Polycycles

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Organocatalytic One-Pot Asymmetric Synthesis of Functionalized Tricyclic Carbon Frameworks from a Triple-Cascade/Diels–Alder Sequence**

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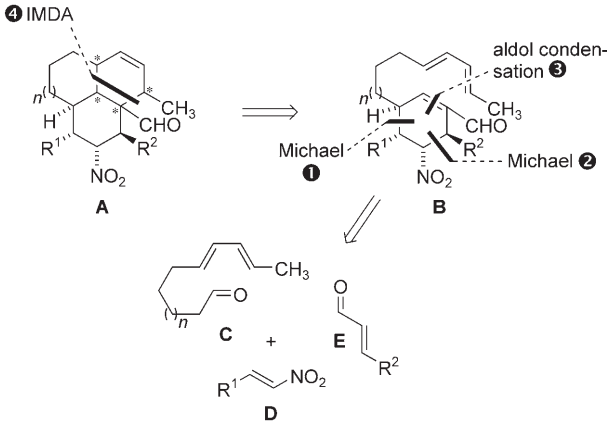
Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

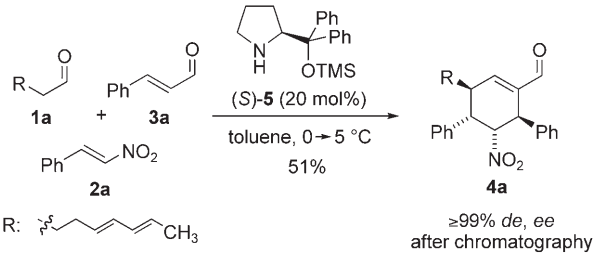
The development of efficient methods for the asymmetric synthesis of complex polycyclic frameworks is an ongoing challenge in preparative chemistry.[1,2] This goal can be accomplished by the use of domino reactions that proceed consecutively and under the same reaction conditions.[2,3b] Thus, the implementation of asymmetric catalysis into domino processes is an important current research area.[2,3] The design of organocatalytic domino reactions[4] is even more appealing, not only because such processes are more efficient than stepwise reactions but also organocatalysts are environmentally friendly, robust, and nontoxic.[5] In particular, chiral secondary amines have been used successfully in cascade reactions because of their two modes of activating carbonyl compounds (enamine and iminium activation).[6] The first example of this strategy in which asymmetric organocatalysts were used originated from Bui and Barbas in 2000.[7] More recently, the research groups of List,[8] MacMillan,[9] and Jørgensen[10] performed two-step domino processes using first iminium and then enamine activation. Shortly after that, we developed a reverse strategy in which the enamine and iminium activation were combined, thus allowing a multicomponent three-step domino reaction.[11]

Based on our previous work, we envisaged a one-pot procedure to construct polyfunctionalized tricyclic carbon frameworks **A**, which contain up to eight stereogenic centers, with high stereocontrol. Such functionalized decahydroacenaphthylene ($n=0$) and decahydrophenalene ($n=1$) carbon cores are typical structural features of diterpenoid natural products, such as the hainanolides and amphilectanes.[12] The retrosynthetic analysis is depicted in Scheme 1. The assembly of the condensed polycyclic structure **A** should be feasible by using the organocatalyzed domino Michael/Michael/aldol condensation sequence[11] starting from the simple aldehyde and nitroalkene substrates **C**–**E**, followed by an intramolecular Diels–Alder reaction (IMDA) of **B**.[13] Ideally the organocatalyzed Diels–Alder reaction would occur directly as fourth step of the cascade.[14]

In a test reaction we investigated the organocatalytic triple-cascade reaction which led to the tetrasubstituted cyclohexenecarbaldehyde **4a** bearing a diene moiety for the IMDA reaction. Following our previously developed protocol,[11] we employed near-stoichiometric amounts of the dienal **1a**, nitroalkene **2a**, and α,β-unsaturated aldehyde **3a** in the presence of the catalyst (*S*)-**5** (20 mol%). To our delight, the reaction smoothly provided the cyclohexene derivative **4a** in good yield (51%) and, after separation from the minor epimer by flash chromatography,[11] in diastereo- and enantiomerically pure form (≥99% *de* and *ee*; Scheme 2). Unfortunately, the domino reaction stopped



Scheme 1. One-pot organocatalytic triple-cascade/Diels–Alder approach to tricyclic frameworks **A** (retrosynthetic analysis).



Scheme 2. Organocatalyzed multicomponent domino reaction. TMS = trimethylsilyl.

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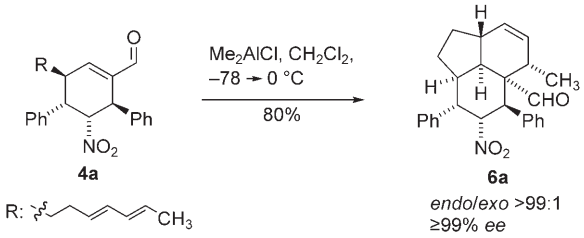
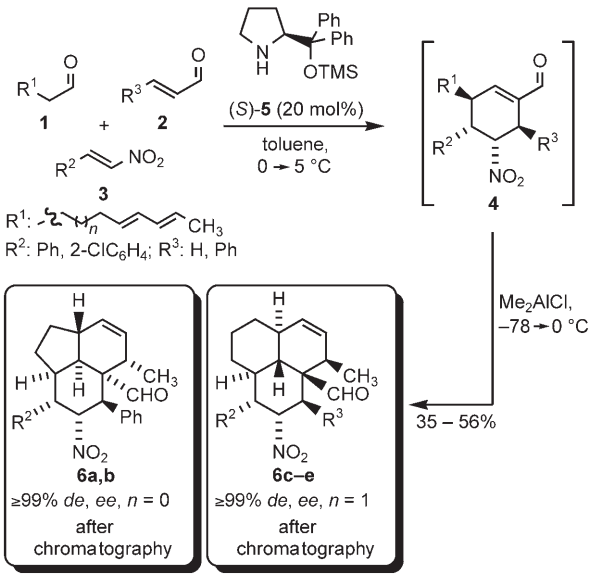
after the third step, and only traces of the [4+2] cycloadduct were detected, probably because of the steric interference between the highly substituted cyclohexene derivative **4a** and the organocatalyst (*S*)-**5**.

We thought of activating the carbaldehyde **4a** with a Lewis acid to facilitate the IMDA reaction. It is well known that similar diene enal systems can be very selectively cyclized through the use of dialkylaluminum chlorides at low temperature.[15] Therefore, **4a** was treated with dimethylaluminum chloride at −78 °C and gradually warmed up the reaction to 0 °C. The isolated cycloadduct **6a** was obtained in 80 % yield and with complete diastereocontrol (*endo*/*exo* > 99:1, ≥ 99 % *ee*; Scheme 3).



Scheme 3. An IMDA reaction mediated by a Lewis acid to afford **6a**.

These results revealed the possibility of combining both protocols in a one-pot reaction to minimize operational demand and thus provide a more practical route to the tricyclic targets **6**. As shown in Scheme 4, the domino reaction was carried out without any change in the reaction conditions. After consumption of the starting materials, the mixture was diluted with dichloromethane and cooled to −78 °C, and an excess of dimethylaluminum chloride was added to ensure complete conversion of the intermediates **4**. When the reaction was complete, the title compounds **6** were successfully isolated after separation of the minor isomers by flash chromatography (Table 1).



Scheme 4. One-pot procedure for the synthesis of the tricyclic carbaldehydes **6**.

Table 1: Results from the one-pot asymmetric synthesis of **6** (Scheme 4).[a]

6	R^2	R^3	*n*	Yield [%][b]	d.r.[c]	*ee* [%][d]
a	Ph	Ph	0	35	5:1:1	≥ 99
b	2-ClC_6H_4	Ph	0	45	12:2:1	≥ 99
c	Ph	Ph	1	56	15:1	≥ 99
d	2-ClC_6H_4	Ph	1	52	11:1	≥ 99
e	Ph	H	1	49	10:1	≥ 99

[a] For a general procedure and the analytical data of **6b**, see the Supporting Information. [b] Yield of isolated products. [c] The *trans*-fused *endo* isomer is the major diastereomer. [d] Determined by HPLC on a chiral stationary phase.

As can be seen from Table 1, the one-pot synthesis was applicable to a range of different substrates, and through variation of the chain length of the residue R^1, the ring size can be adjusted to five- or six-membered rings. We observed very good yields for a four-step procedure (35–56 %). In this process, five new C–C bonds and seven or eight new stereocenters were generated with complete enantioselectivity (≥ 99 % *ee*). The one-pot reaction also generated up to two additional minor diastereomers, which were easily separated by flash chromatography on silica gel. Interestingly, the reactions of structures that consisted of three six-membered rings **6c–e** gave only two diastereomers with a ratio of 10:1 to 15:1, whereas reactions of the more strained structures **6a**,**b** gave three diastereomers in ratios of 5:1:1 to 12:2:1. One of the diastereomers emanates from the triple cascade as an epimer in the position α to the nitro group, the other diastereomer is formed in the course of the IMDA reaction.

The relative and absolute configuration of the complex structures was determined by X-ray analysis of the compound **6b** and also by NOE measurements based on the known configuration of the intermediates **4**. The crystallographic analysis also revealed that **6b** crystallizes as two conformers which differ in the orientation of the *ortho* chlorophenyl substituent. One conformer is shown in Figure 1. The relative and absolute configuration of compound **6b** supports the mechanism that we have proposed earlier,[11] and also the selectivity for *trans*-fused *endo* configuration of the intramolecular cycloaddition promoted by a Lewis acid.[18]

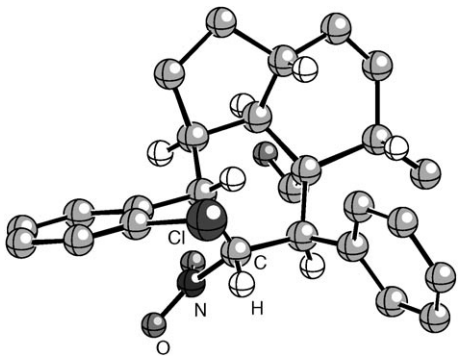
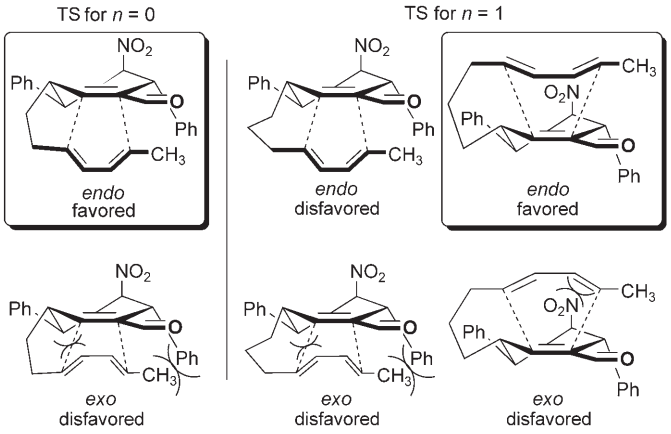


Figure 1. Absolute configuration of **6b** determined by X-ray analysis (Flack parameter $X_{abs} = 0.03(4)$).[16,17]



Scheme 5. Proposed favored transition states (TS in boxes) of the IMDA reaction.

A comparison of the relevant transition states (TSs) of the intramolecular Diels–Alder reaction can explain the observed configuration of the products **6** (Scheme 5). In the case of **4a**,**b** (TS for $n=0$), the diene moiety is more likely to approach from underneath the enal face in an "*endo* manner" (the Alder rule) because of a steric interaction with the phenyl group. The other structures **4c–e** that contain a longer side chain (TS for $n=1$) allow the approach from both beneath and above the enal face, but NOE analyses of the isolated products **6c** revealed that the diene approaches the dienophile from the top. Thus, in both systems, the *trans*-fused *endo* configuration is preferred because of steric interactions with the phenyl substituents and the nitro group.

In conclusion, we have developed an efficient one-pot procedure that provides a direct entry to diastereo- and enantiomerically pure polyfunctionalized tricyclic frameworks, wherein the formation of five C–C bonds and eight stereocenters is controlled. The organocatalytic triple-cascade/Diels–Alder sequence leads to decahydroacenaphthylene and decahydrophenalene cores, which are characteristic structural units of diterpenoid natural products such as the hainanolides and amphilectanes. We are currently investigating the extension of the scope of substrates and also in improvements in the method to reach a fully organocatalyzed procedure.[19]

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