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An Organocatalytic Approach to 2-Hydroxyalkyl- and 2-Aminoalkyl Furanes

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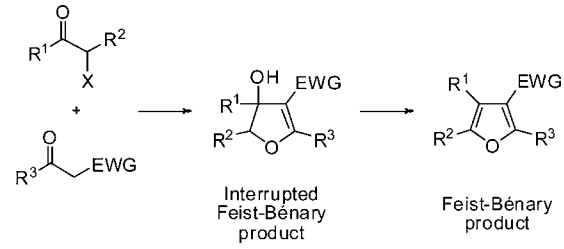
Abstract: The first enantioselective methodology for the synthesis of electron-poor 2-hydroxyalkyl- and 2-aminoalkyl furanes is demonstrated in this study. It utilizes a highly stereoselective organocatalytic one-pot reaction cascade: epoxidation or aziridination of α,β-unsaturated aldehydes followed by Feist−Bénary reaction of various 1,3-dicarbonyl compounds to give the target furanes. This efficient multibond forming reaction cascade benefits from low catalyst loadings and readily available starting materials. Furthermore, the possibility to interrupt the reaction sequence at the stage of the corresponding optically active 2-hydroxyalkyl- and 2-aminoalkyl 2,3-dihydrofuranes with three stereogenic centers is also presented. Finally, models which account for the formation of the optically active 2,3-dihydrofuranes are proposed.

Introduction

The high synthetic usefulness and importance as well as their wide distribution in nature, give furanes and 2,3-dihydrofuranes a privileged role in organic chemistry.[1,2] As a consequence, furanes and 2,3-dihydrofuranes have received considerable attention over the years, and many methods for their preparation have been developed and described in the literature.[1] Among them the Feist−Bénary reaction occupies a prominent position (Scheme 1).[3] This base-promoted reaction between 1,3-dicarbonyl compounds and α-halogenated carbonyls offers direct access to polysubstituted furanes with an electron-withdrawing substituent at the C-3 carbon atom. Recently, the possibility to stop this reaction at the hydroxy dihydrofurane intermediate was demonstrated and this so-called interrupted Feist−Bénary reaction has emerged as a useful method for the preparation of dihydrofurane derivatives.[4] Noteworthily, an enantioselective catalytic variant of this reaction leading to the formation of enantioenriched hydroxy dihydrofuranes with adjacent tertiary and quaternary stereogenic centers was developed in 2005 by Calter et al.[5]

Scheme 1. Synthesis of Furanes and 2,3-Dihydrofuranes by the Feist−Bénary and Interrupted Feist−Bénary Reactions



Optically active 2-hydroxyalkyl- and 2-aminoalkyl furanes constitute a particularly attractive class of furane derivatives that has found widespread applications in organic synthesis due to their ability to participate in various important reactions such as oxidative ring-openings and Achmatowicz or Diels−Alder reactions, enabling the introduction of diverse functional groups at the same time.[6] For this reason they have been also extensively used in asymmetric total syntheses.[6] The classical approaches to optically active 2-hydroxyalkyl- and 2-aminoalkyl

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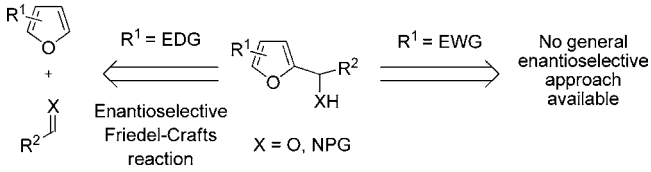
Scheme 2. Classical Friedel−Crafts Approach for the Synthesis of 2-Hydroxyalkyl- and 2-Aminoalkyl Furanes



furanes rely mainly on the asymmetric Friedel−Crafts reaction of substituted furane derivatives with aldehydes or imines (Scheme 2).[7] These powerful C−C bond-forming protocols have been well studied over the years, becoming the method of choice for the preparation of electron-rich 2-hydroxyalkyl- and 2-aminoalkyl furanes with high levels of stereoinduction. On the contrary, methodologies for the stereoselective preparation of nonracemic electron-poor furane and 2,3-dihydrofurane derivatives are rare and in all cases based on the employment of enantiomerically pure starting materials,[6h,8,9] or a kinetic resolution of racemic starting materials.[10,11] Moreover, most of these methods give access to polyhydroxylated furanes, and no general enantioselective approach leading to the formation of electron-poor 2-hydroxyalkyl- and 2-aminoalkyl furanes exists in the literature (Scheme 2). The preparation of electron-poor 2-aminoalkyl furanes appears especially challenging, since the only methods for their synthesis disclosed in the literature require the use of optically active furfuryl alcohols as the starting materials.[9] For these reasons the development of new and more efficient synthetic strategies leading to the formation of these important groups of compounds is of ongoing interest and seems particularly valuable and challenging.

To meet the growing demand for the development of highly effective, atom and step-economical processes that can meet the requirements of green and sustainable chemistry, enantioselective organocatalytic domino and one-pot strategies have emerged as a new and exciting field of research.[12−14] These useful and practical protocols enable efficient construction of various important molecules of complex architecture under mild reaction conditions and with a minimal number of manual operations and purification procedures. Within this field it has recently been demonstrated that α,β-unsaturated aldehydes can participate in enantioselective organocatalytic one-pot cascade reactions in a highly stereoselective fashion, providing valuable chiral building blocks and offering access to various important products.[14,15a] Given the importance of 2-hydroxyalkyl- and 2-aminoalkyl furanes and the lack of a general enantioselective methodology for the preparation of electron-poor furane deriva-

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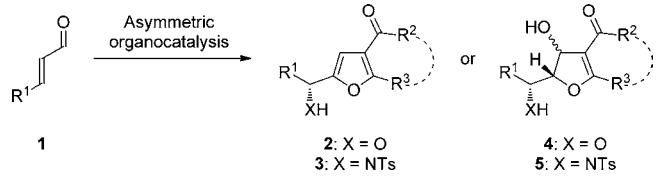
Scheme 3. Asymmetric Synthesis of 2-Hydroxyalkyl- and 2-Aminoalkyl Furanes **2** and **3**, or 2-Hydroxyalkyl- and 2-Aminoalkyl 2,3-Dihydrofuranes **4** and **5**, via Enantioselective Organocatalysis



tives, we envisioned that an efficient method for the preparation of these compounds could rely on the usage of readily available α,β-unsaturated aldehydes as starting materials (Scheme 3). This approach opens the possibility to access optically active 2,3-dihydrofurane derivatives (for details see mechanistic proposal below).

Herein we present that optically active electron-poor 2-hydroxyalkyl- and 2-aminoalkyl furanes can be easily obtained by an organocatalytic multibond-forming one-pot reaction cascade starting from very simple substrates and using low catalyst loadings. Furthermore, the scope of the developed approach is very broad since various α,β-unsaturated aldehydes and 1,3-dicarbonyl compounds can be utilized. Moreover, the reaction cascade can be controlled to the interrupted Feist−Bénary product, offering a facile and stereoselective entry to 2-hydroxyalkyl- and 2-aminoalkyl 2,3-dihydrofuranes with three stereogenic centers.

Results and Discussion

Enantioselective Synthesis of 2-Hydroxyalkyl Furanes. We initiated our screening using *trans*-2-hexenal **1a** and methyl acetoacetate **8a** as model substrates (Table 1). The epoxidation of **1a** was performed according to an improved procedure,[15a] using 2-[bis(3,5-bis(trifluoromethyl)phenyl)(trimethylsilyloxy)-methyl]pyrrolidine **6** as the catalyst.[16] To our delight this organocatalytic protocol turned out to be fully compatible with the 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) promoted Feist−Bénary reaction using 2,3-epoxy aldehydes **7** as 1,2-dielectrophilic species.[6h,17] We were surprised to observe that under these conditions the corresponding 2-hydroxyalkyl 2,3-dihydrofurane **4a** was formed as the only product and no dehydration to **2a** occurred. Gratifyingly, it was found that dehydration of **4a** can be accomplished under acidic conditions using trifluoroacetic acid (TFA), to give the desired product **2a**. Furthermore, the whole procedure could be performed in one-pot without isolation of any of the intermediates, affording **2a** in 59% yield and 82% ee (Table 1, entry 1). Further screening revealed that the amount of the base is an important factor influencing the reaction outcome, and that 0.5 equiv of MTBD was sufficient to furnish **2a** in good yield and enantiomeric excess (Table 1, entry 2). However, further reduction of the amount of base significantly slowed down the reaction and consequently diminished both the yield and enantiomeric excess (Table 1, entry 3). In the next part of the screening the influence of various organic and inorganic bases on the reaction outcome was evaluated. The use of inorganic bases such as K_2CO_3 or Cs_2CO_3 followed by addition of TFA resulted in the formation of the desired product **2a**, albeit in lower enantioselectivity (Table 1, entries 4, 5). Additionally, longer reaction times were required in order to achieve full conversion. Likewise, the use of another organic base such as diaza(1,3)bicyclo[5.4.0]undecane (DBU) was not beneficial for the reaction sequence (Table 1, entries 6, 7), indicating MTBD as the optimal basic promoter of the Feist−Bénary reaction. Additional optimization studies with regard to the effect of the acid used in the dehydration step were also performed (Table 1, compare entries 2, 8−10). Among the acids tested (−)-camphor-10-sulfonic acid (CSA) proved to be most effective, furnishing the target furane **2a** in 72% yield and 92% ee. In this manner the key parameters for the developed enantioselective multibond-forming reaction cascade were established.

With the optimized conditions in hand, we turned our attention to the scope of this reaction sequence. Initially, the aldehyde scope was studied using methyl acetoacetate **8a** as a model 1,3-dicarbonyl compound (Table 2). To our delight, under optimal reaction conditions various linear and γ-branched aliphatic α,β-unsaturated aldehydes **1a-e** reacted smoothly (Table 2, entry 1−5). In all of the cases good yields and high enantioselectivities were observed confirming the generality of the developed approach. Furthermore, the use of the opposite enantiomer of the catalyst **6** afforded access to the enantiomeric product as demonstrated in the synthesis of *ent*-**2e** (Table 2, entry 6). This result also clearly indicates that no matched-mismatched interaction between the chiral catalyst **6** and the chiral acid (CSA) occurs. Further studies on the reaction scope revealed that a variety of functional groups in the side chain of the starting enal **1** such as a double bond, a protected hydroxyl group, an aromatic ring and an ester moiety were very well tolerated (Table 2, entries 7−10). In particular, the use of ethyl

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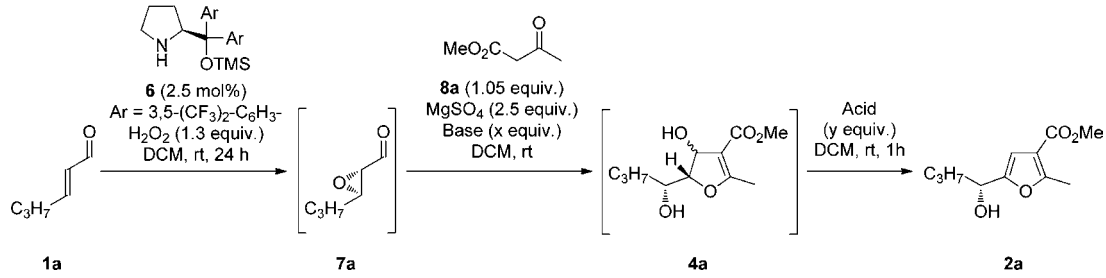
(16) For the first application of silyldiarylprolinol ethers as catalysts, see: (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed* **2005**, *44*, 794. See also: (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (c) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (d) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. For general reviews on the use of silyldiarylprolinol ethers as catalysts see: (e) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922. (f) Xu, L.-W.; Li, L.; Shi, Z.-H. *Adv. Synth. Catal.* **2010**, *352*, 243.

(17) For applications of 2,3-epoxy aldehydes in the Feist−Bénary reaction, see: (a) Williams, P. H.; Payne, G. B.; Sullivan, W. J.; Van Ess, P. R. *J. Am. Chem. Soc.* **1960**, *82*, 4883. (b) Kondo, A.; Ochi, T.; Iio, H.; Tokoroyama, T.; Siro, M. *Chem. Lett.* **1987**, *16*, 1491.

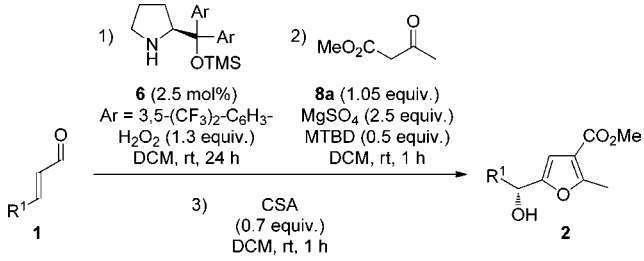
Table 1. Optimization of the Enantioselective Epoxidation/Feist−Bénary Reaction Sequence Using *trans*-2-Hexenal **1a** and Methyl Acetoacetate **8a** As Model Substrates[a]



entry	base (equiv)	time [h][b]	acid (equiv)	yield [%][c] (conv. [%])	ee [%][d]
1	MTBD (1)	1	TFA (1.2)	59 (>95)	82
2	MTBD (0.5)	1	TFA (0.7)	61 (>95)	92
3	MTBD (0.25)	16	TFA (0.45)	39 (>95)	87
4	K_2CO_3 (3)	1.5	TFA (3.2)	56 (90)	81
5	Cs_2CO_3 (1)	16	TFA (1.2)	58 (>95)	87
6	DBU (0.5)	16	TFA (0.7)	35 (>95)	65
7	DBU (1)	1	TFA (1.2)	65 (>95)	88
8	MTBD (0.5)	1	MSA (0.7)	42 (>95)	85
9	MTBD (0.5)	1	PTSA (0.7)	50 (>95)	85
10	MTBD (0.5)	1	CSA (0.7)	72 (>95)	92

[a] Reactions performed on 0.2 mmol scale in 0.4 mL CH_2Cl_2 (see Supporting Information for details). [b] Reaction time for the second step. [c] Overall yield for three steps. Conversion in parentheses determined by ^{1}H NMR spectroscopy is given. [d] Determined by chiral stationary phase HPLC.

Table 2. Aldehyde Scope of the Enantioselective Epoxidation/Feist−Bénary Reaction Sequence[a]



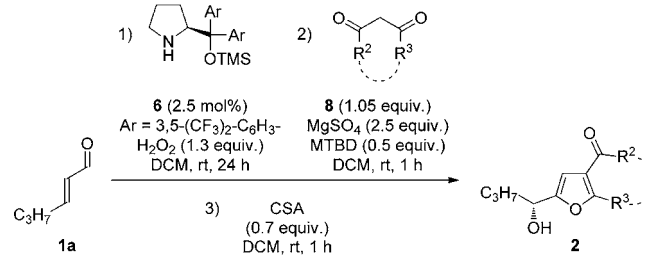
entry	**1** (R^1)	yield [%][b]	ee [%][c]
1	**1a** (Pr)	**2a** - 72	92
2	**1b** (Et)	**2b** - 67	91
3	**1c** (*i*Pr)	**2c** - 62	94
4	**1d** (Pentyl)	**2d** - 70	88
5	**1e** (Hex)	**2e** - 54	91
6[d]	**1e** (Hex)	*ent*-**2e** - 60	90
7	**1f** (*E*-Hex-3-enyl)	**2f** - 68	94
8	**1g** (CH_2OBn)	**2g** - 73	92
9	**1h** (CH_2CH_2Ph)	**2h** - 74	90
10	**1i** (CO_2Et)	**2i** - 53	88
11[e]	**1j** (Ph)	**2j** - 56	88

[a] Reactions performed on 0.2 mmol scale in 0.4 mL of CH_2Cl_2 (see Supporting Information for details). [b] Overall yield for three steps. [c] Determined by chiral stationary phase HPLC. [d] Reaction performed with the opposite enantiomer of the catalyst **6**. [e] Reaction performed with 10 mol % of the catalyst **6** using 1 equiv of DBU as a base and 1.2 equiv of CSA.

(*E*)-3-oxobutanoate **1i** providing a direct access to furanyl hydroxyacetate derivative **2i** is worth noticing (Table 2, entry 10). Importantly, aromatic α,*β*-unsaturated aldehydes could also be employed in the developed one-pot reaction sequence as demonstrated by the use of cinnamaldehyde **1j** (Table 2, entry 11). However, a weaker base (DBU) had to be applied in the Feist−Bénary reaction in order to achieve good enantioselectivity.

To further establish the generality of the developed approach, studies on the scope of 1,3-dicarbonyl compounds **8** were

Table 3. 1,3-Dicarbonyl Compound Scope of the Enantioselective Epoxidation/Feist−Bénary Reaction Sequence[a]



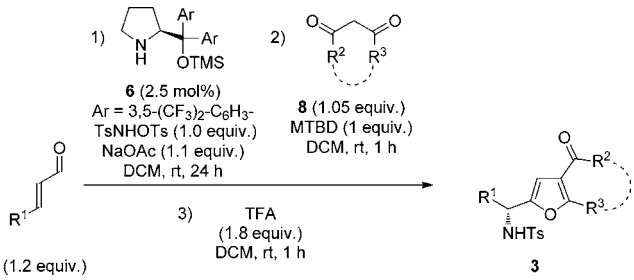
entry	**6**	R^2	R^3	yield [%][b]	ee [%][c]
1	**8b**	OEt	Et	**2k** - 58	86
2	**8c**	O*t*Bu	CH_3	**2l** - 70	88
3	**8d**	OMe	CH_2CO_2Me	**2m** - 40	94
4	**8e**	CH_3	CH_3	**2n** - 75	89
5	**8f**	-$CH_2CH_2CH_2$-		**2o** - 52	92
6	**8g**	-$CH_2C(CH_3)_2CH_2$-		**2p** - 62	94

[a] Reactions performed on 0.2 mmol scale in 0.4 mL of CH_2Cl_2 (see Supporting Information for details). [b] Overall yield for three steps. [c] Determined by chiral stationary phase HPLC.

undertaken using *trans*-2-hexenal **1a** as a model α,*β*-unsaturated aldehyde (Table 3). Esters with different side chains **8b**,**c** were successfully applied in the reaction sequence (Table 3, entries 1, 2) affording **2k**,**l** in good yields, but slightly lower enantiomeric excesses, compared to the reaction with methyl acetoacetate **8a** (Table 2, entry 1). Functional groups were also tolerated in the side chain of the starting *β*-ketoester as demonstrated in the synthesis of furane **2m** (Table 3, entry 3). Moreover, a variety of 1,3-diketones **8e**-**g** were also utilized in the developed enantioselective epoxidation/Feist−Bénary reaction sequence (Table 3, entries 4−6). Particularly attractive is the use of cyclic 1,3-diketones **8f**,**g** that offer a direct entry to bicyclic furfuryl alcohols **2o**,**p** in good yields and high enantiomeric excess.

Enantioselective Synthesis of 2-Aminoalkyl Furanes. Being successful in the development of an enantioselective approach for the preparation of electron-poor 2-hydroxyalkyl furanes we

Table 4. Scope of the Enantioselective Aziridination/Feist−Bénary Reaction Sequence[a]



entry	**1** (R^1)	R^2	R^3	yield [%][b]	ee [%][c]
1	**1a** (Pr)	OMe	CH_3	**3a** - 68	95
2	**1k** (Me)	OMe	CH_3	**3b** - 70	89
3	**1c** (*i*Pr)	OMe	CH_3	**3c** - 38	94
4	**1e** (Hex)	OMe	CH_3	**3d** - 66	93
5[d]	**1f** (*E*-Hex-3-enyl)	OMe	CH_3	**3e** - 61	91
6	**1g** (CH_2OBn)	OMe	CH_3	**3f** - 65	93
7	**1h** (CH_2CH_2Ph)	OMe	CH_3	**3g** - 68	90
8[d]	**1a** (Pr)	OEt	Et	**3h** - 55	95
9	**1a** (Pr)	OMe	CH_2CO_2Me	**3i** - 64	95
10[d]	**1a** (Pr)	CH_3	CH_3	**3j** - 88	95
11[d]	**1a** (Pr)	-$CH_2C(CH_3)_2CH_2$-		**3k** - 66	91

[a] Reactions performed on 0.1 mmol scale in 0.5 mL of CH_2Cl_2 (see Supporting Information for details). [b] Overall yield for three steps. [c] Determined by chiral stationary phase HPLC. [d] Reaction performed using CSA (1.8 equiv).

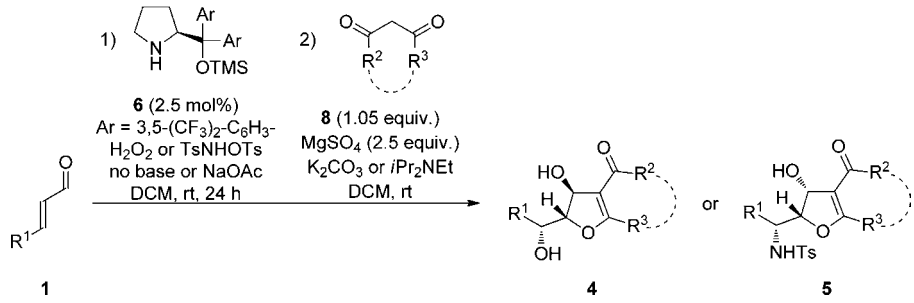
turned the attention to the synthesis of the corresponding amines. It occurred to us that the use of 2,3-aziridine aldehydes as key intermediates in this one-pot reaction sequence would lead to the formation of the desired 2-aminoalkyl furanes. However, at the outset of our studies the development of an aziridination/Feist−Bénary reaction sequence seemed particularly challenging since, to the best of our knowledge, 2,3-aziridine aldehydes or ketones have never been used as electrophiles in the Feist−Bénary reaction before. Recently, we have developed an efficient and highly stereoselective method for the preparation of *N*-tosyl 2,3-aziridine aldehydes that requires only 2.5 mol % of the aminocatalyst **6** to proceed efficiently and in a highly stereoselective fashion.[15a,18] We anticipated that utilization of this reaction should be particularly advantageous since the presence of an electron-withdrawing tosyl group on the nitrogen atom in the corresponding 2,3-aziridine aldehyde should increase its ability to act as a leaving group in the Feist−Bénary reaction. We were pleased to observe that this aziridination protocol was very well suited for the envisioned one-pot reaction sequence. Initial screening using *trans*-2-hexenal **1a** as a model substrate (see Supporting Information for details) revealed that the use of MTBD (1 equiv) as a base and TFA (1.8 equiv) in the dehydration step is optimal for both the reaction yield and the enantioselectivity. Under these conditions various enals **1** reacted smoothly affording the target 2-aminoalkyl furanes **3** in good yields and high enantiomeric excess (Table 4). The scope of the developed one-pot approach was very broad since a variety of aliphatic enals with diverse functional groups in the side chain as well as different 1,3-dicarbonyl compounds **8** easily reacted to give the target furanes **3** efficiently and in a highly stereoselective fashion. In some of the cases (Table 4, entries 5, 8, 10, 11), CSA instead of TFA had to be used in the dehydration step in order to achieve chemoselective transformations into the target products **3**.

Enantioselective Synthesis of 2-Hydroxyalkyl- and 2-Aminoalkyl 2,3-Dihydrofuranes. With the development of the enantioselective one-pot strategy for the synthesis of electron-poor 2-hydroxyalkyl- and 2-aminoalkyl furanes **2** and **3** being accomplished, we investigated the possibility to isolate the cyclization products before dehydration (interrupted Feist−Bénary products), in order to establish an enantioselective route to optically active 2-hydroxyalkyl- and 2-aminoalkyl 2,3-dihyrofuranes with 3 stereogenic centers. Initial screening with regard to the base used as well as reaction temperature using *trans*-2-hexenal **1a** as a model substrate (see Supporting Information for details) revealed that the diastereoselectivity of the interrupted Feist−Bénary reaction with 2,3-epoxy aldehydes as substrates is difficult to control. The best results were obtained using K_2CO_3 as base at room temperature. Under these conditions, the epoxidation/interrupted Feist−Bénary reaction sequence with *trans*-2-hexenal **1a** and methyl acetoacetate **8a** proceeded smoothly affording dihydrofurane **4a** in a 3:1 dr and good yield (Table 5, entry 1). Importantly, the one-pot epoxidation/interrupted Feist−Bénary reaction sequence using more bulky *tert*-butyl acetoacetate **8c** proceeded with slightly better diastereoselectivity (4:1 dr) (Table 5, entry 2). Further investigations of the reaction sequence showed that a variety of α,β-unsaturated aldehydes **1f**,**g**,**i** with different functional groups in the side chain could be employed affording the corresponding 2,3-dihydrofuranes **4c**−**e** in moderate to good yields (Table 5, entries 3−5). Furthermore, different 1,3-dicarbonyl compounds such as acyclic and cyclic 1,3-diketones **8e**,**g** were well tolerated under optimal reaction conditions (Table 5, entries 6, 7). However, the diastereoselectivity of the reaction sequence was highly substrate dependent. Gratifyingly, in all of the cases the determined enantiomeric excesses of both diastereoisomers were excellent. It is also worth noting that in most of the cases diastereoisomers could be separated by means of flash chromatography. Further studies revealed that the stereochemical outcome of the interrupted Feist−Bénary reaction with 2,3-aziridine aldehydes was even more difficult to control and the influence of base was less pronounced (see Supporting Information for details). The best results were obtained using *i*Pr_2NEt as a base leading to the formation of dihydrofuranes **5a**−**c** in moderate diastereoselectivities but with excellent enantiomeric excesses for both diastereoisomers (Table 5, entries 8−10). It should also be noted that the aziridination/interrupted Feist−Bénary reaction sequence proceeded with lower and opposite diastereoselectivity when compared to the synthesis of **4** (for explanations see assignments of the relative and absolute configurations of the products below).

Mechanistic Considerations. The mechanistic proposal for the developed enantioselective epoxidation or aziridination/Feist−Bénary reaction sequence leading to the formation of 2-hydroxyalkyl- and 2-aminoalkyl furanes **2** and **3**, and 2-hydroxyalkyl- and 2-aminoalkyl 2,3-dihydrofuranes **4** or **5**, respectively, is depicted in Scheme 4. It begins with an iminium-catalyzed epoxidation or aziridination of α,β-unsaturated aldehydes **1**. In the first step of the reaction sequence an iminium ion **9** is formed in a reversible reaction between enal **1** and aminocatalyst **6**. Subsequent oxa- or aza-Michael addition to **9** followed by an enamine-catalyzed cyclization leads to the formation of iminium ions **12** and **13**. Hydrolysis of **12** and **13**

(18) For other examples of aziridination of enals, see: (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.

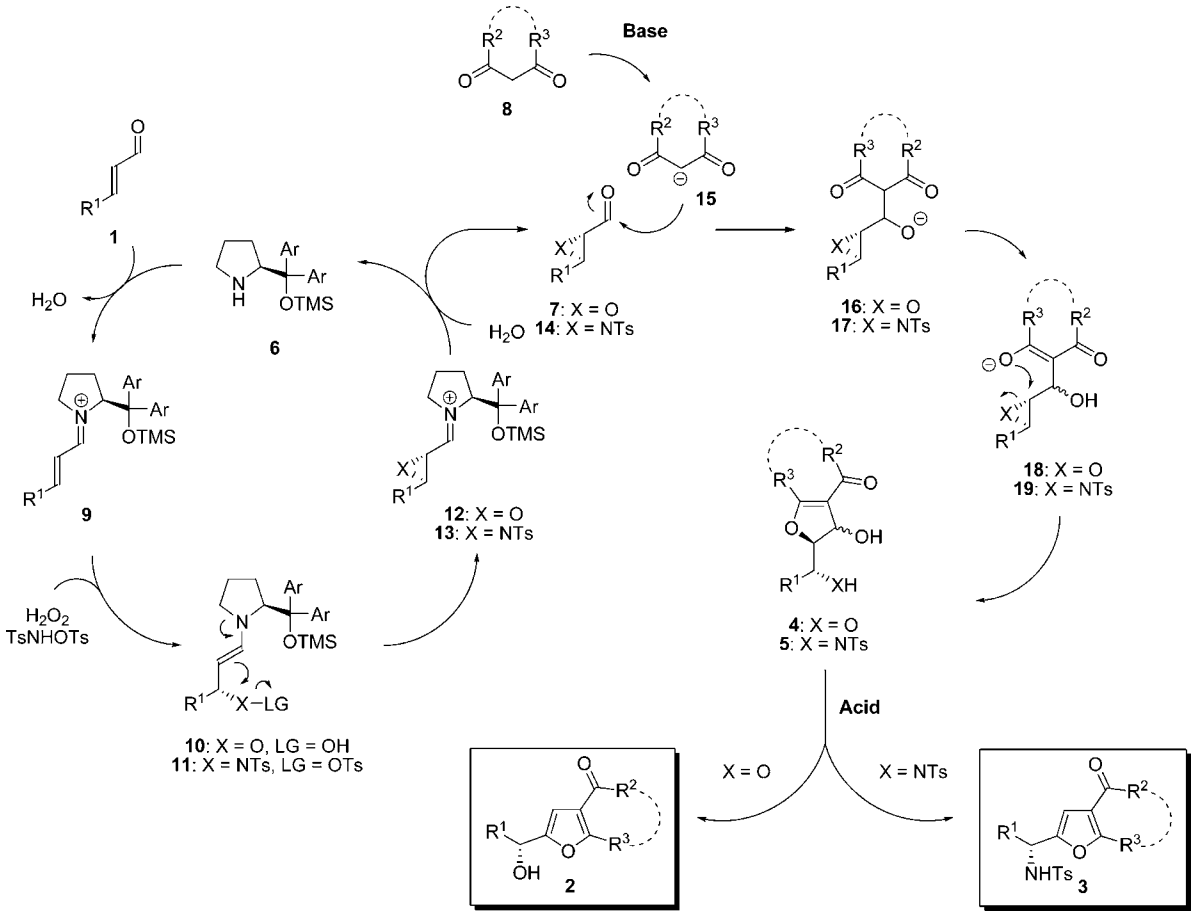
Table 5. Scope of the Enantioselective Epoxidation or Aziridination/Interrupted Feist−Bénary Reaction Sequence



entry	**1** (R^1)	**8**	R^2	R^3	X	yield [%][c]	dr	ee [%][d]
1[a]	**1a** (Pr)	**8a**	OMe	CH_3	O	**4a** - 74	3:1[e]	97/98
2[a]	**1a** (Pr)	**8c**	O*t*Bu	CH_3	O	**4b** - 75	4:1[e]	98/98
3[a]	**1f** (*E*-Hex-3-enyl)	**8c**	O*t*Bu	CH_3	O	**4c** - 86	3:1[e]	95/98
4[a]	**1g** (CH_2OBn)	**8c**	O*t*Bu	CH_3	O	**4d** - 60	2:1	96/nd
5[a]	**1i** (CO_2Et)	**8c**	O*t*Bu	CH_3	O	**4e** - 46	7:1	97/nd
6[a]	**1a** (Pr)	**8e**	CH_3	CH_3	O	**4f** - 87	1.6:1[e]	98/98
7[a]	**1a** (Pr)	**8g**	$-CH_2C(CH_3)_2CH_2-$		O	**4g** - 80	2.5:1[e]	98/nd
8[b]	**1a** (Pr)	**8a**	OMe	CH_3	NTs	**5a** - 70	1:2	96/98
9[b]	**1a** (Pr)	**8e**	CH_3	CH_3	NTs	**5b** - 91	1:2.5[e]	92/98
10[b]	**1a** (Pr)	**8g**	$-CH_2C(CH_3)_2CH_2-$		NTs	**5c** - 80	1:1[e]	97/94

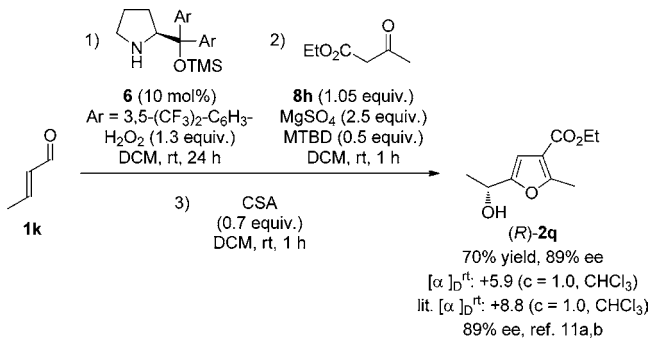
[a] Reaction performed on 0.5 mmol scale in 0.4 mL of CH_2Cl_2 using K_2CO_3 (3 equiv) as a base in the interrupted Feist−Bénary step (see Supporting Information for details). [b] Reaction performed on 0.2 mmol scale in 0.5 mL of CH_2Cl_2 using iPr_2NEt (1 equiv) as a base in the interrupted Feist−Bénary step (see Supporting Information for details). [c] Overall yield for three steps. [d] Determined by chiral stationary phase HPLC. [e] Diastereoisomers separated by FC.

Scheme 4. Mechanistic Proposal for the Enantioselective One-Pot Reaction Cascade for the Synthesis of 2-Hydroxyalkyl- and 2-Aminoalkyl Furanes **2** or **3** and of 2-Hydroxyalkyl- and 2-Aminoalkyl 2,3-Dihydrofuranes **4** or **5**



furnishes 2,3-epoxy- and 2,3-aziridine aldehydes **7** and **14** which in turn can participate in the base-promoted Feist−Bénary reaction initiated by nucleophilic addition of anion **15** to the carbonyl group in **7** or **14.** Subsequent proton transfer and

Scheme 5. Assignment of the Absolute Configuration by Direct Chemical Correlation



enolization affords **18** or **19** which undergo cyclization through epoxide or aziridine ring-opening reaction by the enolate oxygen furnishing the dihydrofurane ring. Acid-catalyzed dehydration of 2,3-dihydrofuranes **4** or **5** takes place in the last stage of the one-pot reaction cascade affording the target 2-hydroxyalkyl- and 2-aminoalkyl furanes **2** and **3**.

Assignments of the Relative and Absolute Configurations of the Products. Taking into account the mechanistic considerations presented above and the results of previous works[14d,15a,b] addressing the epoxidation and aziridination of α,*β*-unsaturated aldehydes catalyzed by **6**, the absolute configuration was assigned to be (*R*) for the products **2a**−**h**,**j**−**p** and **3a**−**k** or (*S*) for the product **2i**. In order to confirm the correctness of this configurational assignments a direct chemical correlation with the known (*R*)-ethyl 5-(1-hydroxyethyl)-2-methylfuran-3-carboxylate **2q** was performed.[11a,b] Compound **2q** was obtained by the enantioselective epoxidation/Feist−Bénary reaction sequence in 70% yield and 89% ee (Scheme 5).

Accordingly, the absolute configuration of the interrupted Feist−Bénary products was assigned (Figure 1). The relative stereochemistry of the C-2 and C-3 stereogenic centers of the 2,3-dihydrofurane ring was elucidated by analysis of the ^{1}H NMR data. Diagnostic were large values of coupling constants $^3J_{H2H3}$ observed in ^{1}H NMR spectra of one of the diastereomers (6.5−7.3 Hz). According to the Karplus equation[19] these values correspond to a small dihedral angel, clearly indicating a *cis*-alignment of the H-2 and H-3 protons in this diastereoisomer. This turned out to be the case for the minor diastereoisomers of the products **4** and major diastereoisomers of the products **5**. On the contrary, the coupling between these two protons was clearly smaller (0−4.0 Hz) in the ^{1}H NMR spectra of the other diastereomers (major for **4** and minor for **5**), indicating a trans arrangement of the protons at C-2 and C-3 of the dihydrofurane ring (a dihedral angel close to 90° according to the Karplus equation). It should be noted that in both of the cases the observed $^3J_{H2H3}$ values are consistent with the previous reports on relative configuration of the stereogenic centers in the similar ring systems.[14d,20]

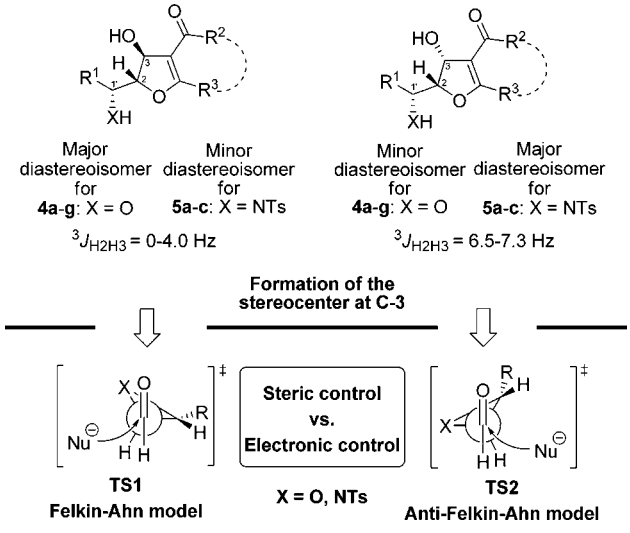


Figure 1. Configurational assignments of the interrupted Feist−Bénary products **4** and **5** and models for the diastereoselective outcome of the reaction.

On the basis of these stereochemical assignments, transition states of the nucleophilic addition to the carbonyl group in **7** and **14** (Scheme 4) were proposed, explaining the observed and opposite diastereoselectivity at C-3 stereogenic centers in the products **4** and **5** (Figure 1 - bottom). The formation of the stereogenic center at C-3 in **4** and **5** can be rationalized in two ways. First, by the classical Felkin-Ahn model in which the nucleophile (1,3-dicarbonyl compound) approaches the carbonyl group opposite to the large substituent (Figure 1, TS1 - steric control). Second, by the anti-Felkin-Ahn model (Figure 1, TS2 - electronic control) in which the epoxide oxygen (X = O) or aziridine nitrogen (X = NTs), being electron-withdrawing substituents, are placed opposite to the approaching nucleophile. In the case of the nucleophilic addition to the carbonyl group in 2,3-epoxy aldehydes **7**, the steric factor dominates giving rise to the Felkin-Ahn product as major diastereoisomer. On the contrary, for the nucleophilic addition to the carbonyl group in 2,3-aziridine aldehydes **14** the selectivity is reversed due to the presence of the more electron-withdrawing *N*-Tosyl group. This results in a stronger electronic contribution and the anti-Felkin−Ahn product is formed as the major diastereoisomer. Noteworthily, the anti-Felkin−Ahn transition state was proposed earlier for the interrupted Feist−Bénary reaction between α-bromoketones and 1,3-dicarbonyl compounds by Calter et al.[4a]

On the basis of our results it can be assumed that in both of the cases the transition states leading to the major and minor diastereoisomers are similar in energies. Consequently, the competition between electronic and steric factors determines the stereochemical outcome of the addition. Moderate or low diastereoselectivities at the C-3 stereogenic center in **4** and **5** are therefore observed in the performed interrupted Feist−Bénary reactions. The competition is particularly pronounced in the case of nucleophilic addition to the carbonyl group in 2,3-aziridine aldehydes **14**. It should be noted that the stereochemical pattern seen in the addition to the carbonyl group of 2,3-epoxy aldehydes was observed before.[14d]

Conclusion

In summary, we have developed the first enantioselective method for the preparation of electron-poor 2-hydroxyalkyl- and 2-aminoalkyl furanes that relies on a multibond-forming organocatalytic reaction cascade. The presented approach proceeds for a wide variety of α,*β*-unsaturated aldehydes and different 1,3-dicarbonyl compounds and allows for the highly stereoselective preparation of the target furanes under mild reaction conditions using low catalyst loadings. The possibility to employ the developed methodology for the synthesis of 2-hydroxyalkyl- and 2-aminoalkyl 2,3-dihydrofuranes with three stereogenic centers is also presented and the mechanism of the one-pot reaction cascade

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outlined. We believe that the developed approach will be complementary to the existing methods for the preparation of optically active electron-rich 2-hydroxyalkyl and 2-aminoalkyl furanes that up to now mainly rely on the asymmetric Friedel−Crafts reaction of furanes with aldehydes and imines.

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

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