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Asymmetric Catalytic Aza-Diels-Alder/Ring-Closing Cascade Reaction Forming Bicyclic Azaheterocycles via Trienamine Catalysis

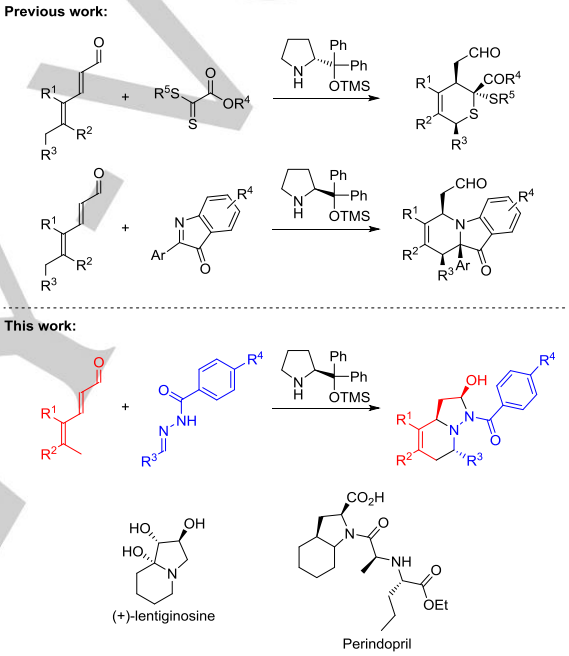
Yang Li,[a] Casper Barløse,[a] Julie Jørgensen,[a] Bjørn Dreiø Carlsen,[a] and Karl Anker Jørgensen*[a]

Abstract: An asymmetric catalytic aza-Diels-Alder/ring-closing cascade reaction between acylhydrazones and *in-situ* formed trienamines is presented. The reaction proceeds through a formal aza-Diels-Alder cycloaddition, followed by a ring-closing reaction forming the hemiaminal ring leading to chiral bicyclic azaheterocycles in moderate to good yield (up to 71%), good enantio- (up to 92% *ee*) and diastereoselectivity (up to >20:1 dr). Furthermore, transformations are presented to show the potential application of the formed product.

Trienamine catalysis has been widely used as a strategy to provide chiral cyclic compounds since this catalytic concept was first established in 2011.[1] Trienamines formed by condensation of an aminocatalyst and 2,4-dienals can react with a variety of dienophiles through a Diels-Alder reaction.[2] In contrast to the development of Diels-Alder reactions based on the trienamine concept, the trienamine catalyzed hetero-Diels-Alder reactions have been much less investigated. According to the best of our knowledge, two examples known are outlined in Scheme 1 (an example of inverse-electron-demand aza-Diels-Alder reaction of 2,5-dienones has also been developed).[3] The first one, is based on the application of dithioester dienophiles leading to a thio-Diels-Alder cycloaddition to generate useful chiral sulfur-containing cycloadducts.[3a] The other example is from the Chen group, who demonstrated that nitrogen-containing tricycles could be constructed through an aza-Diels-Alder cycloaddition applying cyclic imines as the dienophile.[3b] It should also be mentioned that in the latter work aldimines and ketimines were also investigated, but due to their low reactivity or instability, no good reactivity was observed. Thus, it seems to be a challenge to apply linear imines for the [4+2] cycloaddition with 2,4-dienals via trienamine catalysis and we envisioned that applying acylhydrazones as dienophiles might be the solution to this challenge (Scheme 1).

In the following, we will present a novel enantioselective hetero-Diels-Alder reaction of acylhydrazones with trienamines for the formation of azaheterocycles. The reaction proceeds by a formal aza-Diels-Alder cycloaddition, followed by a ring-closing reaction forming the hemiaminal ring. Hydrazones have been applied to construct azaheterocycles through cycloadditions and it has been shown that the reaction takes place at the nitrogen-carbon double bond of the hydrazone affording tetrahydropyridine or δ-lactam rings.[4] In the present work, the second ring-closing step is assumed to generates a more stable end-product and adding more molecular complexity to the product.

Nitrogen-containing heterocycles exist in many biologically active compounds and natural products.[5] The synthesis and study of these compounds have continuously been a challenging and hot topic.[6] The structure of the bicyclic azaheterocycle generated from the present reaction (Scheme 1, bottom) is quite unique and interesting.[7] It has potential as an isosteric skeleton of a natural product (+)-lentiginosine,[8] and the drug Perindopril.[9]



Scheme 1. Trienamine catalysed hetero-Diels-Alder reactions.

The development of the reaction conditions started out with the reaction of the 2,4-dienal **1a** and hydrazone **2a** in the presence of catalyst **3a** in $CHCl_3$ at 40 °C. The reaction only reached 66% conversion after 20 h and **4a** was formed with an enantioselectivity of 63% *ee* (Table 1, entry 1). By adding 0.5 eq. of DABCO, the reaction proceeded faster with almost full conversion, even though slightly lower enantioselectivity was obtained (Table 1, entry 2). This might relevant to the base properties of DABCO that it accelerates the condensation between the catalyst and aldehyde by deprotonating the catalyst, and furnishes the reactive trienamine by deprotonating the doubly unsaturated iminium ion (from the condensation between the catalyst and aldehyde) at ε-position. Moreover, it might also accelerate the ring-closing step by deprotonating the nitrogen involved in the second step.[10] Other solvents were tested with DABCO as an additive, as it was shown that different solvents had an impact on the reaction time and the enantioselectivity (Table 1, entries 3-6). Dichloromethane gave a fast reaction, but low enantioselectivity (Table 1, entry 3). In tetrahydrofuran and toluene, the reaction took longer time and we were pleased to find that higher enantioselectivities were obtained. In both solvents, the reac-

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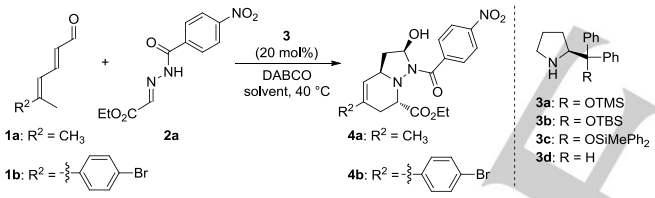
tion reacted to full conversion in 48 h and gave 64% *ee* and 70% *ee*, respectively (Table 1, entries 4,5). The reaction provided even better enantioselectivity in mesitylene, but a much slower reaction time was observed (Table 1, entry 6). Considering the reaction efficiency, we focused on using toluene as the solvent. Different catalysts were also tested (Table 1, entry 7-9). When more bulky silyl protected diphenyl prolinol catalyst **3b** and **3c** were employed, the reactions proceeded slower, and no better enantioselectivities were obtained (Table 1, entry 7,8). Less bulky catalyst **3d** did not give any better result regarding to both the reaction time and enantioselectivity (Table 1, entry 9). Furthermore, various reaction conditions and additives were investigated, but no improvement in both reactivity and selectivity were observed. Acidic additives slowed down the reaction at room temperature. Increasing the temperature to 40 °C, acidic additives or Lewis acids, led to a decomposition of the hydrazones. We then turned our attention to test other 2,3-dienals as substrates. When applying 2,4-dienal **1b**, a significantly higher enantioselectivity was obtained. The reaction took 72 h and gave product **4b** in 91% *ee* (Table 1, entry 10). Lowering the amount of DABCO to 20 mol% did not impact the results (Table 1, entry 11). These reaction conditions were used as standard reaction condition for the scope of the reaction. It should be noted that it is difficult to observe the diastereoisomer peaks from the crude NMR, so we focused our attention on improving the enantioselectivity.

Table 1. Screening and optimization of reaction conditions for the cascade reaction.[a]

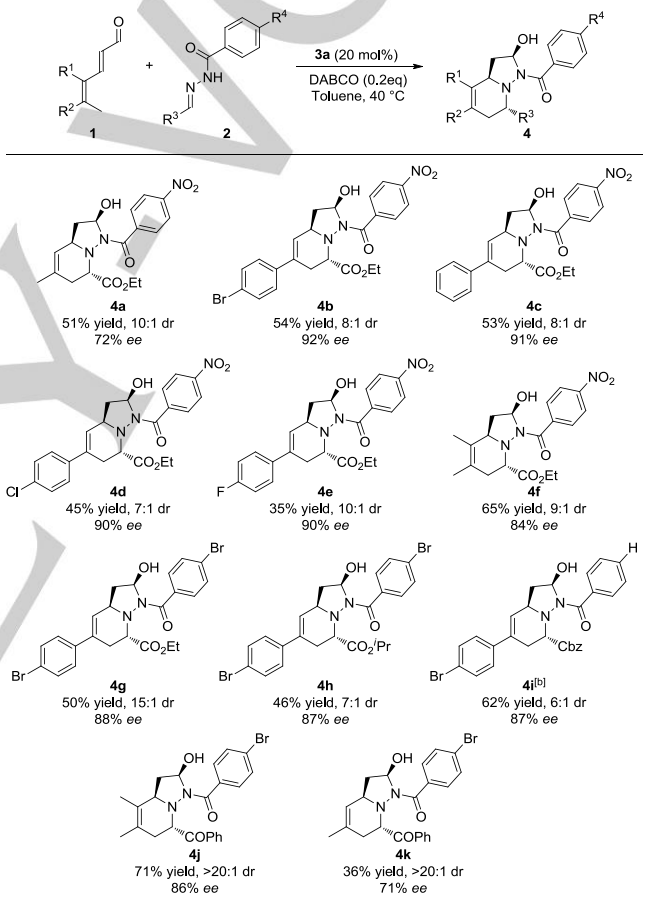


Entry	1	3	DABCO (eq.)	Solvent	T (h)	Conv. (%)[b]	*ee* (%)[c]
1	**a**	**a**	no	$CHCl_3$	20	66	63
2	**a**	**a**	0.5	$CHCl_3$	20	>95	60
3	**a**	**a**	0.5	CH_2Cl_2	24	>95	50
4	**a**	**a**	0.5	THF	48	>95	64
5	**a**	**a**	0.5	toluene	48	>95	70
6	**a**	**a**	0.5	mesitylene	110	>95	80
7	**a**	**b**	0.5	toluene	76	>95	55
8	**a**	**c**	0.5	toluene	110	90	47
9	**a**	**d**	0.5	toluene	72	65	46
10	**b**	**a**	0.5	toluene	72	>95	91
11	**b**	**a**	0.2	toluene	72	>95	91

[a] All reactions were performed using **1a/1b** (0.1 mmol), **2a** (0.05 mmol), **3** (0.01 mmol), 0.25 mL solvent. [b] Conversion of limiting reagent was measured by ^{1}H NMR analysis of the crude reaction mixture. [c] The *ee* value was determined by chiral phase UPC^2.

With optimized reaction conditions in hand, a variety of 2,4-dienals **1** and acylhydrazones **2** were tested to study the scope of the reaction (Table 2). In general, good diastereomeric ratios were obtained after purification. When the screening substrates 2,4-dienal **1a** and acylhydrazone **2a** were applied to the optimized reaction condition, product **4a** was formed with better enantioseletivity (72% *ee*), good diastereoselectivity and yield (Table 1, entry 5; Table 2, **4a**). 2,4-Dienal **1b** gave similar yield and higher enantioselectivity (92% *ee*) as seen in Table 2, **4b**. This gave us a hint that dienals with aromatic substitution at the R^2-position might result in better enantioselectivity, so several aromatic 2,4-dienals were synthesized and tested. Phenyl and *para*-halophenyl substituted 2,4-dienals gave quite consistent enantioselectivities (>90% *ee*) and moderate yields of **4c**-**e**. Finally, a trimethyl-substituted 2,4-dienal was demonstrated to react smoothly and the obtained yield and enantioselectivity of **4f** is higher compared to **4a**.[11]

Table 2. Scope of the trienamine catalysed hetero-Diels-Alder reactions.[a]



[a] All reactions were performed using **1** (0.2 mmol), **2** (0.1 mmol), **3a** (0.02 mmol), DABCO (0.02 mmol) in 0.5 mL toluene. The reported yields are for both diastereoisomers. The *ee* (major diastereoisomer) and dr values were determined by chiral phase UPC^2. [b] Additive DABCO (0.1 mmol) and H_2O (2.0 mmol) were used.

Next, different acylhydrazones **2** were evaluated. It was found that the acylhydrazones with bromo or no substituent at the R^4-position were tolerated (**4g**-**k**). Combining δ-bromophenyl dienal (**1b**) with ethyl and *iso*-propyl glyoxylate aldehyde derived hydrazones, the products **4g** and **4h** were obtained in good yield and enantioselectivity, 88% *ee* and 87% *ee*, respectively. When the benzyl glyoxylate aldehyde derived hydrazone was reacted with aldehyde **1b**, a messy reaction was observed. Applying the standard reaction system to obtain pure product **4i** proved to be difficult. In the early optimizing process, we observed that by

adding water and more DABCO as additives could give a more pure product, even though the selectivities dropped. In this case, we applied the latter reaction conditions to this entry furnishing the corresponding product **4i** in 62% yield 6:1 dr and 87% *ee*. The phenylglyoxal derived hydrazone reacted with aldehyde **1b** sluggishly; however, by applying a trimethyl substituted 2,4-dienal, product **4j** was obtained in good yield and enantioselectivity as one diastereoisomer, while reaction of the dimethyl substituted 2,4-dienal gave **4k** in lower yield and enantioselectivity.

The absolute configuration of the bicyclic azaheterocycle **4k** was established by X-ray crystallography (Figure 1).[12] The remaining configurations were assigned by analogy. It should be noted that the nitrogen atoms are stereocenteres in the crystal state. In the ^{1}H NMR spectra of the products ($CDCl_3$), broadening and unclear peaks were observed, indicating a low barrier of inversion for the nitrogen-nitrogen bond.[13] This was also the main reason for the difficulties to determine the diastereomeric ratio directly by NMR spectroscopy.[14]

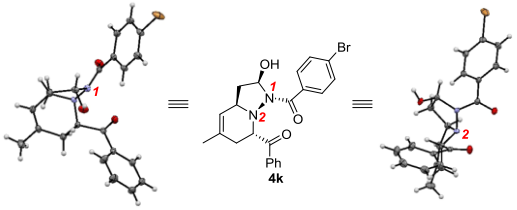
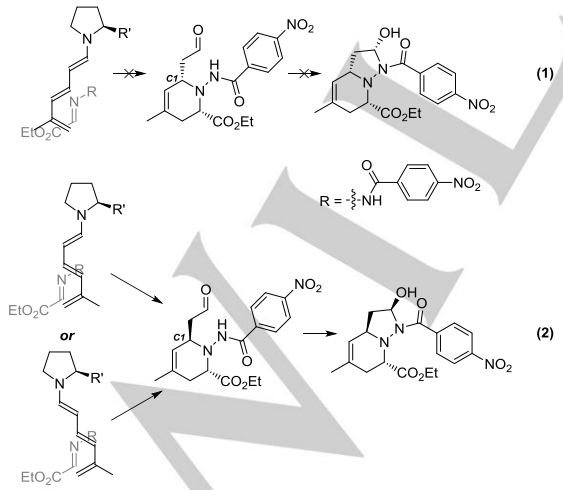


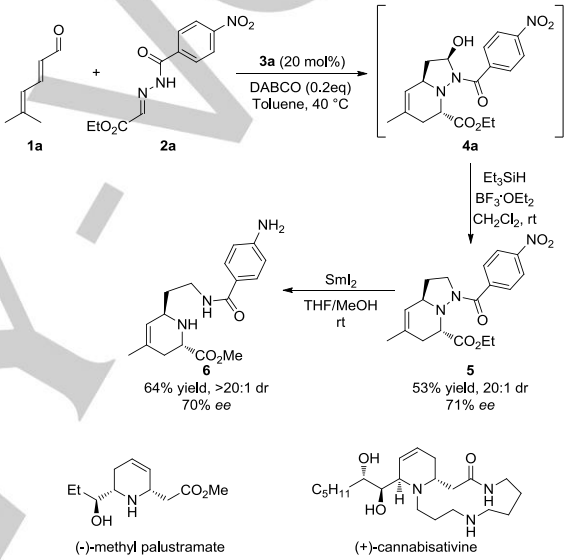
Figure 1. X-Ray structure of **4k**.

The mechanism was expected to proceed by pathway (1) in Scheme 2 which includes the lowest-energy trienamine intermediate.[1] However, the product obtained by this pathway do not provide the right stereochemistry. In order to form the correct stereocenter at the C1-position, two possible trienamine intermediate conformations are given in pathway (2), in which the remote diene will react at the other face, relative to the face reacting in pathway (1). The final step is the formation of the hemiaminal.



Scheme 2. Proposed of the reaction mechanism in which (a) gives the wrong stereochemistry and (b) leads to the observed stereochemistry,

Having established the scope and better understanding of this reaction, a series of transformations were carried out (Scheme 3). A reduction was performed to **4a** in one-pot fashion giving product **5** in 53% overall yield. The obtained enantioselectivity is consistent, while the diastereomeric ratio increased compared to **4a**. This indicates that the diastereoselectivity is mainly generated through the ring-closing step.[15] Samarium(II) iodide was applied to cleave the nitrogen-nitrogen bond. The ring-opened product **6** was obtained in good yield and comparable stereoselectivity along with the transesterification and the reduction of nitro group. The obtained tetrahydropyridine motif is similar to palustrine family,[16] such as (-)-methyl palustramate[17] and (+)-cannabisativeine,[18] and this transformation provides a synthetic strategy towards potential bioactive alkaloids candidates of these natural products.



Scheme 3. Synthetic transformations of **4a**.

In summary, a novel aza-Diels-Alder/ring-closing cascade reaction forming chiral bicyclic azaheterocycles via trienamine catalysis is reported. Acylhydrazone was applied as dienophile to undergo a cycloaddition with *in situ* formed trienamine from an organocatalyst and 2,4-dienals, followed by a hemiaminal ring-closing reaction, leading to the formation of bicyclic azaheterocycles in moderate to good yields (up to 71%) and stereoselectivities (up to 92% *ee* and up to >20:1 dr). The formed bicyclic azaheterocycles and their transformed nitrogen-containing product, can be considered as isosteres or alkaloids of bioactive natural compounds, and might be potentially useful. Finally, the mechanism of the reaction has been discussed and it is postulated that the trienamine intermediate reacts with another geometry of the diene-part compared to what is usually observed.

Acknowledgements

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Keywords: asymmetric catalysis • cycloaddition • heterocycles • organocatalysis • synthetic methods

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[11] It should be noted that the reaction of an aromatic 2,4-dienal substituted with a methoxy group in the *para*-position gave a lot more by-products compared to the other 2,4-dienals and the isolation of the product was not successful.

[12] See Supporting Information for details about X-ray analysis (CCDC: 1405281).

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[14] Some temperature ^{1}H NMR experiments of **4k** have been performed, see Supporting Information for more details.

[15] The same reduction was also performed to **4b**. The obtained product has an increased dr (>20:1) and maintained *ee* (90%). See Supporting Information for more details.

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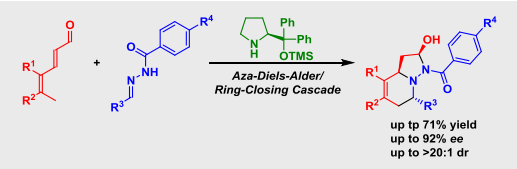

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