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An Organocatalytic Enamine-Activation of Cyclopropanes for Highly Stereoselective Formation of Cyclobutanes

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Supporting Information Placeholder

ABSTRACT: A novel organocatalytic activation mode of cyclopropanes is presented. The reaction concept is based on a design in which a reactive donor-acceptor cyclopropane intermediate is generated by *in situ* condensation of cyclopropylacetaldehydes with an aminocatalyst. The mechanism of this enamine-based activation of cyclopropylacetaldehydes is investigated by the application of a combined computational and experimental approach. The activation can be traced to a favorable orbital interaction between the π–orbital of the enamine and the $\sigma^*_{C\text{-}C}$ orbital of the cyclopropyl-ring. Furthermore, the synthetic potential of the developed system has been evaluated. By the application of a chiral secondary amine catalyst, the organocatalytically activated cyclopropanes show an unexpected and highly stereoselective formation of cyclobutanes, functionalizing at the usually inert sites of the donor-acceptor cyclopropane. By the application of 3-olefinic oxindoles and benzofuranone, biologically relevant spirocyclobutaneoxindoles and spirocyclobutanebenzofuranone can be obtained in good yields, high diastereomeric ratios and excellent enantiomeric excesses. The mechanism of the reaction is discussed and two mechanistic proposals are presented.

Cyclopropanes are highly strained moieties, which exhibit a remarkable reactivity.[1] The inherent features of cyclopropanes have caused them to be exploited in organic synthesis.[2] Since the late 1970's it has been known that the installation of vicinal donor and acceptor substituents on the cyclopropane increases the reactivity of the C-C bond.[3] The potential of such molecules, which are referred to as donor-acceptor (D-A) cyclopropanes, has only been recognized in more recent years, in which their reactivity and application have become an increasingly popular field of research.[4] Typically, the reaction of D-A cyclopropanes is promoted by a Lewis acid, which increase their electrophilicity by coordination to the acceptor unit. This approach has found application in ring-opening reactions,[5] addition reactions,[6] [3+2]-,[7] [3+3]-[8] and [4+3]-cycloadditions[9] as well as rearrangement reactions[10] (Figure 1, a). The developed methodologies and the asymmetric versions hereof have been applied in the synthesis of biologically relevant compounds.[11]

Within the last 15 years, organocatalysis has been established as the third pillar of asymmetric catalysis.[12] Initial research in the field focused on the development of additions of electrophiles and nucleophiles, *via* enamine[13] and iminium-ion catalysis,[14] respectively. In the following years, other applications of organocatalysis were investigated and established, such as cascade reactions,[15] SOMO-catalysis,[16] activation of poly-unsaturated systems by vinylogous aminocatalysis[17] and application in target-oriented synthesis.[18]

Given the high potential of cyclopropanes in asymmetric catalytic transformations[4-11] and the versatility of organocatalysis we envisioned an unprecedented and useful reaction concept, in which a chiral aminocatalyst would activate a cyclopropane and promote stereoselective reactions of the *in-situ* activated system. A crucial feature in this design would be the installation of appropriate substituents on the cyclopropane. The dormant cyclopropane should carry an acceptor unit as well as a molecular handle in form of an aldehyde functionality. This cyclopropane will remain inert until condensation of the aldehyde with the aminocatalyst by which a donor substituent, an enamine, is formed. An activated D-A cyclopropane has now been generated and might participate in stereoselective reactions due to the presence of a stereoinducing unit in the aminocatalyst.

Herein, we present a novel organocatalytic reaction concept describing the activation of cyclopropylacetaldehydes and their subsequent reactivity in stereoselective reactions. We demonstrate, by applying a computational approach, that the activation of the cyclopropane by a secondary amine catalyst is based on a favorable orbital interaction between the π–orbital of the enamine and the $\sigma^*_{C\text{-}C}$ orbital of the cyclopropane. Following a study of the activation of the cyclopropane, an application in a stereoselective reaction is presented. Interestingly, the optically active product formed does not originate from a [3+2]-cycloaddition at the expected carbon atoms in the cyclopropyl ring. Instead, the unique properties of the organocatalytically activated cyclopropyl functionality provides a product, which is based on a novel stereoselective [2+2]-cycloaddition of the dipolarophile at the usually inert C-C bond in the cyclopropane (Figure 1, b).

The presented approach for activation of cyclopropanes is based on a HOMO-raising strategy and is thus in contrast to traditional approaches based on LUMO-lowering strategies using Lewis acids. Previously applied organocatalytic strategies for activation of D-A cyclopropanes include the application of *N*-heterocyclic carbenes as donor-activating organocatalysts,[19] activation of the acceptor moiety by a boronate urea catalyst[20] and acceptor-activation by an aminocatalyst *via* iminium-ion catalysis.[21] In contrast, this activation strategy represents the first case in which the donor unit of a D-A cyclopropane is generated by the condensation with an aminocatalyst. Furthermore, the synthetic potential of the developed method is highlighted by the ability to participate in stereoselective cycloadditions to form substituted cyclobutane structures. Cyclobutanes are prevalent in natural products and biologically relevant compounds.[22] Futhermore, they have found use as intermediates in synthesis, in which they often allow for facile assembly of larger ring systems *via* strain-releasing fragmentation reactions.[23] The direct access to cyclobutanes *via* asymmetric [2+2]-cycloadditions is a challenging task, since the process is not thermally allowed and photochemical reactions are notoriously difficult to perform stereoselectively.[24] Typically, D-A-cyclopropanes react as 3-atom components[7-9] and the ability to carry out a stereoselective [2+2]-cycloaddition highlights the complementarity of the developed organocatalytic approach to the established methods.

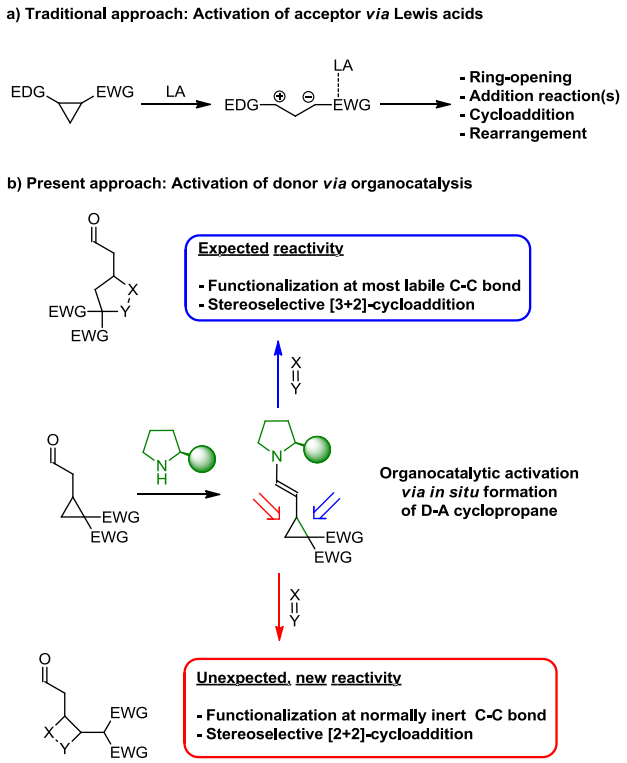


Figure 1: Traditional and the developed organocatalytic approaches for activation of cyclopropanes.

In order to test our hypothesis that the condensation of an aminocatalyst could facilitate the activation of a cyclopropane, we initially investigated a series of model systems by computational methods. Using wB97XD/pcseg-1[25] we calculated the bond lengths of the relevant cyclopropane C-C bonds as a function of the nature of the vicinal substituents on the cyclopropane ring (Figure 2).

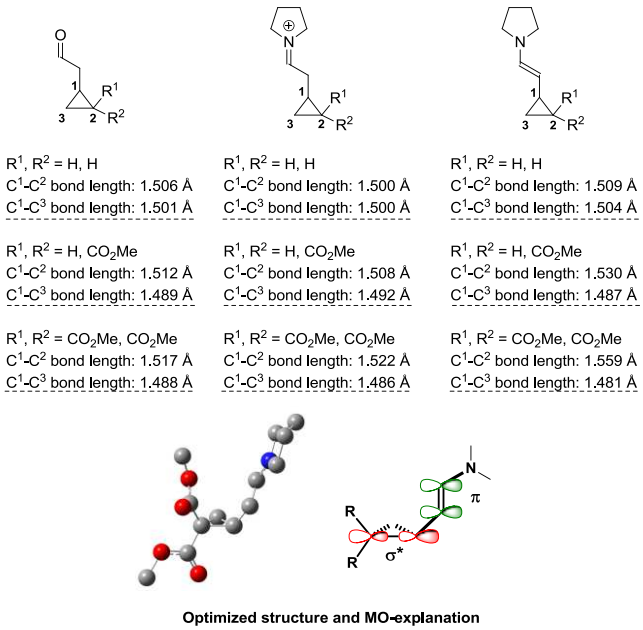
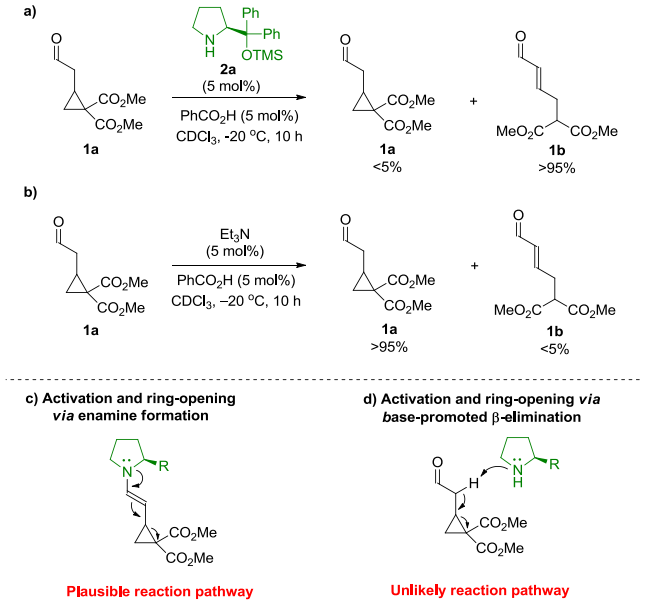


Figure 2: Top: Calculated C^1-C^2 and C^1-C^3 bond lengths for unactivated- and activated cyclopropyl moiety with different acceptor patterns in $CHCl_3$. Bottom: Optimized structure of activated enamine intermediate with R^1, R^2 = CO_2Me and MO-explanation of the activation of the cyclopropyl moiety by the enamine functionality.

Calculation of the C^1-C^2-bond length of the unactivated, iminium- and enamine-activated cyclopropyl moiety with different acceptor patterns in $CHCl_3$ is presented in Figure 2 (see Supporting Information for calculation of the C^1-C^2-bond length in gas-phase, H_2O and further details). The calculated C^1-C^2-bond length in uncondensed cyclopropylacetaldehydes, bearing no, one or two ester substituents as acceptors differentiate only to a minor extend. The same is true for their related iminium-ion activated systems. The most activated systems in these series are the diester substituted cyclopropyl rings (R^1, R^2 = CO_2Me). However, when an enamine is present as the donor functionality of the diester substituted D-A-cyclopropane, the length of the C^1-C^2-bond increases significantly and elongates to 1.559 Å. Therefore, this bond becomes more activated compared to the analogous bonds in the uncondensed cyclopropylacetaldehyde (1.517 Å) and in the iminium-ion-activated system (1.522 Å). These findings are in correspondence with the systematic study by Werz *et al.*, who showed that the cyclopropane C-C bond becomes increasingly labile with more electron-rich donors and more electron-deficient acceptors as the vicinal substituents.[26] It is also notable from the results in Figure 2, that the C^1-C^3-bond is relatively unaffected by the nature of the substituents.

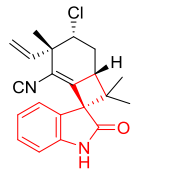
Furthermore, some interesting structural changes take place when forming the enamine from the cyclopropylacetaldehyde. The optimized structure of the enamine-activated cyclopropane is presented at the bottom of Figure 2. For the enamine-activated cyclopropane, the cyclopropyl moiety is rotated to be almost perpendicular to the enamine moiety, compared to the cyclopropylacetaldehyde, in which the C^1-C^2-bond to be activated is in the same plane as the aldehyde functionality (see Supporting Information for details). This rotation allows for a favorable interaction between the π–orbital of the enamine and the $\sigma^*_{C\text{-}C}$ orbital of the cyclopropyl moiety as outlined at the bottom of Figure 2.



Scheme 1: Activation and ring-opening of cyclopropylacetaldehyde **1a** promoted by enamine formation with aminocatalyst **2a**.

Motivated by the computational results, we went on to investigate our design experimentally (Scheme 1). Gratifyingly, we found that racemic cyclopropylacetaldehyde **1a** showed smooth ring-opening to the α,β-unsaturated aldehyde **1b** when mixed with the TMS-protected prolinol catalyst **2a** and benzoic acid (Scheme 1, a).[27] In contrast, aldehyde **1a** was found to be stable in solution when no aminocatalyst was present. We questioned however, whether the ring-opening was facilitated by the formation of an electron-donating enamine (Scheme 1, c) or if the basicity of the secondary amine catalyst was promoting ring-opening *via* a β-elimination pathway as observed in previous studies by Kerr *et al.*[28] (Scheme 1, d). This was tested by replacing the aminocatalyst **2a** with Et_3N, which has basic properties similar to **2a**, but is unable to condense with the aldehyde. In this case, no ring-opening of **1a** was observed (Scheme 1, b). This indicates that the ring-opening indeed takes place by activation through an enamine intermediate. $PhCO_2H$ was added in order to study the system under the same conditions as for the later described [2+2]-cycloaddition. Similar observations were made in the absence of $PhCO_2H$ (for details on these studies, see Supporting Information).

Having ascertained the ability of catalyst **2a** to activate racemic cyclopropylacetaldehyde **1a**, we set out to investigate, if it was possible to use this *in-situ* generated species in subsequent reactions. We were delighted to observe a reaction occurring when 3-olefinic oxindoles were employed; however, the reaction proceeded with an unexpected outcome. Instead of acting as a 1,3-dipole in the expected [3+2]-cycloaddition pathway, the organocatalytically activated cyclopropyl substrate participated, to our surprise, in a [2+2]-cycloaddition yielding a spirocyclobutaneoxindole. Spirocyclic oxindoles are prominent structures, due to their presence in biologically active compounds.[29] More specifically, the spirocyclobutaneoxindole core structure has been found *e.g.* in Welwitindolinone A isonitrile, which has been isolated from blue-green algae *Hapalosiphon welwitschii* and *Westiella intricate* (Figure 3).[30] Following its discovery, it has been the target of a number of total syntheses.[31]

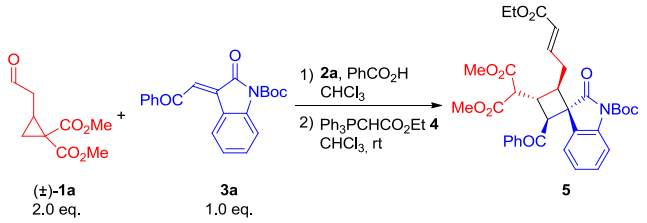


Welwitindolinone A isonitrile

Figure 3: Structure of Welwitindolinone A isonitrile containing the spirocyclobutaneoxindole core (marked in red).

We proceeded to optimize the reaction conditions in order to develop a procedure for the stereoselective formation of spirocyclobutaneoxindoles based on the activation of cyclopropylacetaldehyde **1a** (a one-pot Wittig functionalization was performed after the organocatalytic reaction for handling and characterization purposes). Our initial result revealed that the reaction proceeded in a fast manner and full conversion was achieved in 2 h. The stereoselectivity was promising, although there was room for improvement (Table 1, entry 1). By lowering the temperature to 4 °C, a significant improvement in the enantioselectivity was observed (entry 2). It was found that the diastereoselectivity could be improved by lowering the temperature to -20 °C (entry 3). A further improvement in the diastereoselectivity was achieved by reducing the catalyst loading at the cost of a prolonged reaction time (entry 4). The acid additive did not influence the rate of the reaction to any significant degree; however, when it was omitted a slight drop in diastereoselectivity was observed (entry 5). It was found that it was necessary to use 2 eq. of cyclopropylacetaldehyde **1a** in order to achieve full conversion of 3-olefinic oxindole **3a**.

Table 1: Optimization of the organocatalytic cyclopropane ring-opening and asymmetric cycloaddition of cyclopropylacetaldehyde **1a** with 3-olefinic oxindole **3a**.[a]

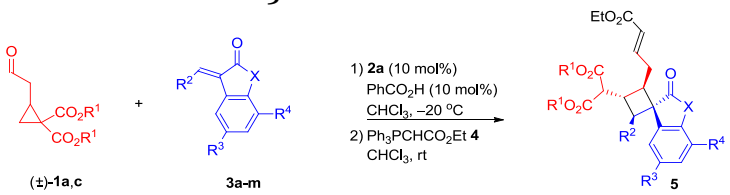


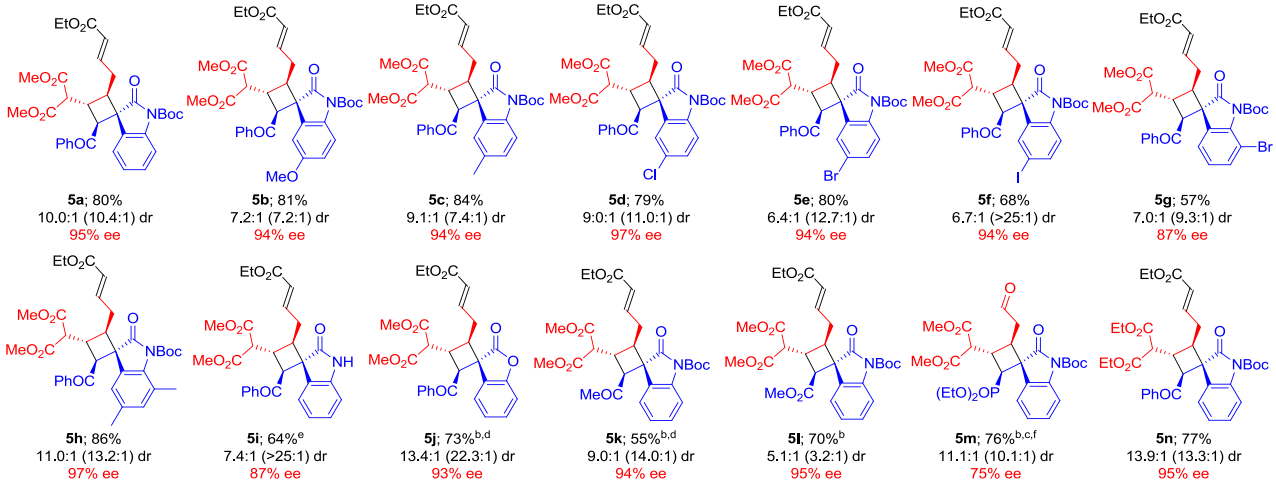
entry	**2a**(mol%)	temp (°C)	time[b] (h)	dr[c]	ee[d] (%)
1[e]	20	rt	2	6.0:1	70
2[e]	20	4	4	6.5:1	94
3	20	-20	18	8.6:1	95
4	10	-20	48	10.0:1	95
5[f]	10	-20	48	8.0:1	95

[a] Experiments performed on a 0.1 mmol scale. Unless otherwise noted, $PhCO_2H$ was employed in the same molar amount as catalyst **2a.** See Supporting Information for details. [b] Required reaction time to achieve full conversion of **1a** or **3a**. [c] Determined by ^1H NMR analysis of the crude mixture before addition of **4.** [d] Determined by chiral stationary phase UPC². [e] 1.5 eq. of **1a** was employed. Full consumption of **1a** was observed with minor amounts of **3a** still present. [f] Reaction performed in the absence of $PhCO_2H$.

With the optimized reaction conditions in hand, we went on to explore the generality of the reaction. Initially structural variations were made on the 3-olefinic oxindole **3** (Scheme 2). The reaction of cyclopropylacetaldehyde **1a** and 3-olefinic oxindole **3a** formed product **5a** in high yield, high diastereoselectivity and an excellent enantioselectivity of 95% ee. Various 5-substituted 3-olefinic oxindoles (**3b-f**) were then employed. It was found that electron-rich substituents such as methoxy and methyl could be installed (**3b**,**c**), furnishing their respective products with similar results (**5b**,**c**). 3-Olefinic oxindoles carrying halogens in the 5-position were also tolerated (**3d-f**) and provided their respective products in high yields, high diastereoselectivity and excellent enantioselectivity (**5d-f**). A 7-substituted (**3g**) and a 5,7-di-substituted oxindole (**3h**) also performed well in the reaction yielding their respective products with similar results (**5g**,**h**). The reaction could be performed with an *N*-unprotected oxindole (**3i**); however, significantly longer reaction time was necessary in order to achieve high conversion due to solubility issues (**5i**). Furthermore, a slight drop in enantioselectivity was observed.

Scheme 2: Scope of the organocatalytic cyclopropane ring-opening and asymmetric cycloaddition of cyclopropylacetaldehyde **1** and 3-olefinic oxindoles and benzofuranone **3**.[a]





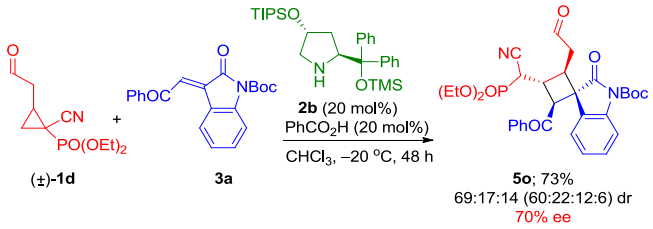
[a] Reactions were performed on a 0.1 mmol scale using 2.0 eq of **1a**. Unless indicated otherwise, the organocatalytic reaction was performed for 48 h and the Wittig reaction for 2.5 h. See Supporting Information for details. The diastereomeric ratios were determined by crude ^1H NMR analysis of the aldehyde intermediate. The values given in parenthesis were found in the isolated products. Enantiomeric excesses were determined by chiral stationary phase UPC². [b] Reaction performed with 20 mol% **2a** and $PhCO_2H$. [c] Reaction performed at 5 °C. [d] 72 h reaction time. [e] 144 h reaction time. [f] Isolated as the aldehyde. The enantiomeric excess was measured after transformation.

Interestingly, the related 3-olefinic benzofuranone dipolarophile **3j** also performed well in the reaction, yielding product **5j** in a good yield, high diastereoselectivity and excellent enantioselectivity. The substituent on the olefinic moiety of the oxindole proved to be quite influential on the reaction. Oxindole **3k** carrying a methylketone performed similarly in terms of stereoselectivity, although a slightly lower yield was obtained (**5k**). Oxindoles carrying an ester (**3l**) or a phosphonate (**3m**) could be applied, albeit a drop in diastereoselectivity or enantioselectivity, respectively, was observed (**5l**,**m**). The reaction was also investigated for cyclopropylacetaldehyde **1c** carrying ethyl esters, by which similar results to the model substrate were achieved (**5n**).

It should be noted that the Boc-group in the oxindole can be removed in quantitative yields by standard methods.

In order to further expand the scope of the developed reaction, it was decided to investigate whether non-carbonyl acceptors could be employed in the cyclopropane aldehyde. Furthermore, we found it intriguing to test the performance of aldehydes carrying two different acceptors in the reaction. This substitution pattern would give rise to an additional stereocenter, which could potentially be difficult to control. For this reason cyclopropylacetaldehyde **1d** was synthesized and employed in the reaction. Gratifyingly, when catalyst **2b** was applied,[32] the product **5o** was formed in a good yield and with a good control of the distribution of the three diastereomers observed in the crude reaction mixture (Scheme 3). Upon purification a minor amount (6%) of a fourth diastereomer was observed. The major diastereoisomer was obtained in 70% ee.

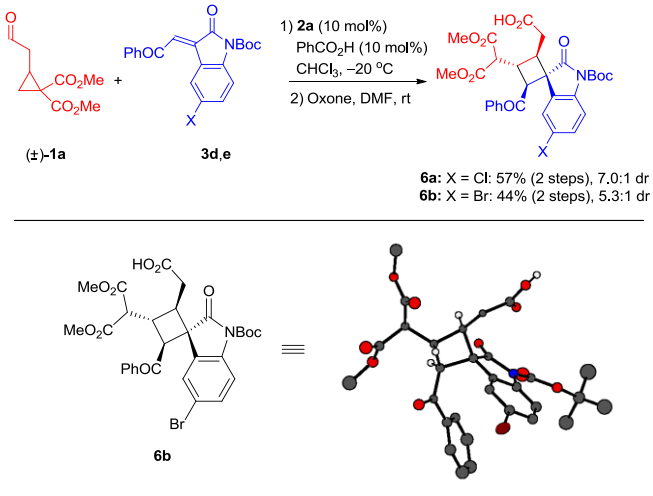
Scheme 3: Organocatalytic cyclopropane ring-opening and asymmetric cycloaddition of cyclopropylacetaldehyde **1d** and 3-olefinic oxindole **3a**.[a]



[a] Reaction was performed on a 0.1 mmol scale. The diastereomeric ratios were determined by crude ^{1}H NMR analysis of the aldehyde intermediate. The value given in parenthesis was found in the isolated product. Enantiomeric excess for the major diastereoisomer was determined by chiral stationary phase UPC^2 after transformation. See Supporting Information for details.

At this point, our attention turned towards establishing the absolute structure of the products. In this regard, it was found that the crude aldehyde mixture could be oxidized to form compounds **6a** containing a carboxylic acid in decent overall yields.[33] By recrystallization of **6b**, crystals suitable for X-ray analysis were obtained, and it was possible to determine the absolute configuration of this compound.[34] The configuration of the remaining products was assigned by analogy assuming a common reaction pathway.

Scheme 4: Formation of products **6a** and **6b** and X-ray crystal structure of **6b**.[a]

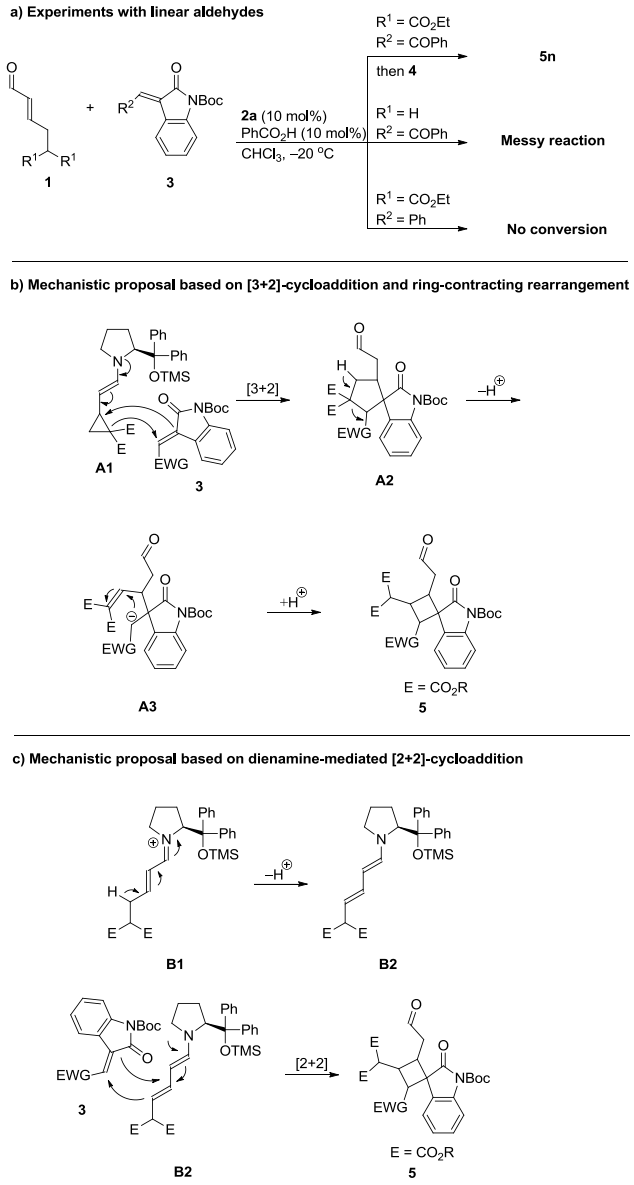


[a] Reaction was performed on a 0.1 mmol scale. See Supporting Information for details.

Finally, our attention turned towards the mechanism of the reaction, which was intriguing given the unexpected reaction outcome. In order to gain a better understanding of the reaction, some experiments with linear α,β-unsaturated aldehydes were performed (Scheme 5, a). When the ring-open isomer of cyclopropylacetaldehyde **1c** was employed in the reaction, product **5n** was formed in similar results. This indicates that the reaction can proceed through an organocatalytic ring-opening of the cyclopropane (see Scheme 1, c). When *trans*-2-pentenal was employed as the α,β-unsaturated aldehyde under the reaction conditions a messy reaction was observed. This result indicates that the diester functionality has an important influence on the reaction outcome. Furthermore, it was found that an electron-withdrawing substituent on the 3-olefinic oxindole was essential for the reaction, since no reaction was observed, when this functionality was not present. These observations open up for two possible mechanisms for the formation of the spirocyclobutaneoxindole. An initial [3+2]-cycloaddition may take place between the 3-olefinic oxindole **3** and the organocatalytically activated cyclopropane **A1**. Subsequently, a ring-contracting rearrangement of the spirocyclopentane oxindole **A2** may take place to form the spirocyclobutaneoxindole product **5** *via* an initial deprotonating ring-opening to form **A3** followed by a conjugated addition of the carbanion (Scheme 5, b). Although ring-contracting rearrangements have previously been a successfully applied strategy in the synthesis of Welwitindolinone A isonitrile,[31a,c,e] this mechanism seems unlikely in this case, since there is no obvious driving force for the ring-contracting rearrangement.

Another plausible mechanism involves the organocatalytic activation of the cyclopropyl functionality leading to

the formation of the iminium-ion intermediate **B1** by a ring-opening. From this intermediate a dienamine **B2** can be formed by deprotonation. This dienamine intermediate may then react in a formal [2+2]-cycloaddition with the 3-olefinic oxindole **3** to form the spirocyclobutaneoxindole product **5** (Scheme 5, c). This reaction mechanism can be supported by the fact that [2+2]-cycloadditions have been achieved between α,β-unsaturated aldehydes and electron-deficient alkenes by combined amino- and hydrogen-bonding catalysis.[35] Considering the presented experimental results and the literature precedence, the mechanism described in Scheme 5 c is deemed the most probable at the present time.



Scheme 5: a) Experiments with linear aldehydes. b) Mechanistic proposal based on [3+2]-cycloaddition followed by ring-contracting rearrangement. c) Mechanistic proposal based on dienamine-mediated [2+2]-cycloaddition. Condensation and hydrolysis of the amino-catalyst has been omitted for simplicity.

In conclusion, we have disclosed the first example of an organocatalytic enamine-based activation of cyclopropanes. The activation mechanism was first studied by computational methods showing an increase of the relevant C-C bond length in the enamine-activated cyclopropane. This increase was accounted for by a favorable orbital interaction between the π–orbital of the enamine and the $\sigma^*_{C\text{-}C}$ orbital of the cyclopropyl moiety. Subsequently, the results of this computational approach were underlined by experiments towards the enamine-mediated ring-opening of cyclopropylaldehydes in solution using a chiral secondary amine catalyst. The synthetic potential of the reaction was investigated and resulted in the discovery of an unexpected and highly stereoselective cycloaddition reaction leading to optically active cyclobutanes, in which the cyclopropane was functionalized at the usually inert C-C bond. Applying this methodology, a series of spirocyclobutaneoxindoles as well as spirocyclobutanebenzofuranone were obtained in good yields, high diastereoselectivities and excellent enantioselectivities. Finally, the mechanism for the formation of the cyclobutane from the organocatalytically activated cyclopropane is discussed and two mechanistic proposals are presented.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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