Dienamine-Mediated Inverse-Electron-Demand Hetero-Diels-Alder Reaction by Using an Enantioselective H-Bond-Directing Strategy**

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The reaction between an electron-rich diene and an electronpoor dienophile, commonly known as the Diels–Alder reaction, was discovered in 1928.^[1] This [4+2] cycloaddition constitutes one of the most fundamental reactions in organic chemistry and still attracts much attention.^[2] Its inverseelectron-demand variant, where an electron-poor diene reacts with an electron-rich dienophile, was discovered later, and immense progress within this field has been made over the years.^[3] Importantly, asymmetric versions of this reaction utilizing both transition metal catalysis and organocatalysis have also been developed.^[4] In this context, asymmetric aminocatalytic strategies involving HOMO activation of the dienophile constitute an important alternative to classical LUMO-lowering pathways.^[5]

Already in 2003, shortly after asymmetric organocatalysis was rediscovered and when the entire field was still in its infancy, the possibility to employ enamine chemistry in the inverse-electron-demand hetero-Diels-Alder reaction was demonstrated (Scheme 1, top).^[5a] Chen and co-workers later developed a modification of this reaction, namely an aza-Diels-Alder reaction, to access chiral tetrahydropyridine derivatives.^[5b] The same research group also showed that dienamines were capable of participating in an inverseelectron-demand aza-Diels-Alder reaction occurring at the proximal double bond (enamine-like, 1,2-reactivity) (Scheme 1, bottom).^[5c] However, obtaining regioselective 3,4-reactivity at the distal alkene moiety, enabling remote, enantioselective functionalization five bonds away from the stereogenic center of the catalyst,^[6] turned out to be problematic. Such a reactivity pattern was only feasible for crotonaldehyde, albeit low stereoselectivity was obtained.^[5b]

The dihydropyran framework constitutes a privileged structural motif in organic and medicinal chemistry.^[7] Owing to the presence of an olefinic moiety, dihydropyrans can undergo various chemical transformations and can easily be converted into biologically relevant tetrahydropyran deriva-

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Scheme 1. Enamines and dienamines in the inverse-electron-demand hetero-Diels-Alder reaction. Ts = toluenesulfonyl, TMS = trimethylsilyl.

tives.^[8] Therefore, dihydropyrans constitute important intermediates for the preparation of carbohydrates and related natural products.^[9]

Given the importance of the dihydropyran framework and the difficulties in obtaining the regio- and stereoselective inverse-electron-demand hetero-Diels–Alder reaction at the distal double bond of the dienamine intermediate, we envisioned that a possible solution could rely on applying H-bond-directing aminocatalysis (Scheme 2).^[10] It was anticipated that simultaneous activation of an α,β -unsaturated aldehyde (through dienamine formation) and the recognition of the heterodiene system by an H-bond donor site of the catalyst might facilitate the reaction. Furthermore, such a dual activation strategy should promote the inverseelectron-demand hetero-Diels–Alder reaction to occur at



Scheme 2. Aminocatalytic H-bond-directing strategy for the inverseelectron-demand hetero-Diels–Alder reaction.

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the distal olefinic moiety of the dienamine intermediate, thereby resulting in regioselective 3,4-functionalization. In particular, the application of alkyl 2-oxo-4-arylbut-3-enoates as heterodienes seemed promising, since the α -ketoester moiety is a well-recognized motif in H-bonding catalysis.^[11]

To evaluate the concept, the reaction between methyl 2oxo-4-phenylbut-3-enoate (2a) and (E)-4-phenylbut-2-enal (1a) in the presence of various aminocatalysts was performed (Table 1). It was found that both steric shielding catalysts **4** (Table 1, entry 1) and H-bond-directing catalysts **5a**,**b**

Table 1: Enantioselective dienamine-mediated inverse-electron-demand hetero-Diels–Alder reaction: optimization studies.^[a]



[a] Reactions performed on a 0.1 mmol scale (see the Supporting Information for details). MTBE = methyl *tert*-butyl ether, DME = 1,2dimethoxyethane. [b] Conversion of **2** as determined by ¹H NMR spectroscopy. [c] Determined by ¹H NMR spectroscopy. [d] Determined by HPLC using a chiral stationary phase after Ramirez olefination. [e] Reaction performed in the absence of DEA using 20 mol% of the catalyst. *ent-***3** a was obtained.

90

88

THF

tBu (2d)

(Table 1, entries 2,3) promoted the desired inverse-electrondemand hetero-Diels–Alder reaction. Interestingly, the Hbond-directing approach outperformed the classical steric shielding strategy^[12] in terms of both chemical efficiency and stereoselectivity, and aminocatalyst **5a** proved to be the most effective (Table 1, entry 2). Notably, in the case of H-bonddirecting aminocatalysts **5a,b**, *N,N*-diethylacetamide (DEA) was used as an additive influencing the catalytic activity of the system.^[10] Further screening revealed that increasing the bulk of the ester moiety of **2** led to improved enantiocontrol of the reaction (Table 1, entries 2,4–6), with *tert*-butyl ester **2d** giving the best result (Table 1, entry 6). Subsequent solvent survey (Table 1, entries 6–11) indicated that the use of THF resulted in pronounced increase in selectivity, albeit longer reaction times were required to achieve high conversion (Table 1, entry 11). Further screening concerning concentration and additives applied did not lead to improvement of the results (see the Supporting Information for details).

After having optimized the conditions for the inverseelectron-demand hetero-Diels–Alder reaction, the scope of the methodology was evaluated. Initially, various β , γ -unsaturated α -ketoesters **2** with different substitution patterns and electronic properties were examined (Table 2). Gratifyingly, ketoesters **2e–I** bearing different electron-withdrawing sub-

Table 2: Enantioselective dienamine-mediated inverse-electron-demand hetero-Diels–Alder reaction: β , γ -unsaturated α -ketoester scope.^[a]



2d–n

Entry	R (2)	<i>t</i> [h]	Yield [%] (3)	d.r. ^[b]	ee [%] ^[c]
1	Ph (2 d)	96	82 (3 d)	11:1	90
2	4-Br-C ₆ H ₄ (2e)	42	74 (3 e)	11:1	90
3	3-Br-C ₆ H ₄ (2 f)	24	66 (3 f)	9:1	91
4	2-Br-C ₆ H ₄ (2 g)	120	64 (3 g)	3:1	79
5	2-F-C ₆ H ₄ (2h)	72	75 (3 h)	6:1	91
6	4-CF ₃ -C ₆ H ₄ (2i)	24	73 (3 i)	10:1	93
7	4-CO ₂ Me-C ₆ H ₄ (2 j)	48	60 (3 j)	8:1	87
8	4-NO ₂ -C ₆ H ₄ (2k)	24	74 (3 k)	11:1	91
9	2,6-Cl ₂ -C ₆ H ₃ (2 I)	27	78 (3 I)	>20:1	90
10	4-CH ₃ -C ₆ H ₄ (2m)	72	51 (3 m)	17:1	85
11	3-pyridyl (2 n)	48	59 (3 n)	10:1	89
12 ^[d]	Me (2o)	24	42 (3 o)	10:1	90

[a] Reactions performed on a 0.2 mmol scale (see the Supporting Information for details).
[b] Determined by ¹H NMR spectroscopy.
[c] Determined by chiral-stationary-phase HPLC or ultraperformance convergence chromatography (UPC²; see the Supporting Information for details).
[d] Isolated after reduction to the corresponding alcohol. Yield over two steps given.

stituents on the aromatic ring were easily reacted under the established reaction conditions (Table 2, entries 2–9). In most of the cases, good yields and high stereoselectivities were obtained. With respect to the substitution pattern, introduction of a sterically demanding ortho-bromo substituent on the aromatic ring of 2 led to deterioration of selectivity (Table 2, entry 4). However, this was not the case for the smaller orthofluoro substituent (Table 2, entry 5). Furthermore, an aromatic ring having two ortho-substituents was well-tolerated as demonstrated for 21 affording 31 in good yield and in a highly stereoselective manner (Table 2, entry 9). Interestingly, heterodiene 2m bearing an electron-rich substituent on the aromatic ring was less reactive and yielded the target product 3m with slightly inferior results (Table 2, entry 10). Furthermore, stereoselective synthesis of heteroaromat-containing dihydropyrans proved possible affording 3n in good yield and

11

5a

90

11:1

enantioselectivity (Table 2, entry 11). Importantly, the developed strategy could also be applied to aliphatic β , γ -unsaturated α -ketoesters as demonstrated in the synthesis of **30** (Table 2, entry 12).

To further explore the generality of the developed [4+2] cycloaddition, the aldehyde scope was investigated (Scheme 3).



Scheme 3. Enantioselective dienamine-mediated inverse-electrondemand hetero-Diels–Alder reaction: α , β -unsaturated aldehyde scope (see the Supporting Information for details).

It was found that the inverse-electron-demand hetero-Diels–Alder reaction proceeded efficiently for the various aldehydes tested.^[13] Importantly, aldehydes bearing either electron-donating or electron-withdrawing substituents afforded the corresponding products in good yields and in a highly enantio- and diastereoselective manner. However, the obtained stereoselectivities were slightly lower than in the β , γ -unsaturated α -ketoester scope. Surprisingly, introduction of a heteroaromatic moiety in the 4-position of the starting α , β -unsaturated aldehyde resulted in a decrease of selectivity as demonstrated in the synthesis of thiophene-containing dihydropyran **3u**. This result suggests that π -stacking interactions between the aromatic moieties of heterodiene **2** and the dienamine intermediate might be an important factor influencing the cycloaddition outcome.

In the course of the further studies, the possibility to utilize the chiral dihydropyran framework for the construction of more elaborate derivatives was evaluated. Initially, the synthesis of tetrahydropyran derivatives was investigated by stereoselective functionalizations of the olefinic moiety present in **3** (Scheme 4). Hydrogenation of the double bond in **3d** could be successfully performed using Pd/C as the catalyst. However, protection of the aldehyde moiety as its corresponding dimethyl acetal prior to hydrogenation was necessary. Gratifyingly, both reactions could be performed in



Scheme 4. Diastereoselective synthesis of optically active tetrahydropyrans **6** and **7**. Reagents and conditions: a) 1) PTSA (10 mol%), MeOH, RT, 3 h; 2) H₂ (20 bar), Pd/C, MeOH, RT, 20 h; b) 1) 2-methoxy-1,3-dioxolane (2 equiv), PTSA (3 mol%), CH₂Cl₂, RT, 3 h; 2) K₂OsO₂(OH)₄ (2 mol%), CH₃SO₂NH₂ (1 equiv), K₂CO₃ (3 equiv), K₃[Fe(CN)₆] (3 equiv), H₂O/*t*BuOH (1:1), RT, 20 h. PTSA=*p*-toluene-sulfonic acid.

a one-pot fashion increasing the operational simplicity of the approach. Furthermore, diastereoselective dihydroxylation of the dihydropyrans **3d,e** was performed. In such a manner, tetrahydropyrans **7a,b** containing five contiguous stereogenic centers were obtained as single diastereoisomers. Notably, a quaternary stereogenic center, bearing a hemiacetal moiety was introduced in this reaction. The high diastereoselectivity of both processes indicates that the C-4 aryl substituent plays an important role on the stereochemical outcome of these reactions. It can be assumed that the dihydropyran ring reacting in its half-chair conformation is approached from the face opposite to the C-4 substituent.

Further application studies were focused on the possibility to construct an additional 6-membered ring through a Friedel–Crafts reaction (Scheme 5).



Scheme 5. Utilization of **3 r** for the diastereoselective construction of polycyclic framework **9**.

Owing to the presence of an electron-rich aromatic moiety, dihydropyran 3r was chosen as the model substrate for this attempt. It was found that a sequence of reactions involving Wittig olefination of the aldehyde group in 3r with a stabilized ylide 8 followed by Lewis acid promoted Friedel– Crafts reaction on the electron-deficient alkene moiety introduced in the first step afforded the corresponding polycyclic compound 9 in high overall yield. Furthermore, the diastereoselectivity of the cyclization was good.^[14] The absolute configuration of the products was unambiguously assigned by single-crystal X-ray analysis of **7b** (Scheme 6, top).^[15] To explain the stereochemical outcome, a transition state model was proposed, and the plausible



Scheme 6. Absolute configuration assignment (C gray, O red, Br orange, H white) and mechanistic considerations.

reaction mechanism is outlined in Scheme 6 (bottom). It is postulated that initial condensation of the aminocatalyst 5 with the α,β -unsaturated aldehyde followed by deprotonation/isomerization leads to the formation of the corresponding dienamine intermediate 10. Subsequently, heterodiene 2, reacting in its s-trans conformation, is recognized by the squaramide moiety of the catalyst through H-bonding interactions with its α -ketoester functionality. In such a manner, the two reagents become independently activated—the α,β unsaturated aldehyde through HOMO activation and the β , γ unsaturated α-ketoester through LUMO lowering. Moreover, they are positioned in close spatial proximity, which further facilitates the cycloaddition step. Interestingly, the π -stacking interactions between the aromatic moieties of heterodiene 2 and the dienamine intermediate are postulated to play an important role contributing to the stabilization of the transition state. Furthermore, the H-bonding interactions with participation of the α -ketoester moiety align the diene above the remote double bond of the dienamine system. Thereby, heterodiene 2 undergoes regioselective 3,4-reaction with the dienamine from the side of the squaramide directing group. Importantly, by taking into account the observed diastereoselectivities of the reaction, a step-wise mechanism of the developed inverse-electron-demand hetero-Diels– Alder reaction can be assumed. This proposal is in accordance with earlier calculations for the related formal [2+2] cycloaddition.^[10a]

In summary, the first H-bond-directed inverse-electrondemand hetero-Diels–Alder reaction proceeding via a dienamine intermediate was developed. Under optimized reaction conditions, the corresponding dienamine species underwent regio- and stereoselective functionalization at the remote double bond, five bonds away from the stereogenic center of the catalyst, to give dihydropyran derivatives bearing three contiguous stereogenic centers. High stereoselectivities were obtained by employing a bifunctional squaramide-containing aminocatalyst, and the rationalization for the stereochemical outcome of the reaction was provided. Furthermore, the possibility to employ the introduced chiral framework for the synthesis of tetrahydropyrans as well as polycyclic compounds was demonstrated.

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- [15] See the Supporting Information for the crystal structure. CCDC 899243 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data_request/cif.