** was accomplished by means of the Wittig reaction of **28b** with (triphenylphosphoranylidene)acetaldehyde. To our delight, epoxidation of **36** with 2.5 mol % of (*S*)-**6** as the catalyst proceeded smoothly and was completed within 24 h. The NaOMe-initiated rearrangement afforded the protected D-allose **37** in good overall yield. We were pleased to observe that the second ENaMIR cascade proceeded with complete diastereoselectivity, as the final product **37** was formed as a single diastereoisomer. The ANaMIR cascade was performed using 10 mol % of (*S*)-**6** as the catalyst. The product **38** bearing five continuous stereogenic centers was obtained in 55% yield, again as a single diastereoisomer. It is notable that all the stereogenic centers in target compounds **37** and **38** have been stereoselectively introduced by using combinations of ENaMIR and ANaMIR cascades, demonstrating the high synthetic usefulness of the established methodologies. It should also be pointed out that clear mismatched interactions between the chiral substrate and the chiral catalyst in ENaMIR or ANaMIR cascades with **36** were observed with (*R*)-**6** as the catalyst. In these cases, the reactions were significantly suppressed and low diastereoselectivities were obtained.

(30) Enders, D.; Narine, A. A. *J. Org. Chem.* **2008**, *73*, 7857, and references cited therein.

Conclusion

In summary, we have developed a novel organocatalytic strategy for asymmetric formal *trans*-dihydroxylation and *trans*-aminohydroxylation of α,β-unsaturated aldehydes. The presented methodology proceeds with excellent enantio- and diastereoselectivity for a broad range of substrates. Additionally, in the case of aminohydroxylation full regioselectivity is observed. To understand the mechanism of the developed approach, labeling experiments with $H_2{}^{18}O$ were performed, and a mechanistic proposal for the ENaMIR and ANaMIR cascades was presented. Furthermore, we have demonstrated the applicability of the optically active compounds in a number of important transformations. Finally, we have demonstrated that double ENaMIR−ENaMIR and ENaMIR−ANaMIR cascades offer efficient entries to carbohydrates enabling the introduction of up to five continuous stereogenic centers with complete enantio- and diastereoselectivity.

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Supporting Information Available: Complete experimental procedures and characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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