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Directing the Activation of Donor-Acceptor Cyclopropanes Towards Stereoselective 1,3-Dipolar Cycloaddition Reactions by Brønsted Base Catalysis

Jakob Blom, Andreu Vidal-Albalat, Julie Jørgensen, Casper L. Barløse, Kamilla S. Jessen, Marc V. Iversen and Karl Anker Jørgensen*

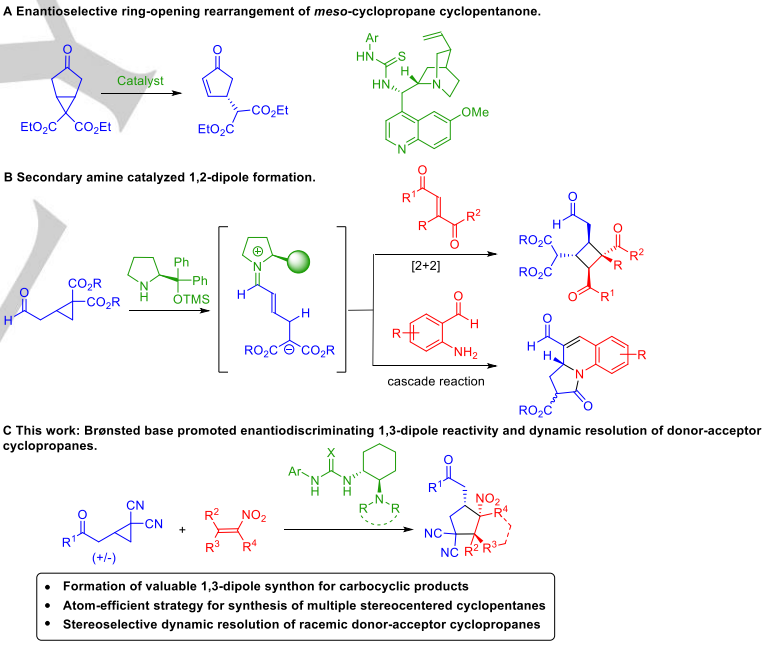
Abstract: The first organocatalyzed stereoselective [3+2] cycloaddition reaction of donor-acceptor cyclopropanes is presented. It is demonstrated that applying an optically active bifunctional Brønsted base catalyst, racemic bis-cyano cyclopropylketones can be activated to undergo a stereoselective 1,3-dipolar reaction with mono- and polysubstituted nitroolefins. The reaction affords functionalized cyclopentanes with three consecutive stereocenters in high yield and stereoselectivity. Based on the stereochemical outcome a mechanism in which the organocatalyst activates both the donor-acceptor cyclopropane and nitroolefin is proposed. Finally, chemoselective transformations of the cycloaddition products are demonstrated.

Cyclopropanes are important organic molecules that display interesting properties in various fields of chemistry. An attractive feature of cyclopropanes is their diverse reactivity towards different reaction types, which has resulted in their use in contemporary organiccy synthesis.[1] The outcome of these reactions is dependent on the substituent pattern of the cyclopropanes and the activation mode.[2]

Although cyclopropanes are thermodynamically unstable, ring-opening and rearrangement reactions of unactivated cyclopropanes require high activation energy and therefore they behave as kinetically stable molecules with limited use as reactants in organic synthesis.[1a] To overcome this limitation, various activation strategies have been developed to release the synthetic potential of cyclopropanes.[2] The introduction of vicinal donor and acceptor substituents attached to the cyclopropyl ring, termed donor-acceptor (D-A) cyclopropanes, promoted the synthetic application of cyclopropanes.[3]

In recent years the major focus on D-A cyclopropanes has been devoted to stereoselective reactions.[3h] The dipolar nature of D-A cyclopropanes allows for both electrophilic and nucleophilic activation. Lewis acid catalysis can promote the activation of D-A cyclopropanes, leading to an increased electrophilic character of the system which has resulted in *e.g.* ring-opening-, addition- and cycloaddition reactions.[2e-f,3h,4] In contrast to the electrophilic activation of D-A cyclopropanes, nucleophilic activation strategies are less common and only little progress has been achieved since the initial work by Reissing[3a-f] and Wenkert.[3g]

The application of organocatalysis has recently led to innovative examples of nucleophilic activation strategies, which has allowed for further development of enantioselective systems. The first enantioselective organocatalytic reaction was a ring-opening rearrangement of a *meso*-cyclopropane cyclopentanone applying a bifunctional quinine-based thiourea catalyst (Scheme 1A).[5] This was followed by activation of cyclopropylacetaldehydes using aminocatalysis leading to two different reactions depending on the reagents (Scheme 1B). The reaction with an activated olefin provides a [2+2] cycloadduct via a dienamine intermediate,[6] while 2-aminobenzaldehydes give nucleophilic addition to an iminium-ion intermediate, causing an iminium-enamine-cascade reaction.[7] According to the best of our knowledge, only two other enantioselective organocatalytic reactions have been presented. One is a NHC-catalyzed activation of a formyl substituted acceptor cyclopropane, trapping the ring-opening of the in situ formed D-A cyclopropane in an hetero [4+2] cycloaddition reaction,[8] while the other is an enantioselective synthesis of 1,3-dichlorides by an electrophilic activation of formyl substituted *meso*-cyclopropanes.[9]



Scheme 1. Selected examples of enantioselective organocatalytic reactions of D-A cyclopropanes through a nucleophillic activation strategy.

The [2+2] cycloaddition in Scheme 1B proceeds via a 1,2-dipole generated at the non-activated carbon-carbon bond in the cyclopropane moiety and previous organocatalytic attempts to develop enantioselective [3+2] cycloadditions across the D-A-activated bond in cyclopropanes has not been achieved.[10] We envisioned that the challenge to develop organocatalytic [3+2] cycloaddition reactions with D-A cyclopropanes might be due to a mis-match of the activation mode with the D-A cyclopropanes chosen. In the present work, we will demonstrate that this challenging reactivity can be achieved by the application of an optically active Brønsted base and bis-cyano-substituted D-A cyclopropylketones (Scheme 1C).

[a] J. Blom, Dr. A. Vidal-Albalat, J. Jørgensen, C. L. Barløse, K. S. Jessen, M. V. Iversen and Prof., Dr. K. A. Jørgensen
Department of Chemistry, Aarhus University
Langelandsgade, DK-8000 Aarhus C, Denmark
E-mail: kaj@chem.au.dk

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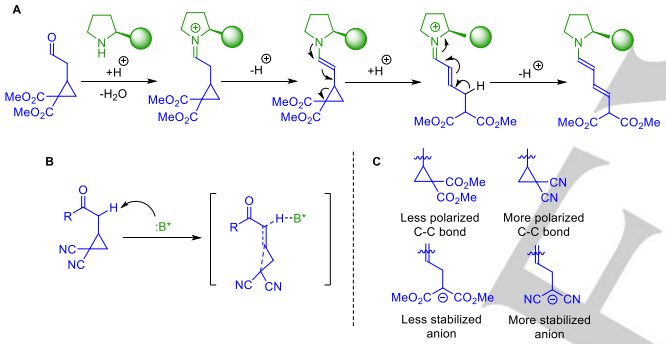
Reaction design: Inspired by the enamine induced activation of the cyclopropylacetaldehyde (Scheme 2A) which provided the [2+2] cycloadduct in Scheme 1B, we questioned if it was possible to facilitate a novel activation mode of the cyclopropylacetaldehyde that promotes the 1,3-dipole, rather than the 1,2-dipole previously observed. The strategy chosen is based on a Brønsted base activation of bis-cyano substituted cyclopropylketones (Scheme 2B). The reason for choosing this less common substrate is that bis-ester cyclopropylacetaldehyde (Scheme 2A) has previously shown limitations towards activation when applying a tertiary amine as the Brønsted-base catalyst[6,11] and so far has only reacted as the 1,2-dipole (vide supra). It was hypothesized that the bis-cyano cyclopropyl analogue would present the desired complementary reactivity. One of the reasons for the differences in reactivity between the bis-ester- and bis-cyano cyclopropane is readable from the ^{13}C NMR shift of the disubstituted carbon atom in the cyclopropyl ring. The chemical shift of the bis-ester carbon is shifted approximately 30 ppm down-field compared to that of the bis-ester analogue (see Supporting Information).[12] Thus, in the bis-cyano system, this carbon atom possesses a higher electron density, indicating an increased polarization of the labile carbon-carbon bond which promotes the 1,3-dipolar character of the system (Scheme 2C). Furthermore, the anion formed from ring-opening of the bis-cyano cyclopropane should be more stabilized than the corresponding bis-ester anion according to the pK_a-values of the related acids (pK_a (DMSO) $MeCH(CN)_2$: 12.5,[13a] pK_a (DMSO) $MeCH(CO_2Me)_2$: 18.0[13b]) (Scheme 2C).

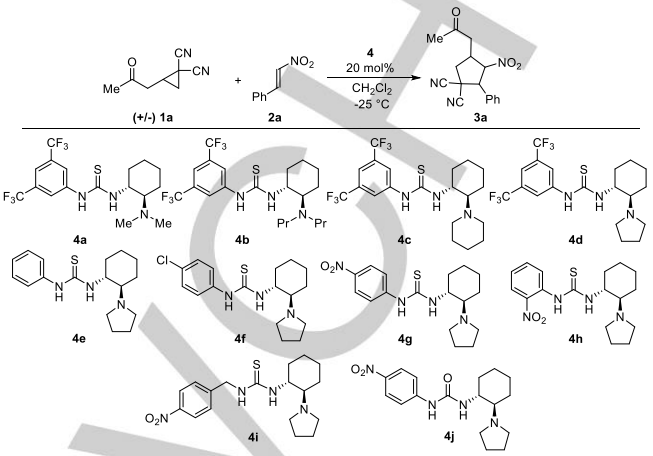


Scheme 2. Comparison of previous nucleophilic activation strategy and this work.

The stereoselective synthesis of multiple functionalized carbocyclic compounds from 1,3-dipole synthons represents an attractive, but challenging synthetic transformation.[14] In this paper, we present the first diastereo- and enantioselective Brønsted base promoted activation of cyclopropylketones, trapping the generated 1,3-dipole in a [3+2] cycloaddition reaction with nitroolefins (Scheme 1C). The strategy is based on a dynamic resolution of racemic D-A cyclopropanes to give highly functionalized cyclopentanes with three stereocenters. Optically active polysubstituted cyclopentanes are common motifs in a wide variety of natural products and bioactive compounds.[14] A varied substituent pattern gives a useful handle to which chemoselective transformations can be performed to further increase the complexity and the synthetic value of the formed cyclopentane products.

The desired [3+2] cycloaddition reaction of racemic cyclopropylmethylketone **1a** with *trans*-β-nitrostyrene **2a** to give cycloadduct **3a** proceeds in the presence of a catalytic amount of Et_3N, while the corresponding bis-ester analogue showed no reactivity under the same conditions (see Supporting Information). Satisfyingly, cycloadduct **3a** was formed in 80% yield and as one single diastereoisomer. In the absent of the base, no product formation was observed. Encouraged by these results, a number of different families of optically active Brønsted bases were tested as catalysts (see Supporting Information).

Table 1. Catalyst optimization towards the enantioselective [3+2] cycloaddition reaction of cyclopropyl methylketone **1a** with *trans*-β-nitrostyrene **2a**.



Entry	Cat.	Reaction times	dr[b]	*ee*[c] (%)
1	**4a**	30 h	>20:1	62
2	**4b**	11 d[d]	>20:1	51
3	**4c**	8 d	>20:1	65
4	**4d**	30 h	>20:1	69
5	**4e**	13 d[f]	>20:1	66
6	**4f**	5 d[e]	>20:1	71
7	**4g**	30 h	>20:1	79
8	**4h**	10 d[d,g]	>20:1	43
9	**4i**	n.r.	n.d.	n.d.
10	**4j**	40 h	>20:1	79

[a] All reactions were performed with 0.05 mmol of **1a**, 0.06 mmol of **2a**, and 20 mol% **4** in 0.50 mL of CH_2Cl_2 at -25 °C. n.r. = no reactivity; n.d.= not determined. [b] Determined from ^1H NMR of the crude mixture. [c] Determined by chiral stationary phase UPC^2. [d] At room temperature instead of -25 °C. [e] 50% conv. [f] 70% conv. [g] 15% conv.

The commercially available bifunctional Takemoto catalyst[15] **4a** gave the most promising enantioselectivity (52% *ee* in CH_2Cl_2 at room temperature) of the initially tested bases. Lowering the reaction temperature to -25 °C increased the enantioselectivity to 62% *ee* (Table 1, entry 1). However, further attempts using **4a** under various reaction conditions did not improve the enantioselectivity (see Supporting Information). Inspired by the bifunctional character of **4a**, a library of bases based on this scaffold was prepared. We first addressed our attention to the tertiary amine moiety of the catalyst. Exchanging the *N,N*-dimethyl with *N,N*-dipropyl (**4b**) resulted in a significant decrease in both the catalyst reactivity and enantioselectivity (Table 1, entry 2). Likewise, implementing a *N*-pipiridyl group as the Brønsted base (**4c**) also led to a less active catalyst, but with a slight increase on the enantioselectivity (Table 1, entry 3). Decreasing the ring size to a *N*-pyrrolidinyl group (**4d**) recovered the reactivity of the catalyst and gave an improvement of the enantioselectivity compared to **4a** (Table 1, entry 4). Next, we centered our efforts towards the H-bond donor moiety in the catalyst by varying the substitution pattern in the aromatic ring. A catalyst with a non-substituted phenyl group (**4e**) was prepared and tested for the model reaction. Unfortunately, despite showing similar results in terms of enantioselectivity, a drastic drop in reactivity was observed (Table 1, entry 5). Introducing a Cl-substituent in the *para*-position (**4f**) led to a minor increase in the enantioselectivity, however, the catalyst still suffered from low reactivity (Table 1, entry 6). We assumed that an increase in the electron-withdrawing ability of the substituents

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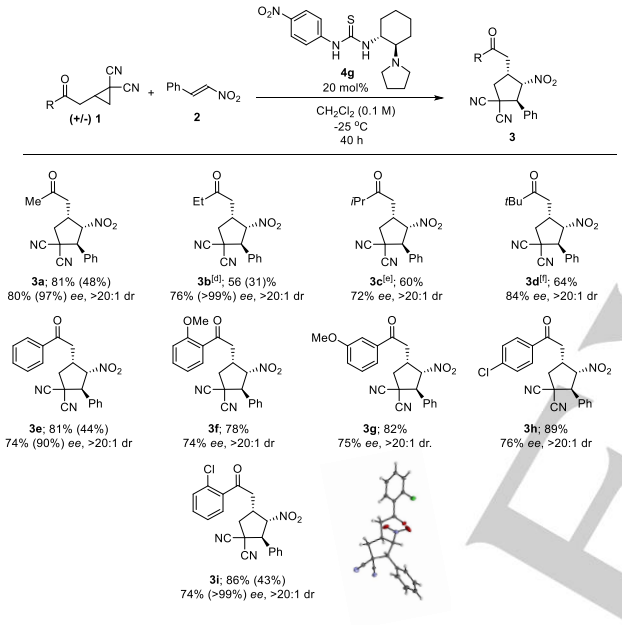
would be correlated with an increase in reactivity and indeed, installing a NO_2-substituent in the *para*-position gave a catalyst (**4g**), which provided full consumption of **1a** within 30 h and gave an enantioselectivity of 79% *ee* (Table 1, entry 7). Changing the position of the NO_2-substituent to an *ortho*-position (**4h**) severely decreased the reactivity and caused lower enantioselectivity (Table 1, entry 8). It is hypothesized that the bulk of the *ortho*-substituent forces the aromatic moiety to position itself out of the plane of the thiourea and that this may cause weaker coordination between substrate and catalyst. The *para*-NO_2-substituted benzylic analogue (**4i**) was inactive (Table 1, entry 9). Finally, substituting the thiourea moiety of catalyst **4g** with the less donating urea (**4j**) gave similar reactivity and enantioselectivity (Table 1, entries 7, 10). As bifunctional thiourea catalysts have been shown to suffer less from aggregation than their urea counterparts,[16] further optimization was based on the *para* NO_2-substituted thiourea catalyst (**4g**).

Table 2. Reaction scope of the Brønsted base catalyzed [3+2] cycloaddition reaction of cyclopropylketones **1** with *trans*-β-nitrostyrene **2a**.



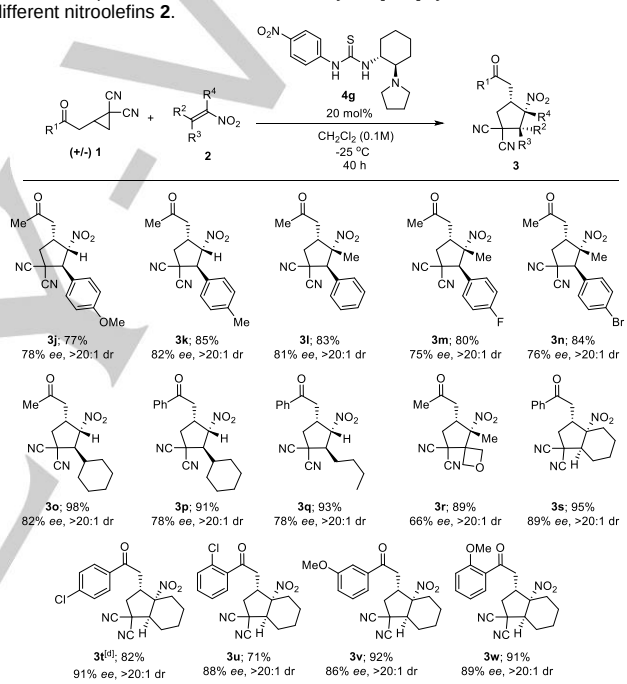
[a] All reactions were performed with 0.20 mmol of **1**, 0.30 mmol of **2a**, and 20 mol% **4g** in 2.0 mL of CH_2Cl_2 at -25 °C; results in brackets: after recrystallization from toluene. [b] Determined from ^{1}H NMR of the isolated products. [c] Determined by chiral stationary phase UPC^2. [d] 71 h. [e] 70 h at 5 °C. [f] 0.30 mmol of **1d** and 0.20 mmol of **2a**, 4 d at room temperature.

Based on the results obtained with catalyst **4g**, further optimization focused on the yield of the reaction and led to a minor change in reaction conditions before the final conditions were obtained (see Supporting Information). The scope of the reaction conditions was investigated on cyclopropylketones **1a-i** (Table 2). We were pleased to find that the [3+2] cycloadducts, **3a-i** were obtained in good yields, high enantio- and diastereoselectivities. The system tolerates both aliphatic and aromatic substituents, though it was observed that increasing the steric hindrance of the ketone substituent led to a less reactive reactant (Table 2, entries **3a**-**d**). We were pleased to observe, that both electron-poor and electron-rich aromatic substituents gave similar results and did not cause limitations in the system (Table 2, entries **3e**-**i**). The enantiomeric excess of the cycloadducts can be improved to give highly enantioenriched products as shown for **3a**,**b**,**e**,**i** by recrystallization from toluene.

The absolute configuration of the products **3**, was determined on the basis of the X-ray crystal structure of the cycloadduct **3i**.

Encouraged by the tolerance towards the different D-A cyclopropylketones, the generality of the system was probed on a scope of different nitroolefins **2** (Table 3). Electron-rich *trans*-β-nitrostyrenes was found to give similar results as nitroolefin **2a**, in the reaction with **1a** (Table 3, **3j**,**k**). Disubstituted nitroolefins allowed not only for the formation of a quaternary stereocenter, but also for the use of electron-poor *trans*-β-nitrostyrenes, while maintaining the high yields and enantioselectivity (Table 3, **3l**-**n**). Aliphatic nitroolefins also underwent a smooth reaction with the D-A cyclopropanes and the cycloadducts were isolated in very high yields (up to 98%) without observing a drop in enantioselectivity (Table 3, **3o**-**q**). The reaction of **1a** with nitroolefin oxetane **2r** gave the spirocyclic cycloadduct **3r**, indicating that trisubstituted nitroolefins are tolerated as well. Finally, 1-nitrocyclohexene was tested in the reaction with the D-A cyclopropylketones **1e**-**i**. To our satisfaction, the more synthetically complex bicyclic products were isolated in high yield and high optical purity (up to 90% *ee*) (Table 3, **3s**-**w**).

Table 3. Scope of the Brønsted base catalyzed [3+2] cycloaddition reaction with different nitroolefins **2**.



[a] All reactions were performed with 0.20 mmol of **1**, 0.30 mmol of **2**, and 20 mol% catalyst in 2.0 mL of CH_2Cl_2 at -25 °C. [b] Determined from ^{1}H NMR of the isolated products. [c] Determined by chiral stationary phase UPC^2. [d] 0.10 mmol of **1**, 0.15 mmol of **2**, and 20 mol% **4g** in 1.0 mL of CH_2Cl_2 at -25 °C.

The experimental results and stereochemical outcome of the reaction promoted us to propose the mechanistic pathway outlined in Scheme 3. Initially, the catalyst acts as a Brønsted base and deprotonates the cyclopropylketone providing the reactive D-A cyclopropane. This acid-base reaction generates the protonated organocatalyst, which now has three hydrogen-bond donors which can interact with the generated enolate and the two cyano groups as shown in Scheme 3 **I**. We expect that the energy differences between the possible hydrogen bonding interactions are low and therefore open up for a high degree of mobility in the coordination sphere of the catalyst.[17] This allows the approach of the nitroolefin to the substrate-catalyst complex **I** from the less hindered face to form intermediate **II**. Now the nitroolefin is activated and in proximity of the nucleophilic carbon of the D-A cyclopropane which promotes the addition to the β-position of the nitroolefin giving intermediate **III**. The final bond formation takes place by the nitronate attacking the cyclopropyl moiety, now acting as the acceptor, affording the product-catalyst complex **IV**.

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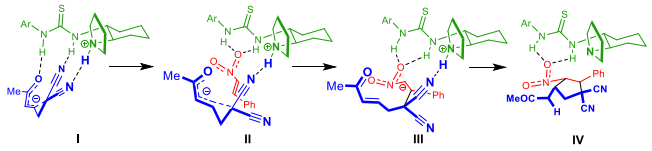
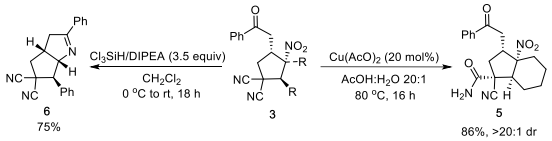


Scheme 3. Proposed mechanistic pathway.

To further expand the synthetic value of the presented methodology, chemoselective transformations of the cycloadducts have been performed. It was found that a Cu(II) catalyzed stereoselective monohydrolysis of one of the two geminal cyano-substituents was possible (Scheme 4). This allows for the formation of amide **5** with an additional quaternary stereocenter formed in 86% yield as a single diastereomer. The relative configuration of the newly formed stereocenter was determined by X-ray analysis (see Supporting Information). Furthermore, we achieved a chemoselective reduction of the nitro group with Cl_3SiH/DIPEA as reducing agent, followed by an intramolecular condensation affording the bicyclic imine **6** in 75% yield.



Scheme 4. Chemoselective transformations of the cycloadducts.

In conclusion, we have presented a new organocatalytic nucleophilic activation mode for D-A cyclopropanes resulting in an unprecedented [3+2] cycloaddition which proceeds in high yield and stereoselectivity. An optically active Brønsted base catalyst promoted the desired 1,3-dipolar reactivity of a series of cyclopropylketones with nitroolefins to give substituted cyclopentanes with three contiguous stereocenters in enantioselectivities up to 91% *ee*. It has been demonstrated that the enantiomeric excess can be increased by recrystallization to >99% *ee*. In addition, we have also presented a proposal for a mechanistic pathway that explains the observed stereoselectivity. Finally, we have shown that the optically active cyclopentanes can undergo chemoselective transformations, *e.g.* a stereoselective reduction of a cyano group to form the corresponding amide and reduction of the nitro group to generate a bicyclic imine.

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Keywords: Asymmetric organocatalysis • Brønsted base catalysis • donor-acceptor cyclopropanes • enantioselective [3+2] cycloaddition reaction • enantiodiscriminating 1,3-dipoles.

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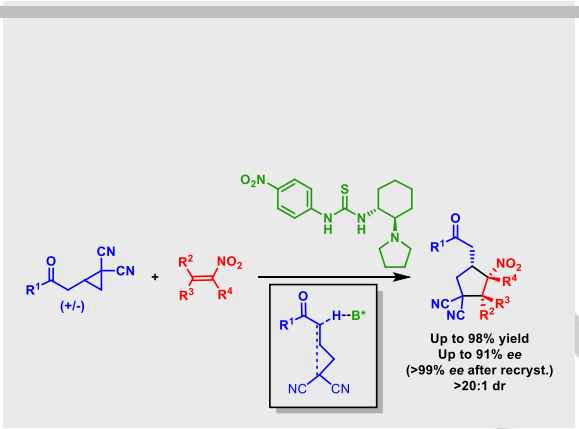

*Jakob Blom, Andreu Vidal-Albalat, Julie Jørgensen, Casper L. Barløse, Kamilla S. Jessen, Marc V. Iversen and Karl Anker Jørgensen**

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Directing the Activation of Donor-Acceptor Cyclopropanes Towards Stereoselective 1,3-Dipolar Cycloaddition Reactions by Brønsted Base Catalysis