Organocatalysis

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Organocatalytic, Asymmetric Eliminative [4+2] Cycloaddition of Allylidene Malononitriles with Enals: Rapid Entry to Cyclohexadiene-Embedding Linear and Angular Polycycles**

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Abstract: *A direct aminocatalytic synthesis has been developed for the chemo-, regio-, diastereo-, and enantioselective construction of densely substituted polycyclic carbaldehydes containing fused cyclohexadiene rings. The chemistry utilizes, for the first time, remotely enolizable π-extended allylidene-malononitriles as electron-rich 1,3-diene precursors in a direct eliminative [4+2] cycloaddition with both aromatic and aliphatic α,β-unsaturated aldehydes. The generality of the process is demonstrated by approaching 6,6-, 5,6-, 7,6-, 6,6,6-, and 6,5,6-fused ring systems, as well as biorelevant steroid-like 6,6,6,6,5- and 6,6,6,5,6-rings. A stepwise reaction mechanism for the key [4+2] addition is proposed as a domino bis-vinylogous Michael/Michael/retro-Michael reaction cascade. The utility of the malononitrile moiety as traceless activating group of the dicyano nucleophilic substrates is demonstrated.*

Six-membered carbocycles, as well as five- and seven-membered rings, are common motifs in nature and they can be found in many terpenoid, polyketide, and shikimate-derived monocyclic and polycyclic molecular architectures.[1,2] The synchronous or stepwise Diels–Alder [4+2] cycloaddition reaction is, no doubt, an effective and rapid avenue to access six-membered rings, a route that nature has admirably pursued and chemists have diligently imitated.[3] Since the advent of modern organocatalysis at the turn of the 21st century, amine-triggered reactions have been at the center of an explosive growth, and culminated in the implementation of myriad of high-impact organic transformations, including efficient and creative organocatalytic [4+2] cycloadditions.[4] Figure 1 (top) shows a possible retrosynthesis of the fused

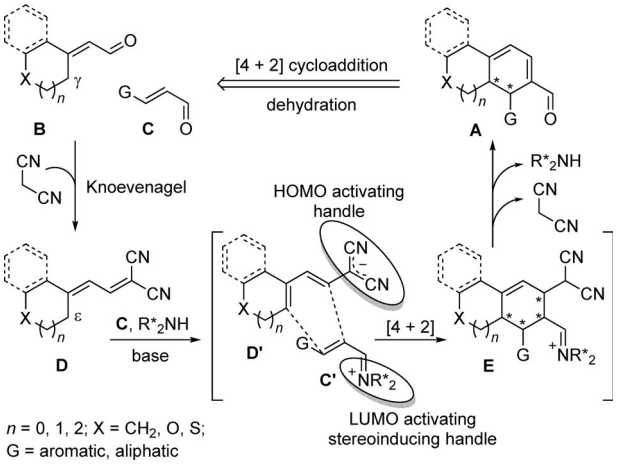

Figure 1. Retrosynthetic analysis of the prototypical cyclohexadiene-containing structures **A** (top) and the allylidene malononitrile-based strategy to access them (bottom, this work).

cyclic structure **A**, with an embedded cyclohexadiene motif, into two elements, **B** and **C**, with **B** (a γ-enolizable α,β-unsaturated carbonyl) acting as the diene precursor and the **C** (an enolizable or non-enolizable enal) serving as the dienophile. Direct [4+2] cycloaddition between **B** and **C** to give **A** seems short and facile. However it is not, especially when the reactivity of the two carbonyl groups is similar. Several challenges are indeed associated with such a cross-cyclizative strategy, with the control of chemoselectivity being a stringent issue. To avoid the competition of alternate reaction pathways, such as self-condensations or reversal in the addition, one should distinguish a priori which is the diene component and which is the dienophile, so that the process can proceed cleanly and productively.

Even with these challenges, direct, intermolecular [4+2] cycloadditions merging two α,β-unsaturated carbonyls have

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been achieved with success, notably in the dienamine- or trienamine-triggered catalytic modalities, where maximum selectivity was attained when the reactivity of the two reaction partners was properly differentiated.[5–8] Despite these achievements, a truly viable and general approach to chemo- and stereoselectively merging two similarly reactive α,β-unsaturated carbonyls remains elusive. Hence, we became interested in designing a reliable organocatalytic strategy which could impart precise assignment of the roles between the reaction components, and would subsequentially react in a chemoselective, asymmetric aminocatalytic cycle to produce a single product.

Following this ideal, we planned to temporarily alter the carbonyl reactivity of one α,β-unsaturated component (e.g., **B**) with a malononitrile handle by a Knoevenagel reaction (Figure 1, bottom), a modification that would arguably render the deprotonation at its remote ε-position much easier than that of the other participant (e.g., **C**). Thus, the formed doubly unsaturated malononitrile **D**, a surrogate of **B**, would decidedly work as a nucleophilically activated diene (**D′**), with the second partner playing the role of the dienophile, thereby largely avoiding any selectivity concern. Once the cycloadduct **E** formed, release of the amine catalyst along with the malononitrile handle would deliver the targeted polycyclic skeleton **A**.[9,10] The high competence of this approach was herein demonstrated by targeting several carbo- and hetero-polycycles, all featuring a fused cyclohexadiene carbaldehyde framework. The utility of the dicyano moiety was also demonstrated by direct one-pot executions, where the present malononitrile-based procedure was compared to the traditional carbonyl cross-coupling reaction.

At the outset of our study we synthesized the cyclohexanone-derived allylidene malononitrile **1a** and screened its capability in a [4+2] cycloaddition with cinnamaldehyde (**2a**; Figure 2 and Table 1) under the catalysis of several chiral

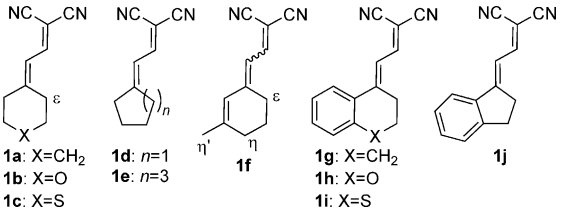
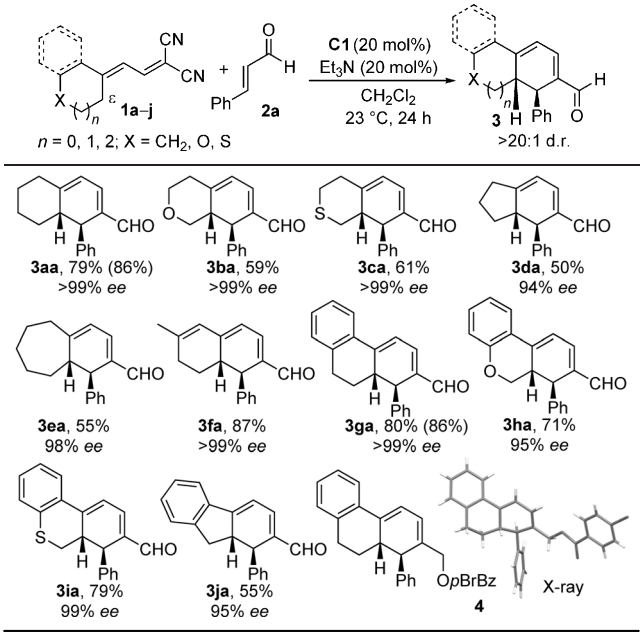


Figure 2. Structures of the pro-diene dicyano substrates **1** of this study.

secondary amines. After extensive optimization studies (see the Supporting Information for details), it was found that treatment of **1a** and **2a** (1.0:1.8 mol ratio) with the L-prolinol TMS-ether **C1**[11] (20 mol%) and Et_3N (20 mol%) in CH_2Cl_2 at room temperature gave the expected naphthalene-type carbaldehyde **3aa**[12] in 79% yield, greater than 20:1 d.r., and greater than 99% *ee*.

After having optimized reaction conditions for the eliminative [4+2] cycloaddition, the scope of the methodology was evaluated. First, various carbocyclic and heterocyclic allylidene malononitriles with diverse ring features and

Table 1: Scope of the direct amine-catalyzed vinylogous asymmetric [4+2] cycloaddition varying the donor component.[a–d]



[a] Additional reaction conditions: **1a** (0.25 mmol, 1.0 equiv), **2a** (1.8 equiv), $[\mathbf{1a}]_0 = 0.2$ M, in air. [b] Yields refer to the isolated products **3**. Yield of **3** obtained on a 5× scale is reported within parentheses. [c] Diastereomeric ratio (d.r.) determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Enantiomeric excess (*ee*) determined by HPLC analysis using a chiral stationary phase. *p*BrBz = *p*-bromobenzoyl.[14]

substitutions were examined. Gratifyingly, the monocyclic and bicyclic substrates **1a–f** and **1g–j**, respectively, easily reacted with **2a** under the established reaction conditions to deliver the expected naphthalene- or phenanthrene-type carbaldehydes **3aa–fa** and **3ga–ja**, respectively, in moderate to good yields upon isolation, and with outstanding levels of chemo-, diastereo-, and enantiocontrol.[13] In particular, it was pleasing that the dicyano substrate **1f**, embodying a ring with three enolizable sites (ε-, η-, and η′-positions), solely reacted at the ε-site, thus furnishing the adduct **3fa** with complete regio- and stereocontrol. Variously substituted aromatic, heteroaromatic, and aliphatic α,β-unsaturated aldehydes, beyond **2a**, participated in this [4+2] coupling, and these included the *o*-, *m*-, and *p*-substituted aromatic aldehydes **2b–h**, aliphatic 2-pentenal (**2i**), 4-methyl-2-pentenal (**2j**), 2,4-heptadienal (**2k**), as well as the furanyl derivative **2m** (Table 2). By using either **1a**, **1f**, or **1g**, a variety of fused multicyclic carbaldehyde scaffolds were constructed in fairly good yields and with outstanding levels of diastereo- and enantioselectivity. As an exception, the β,β-disubstituted 3-methyl-2-butenal **2l** did not provide the desired cyclohexadiene **3al**, even when forced experimental conditions were applied.

The relative and absolute configuration of the products **3** was assigned as shown in Tables 1 and 2 on the basis of a X-ray crystallographic analysis of the *p*-bromobenzoate ester **4** derived from **3ga** (see Table 1 and Figure S1 in the Supporting Information).[14,15]

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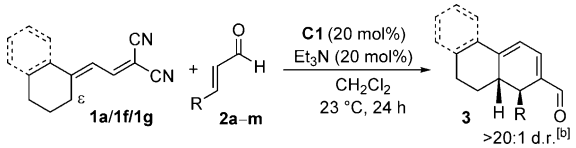
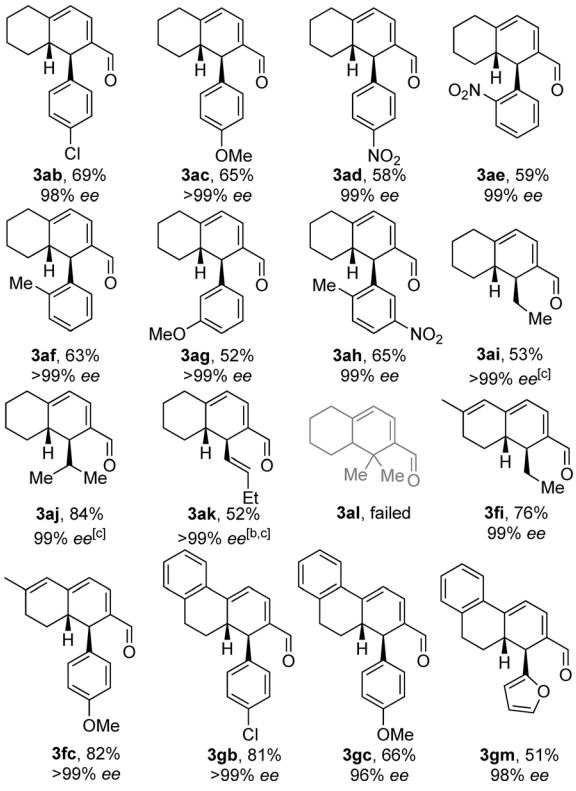
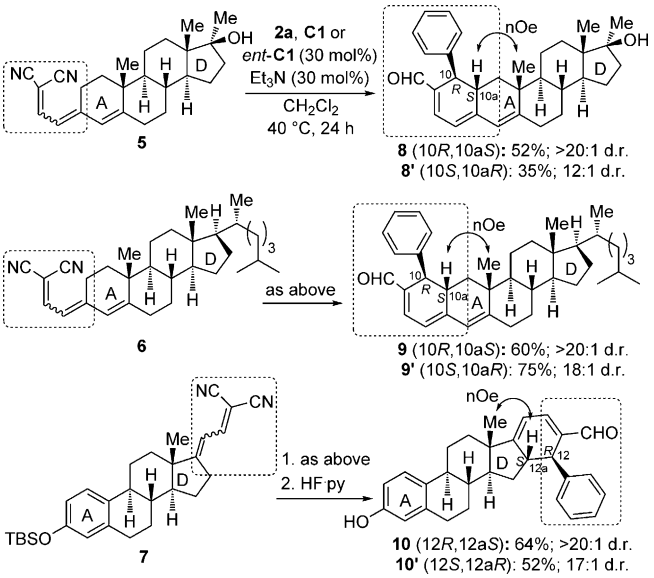
Table 2: Scope of the direct amine-catalyzed vinylogous asymmetric [4+2] cycloaddition varying the acceptor component.[a]





[a] For details, see footnotes [a–d] in Table 1. [b] Compound **3ak** 14:1 d.r. [c] The *ee* values for **3ai**, **3aj**, and **3ak** were determined for the corresponding thiosemicarbazone derivatives (see the Supporting Information for details).



Scheme 1. The amine-catalyzed vinylogous [4+2] cycloaddition as applied to steroid-based allylidene malononitriles.

To further demonstrate the general applicability of this [4+2] eliminative cycloaddition in more challenging scenarios, three tetracyclic steroid-based dicyano substrates (**5**–**7**), respectively derived from commercially available 17α-methyltestosterone, 3-keto-4-cholestenone, and estrone, were used (Scheme 1). By slightly modifying the above optimized standard reaction conditions (30 mol% catalyst loading, 40 °C reaction temperature) the reactions with **2a** were productive and clean and returned the expected ring-A or ring-D-modified steroidal carbaldehydes **8**, **9**, and **10** as the sole detectable isomers in excellent yields. Detailed one- and two-dimensional NMR analyses confirmed the respective stereo-structures as shown, in line with the previously disclosed results with naphthalene and phenanthrene derivatives. As expected, changing *ent*-**C1** (*R*) for **C1** (*S*) produced *trans*-configured isomers **8′**, **9′**, and **10′** with complete reversal of the catalyst-induced chirality.

Interestingly, the modified methyltestosterone **8** did not show any cell toxicity and retained biological activity in a cell proliferation assay. It stimulated human smooth muscle cell expansion, although at a slightly lesser extent than the 17α-methyltestosterone progenitor (see Figure S2).

One-pot reactions based on in situ formation of the allylidene malononitriles were performed, and involved the concomitant addition of the donor aldehyde component (**11** or **12**), **2a**, stoichiometric or even substoichiometric malononitrile, as well as the **C1**/Et_3N catalyst system (Scheme 2). Remarkably, in the presence of 100 mol% of the malononitrile activator the reactions performed well [Eqs. (1) and (3) in Scheme 2], thus giving rise to the expected products **3aa** and **3ga** quite efficiently and stereoselectively, almost in line with the previously disclosed two-step experiments. When substoichiometric malononitrile was used (20 mol%), the reaction gave product **3aa** in 41% yield [Eq. (5) in Scheme 2] after a much longer reaction time (19 days), and is indicative of slow malononitrile recycle. In contrast, control experiments with no malononitrile [Eqs. (2) and (4) in Scheme 2] gave inferior results, thus testifying to the cardinal role of the malononitrile handle in the cycloadditive processes.[16]

A plausible mechanistic scenario for these formal [4+2] eliminative cycloadditions is shown in Figure 3, using substrates **1a** and **2a** for illustrative purposes. First, interaction of **2a** with **C1** is likely to form the chiral iminium species **I**, which can undergo a bis-vinylogous Michael addition[17] with the activated nitrile anion **II** (from remote deprotonation of **1a**) to give the adduct **III**. A favorable Coulombic interaction between the nitrile anion within **II** and the iminium ion **I** could be invoked,[18] thus accounting for a stabilized *endo*-Diels–Alder-like approach. A second intramolecular Michael addition can then occur to give the cycloadduct **IV**, which liberates the prolinol ether catalyst upon hydrolysis and eliminates one mole of malononitrile (by retro-Michael reaction), thus finally delivering **3aa** as the sole product. Overall, the reaction can be viewed as a stepwise domino process involving a bis-vinylogous Michael/Michael/retro-Michael organocascade.[19]

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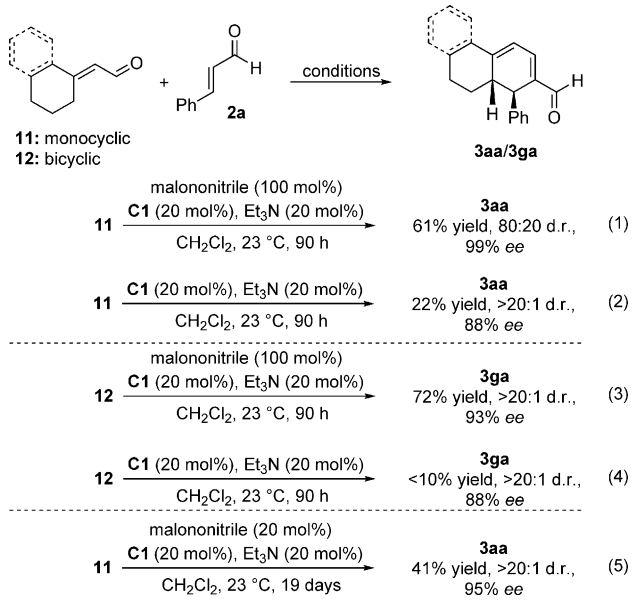

Scheme 2. One-pot malononitrile-driven [4+2] annulations on monocyclic and bicyclic aldehydes **11** and **12**, respectively, and comparison to control experiments.

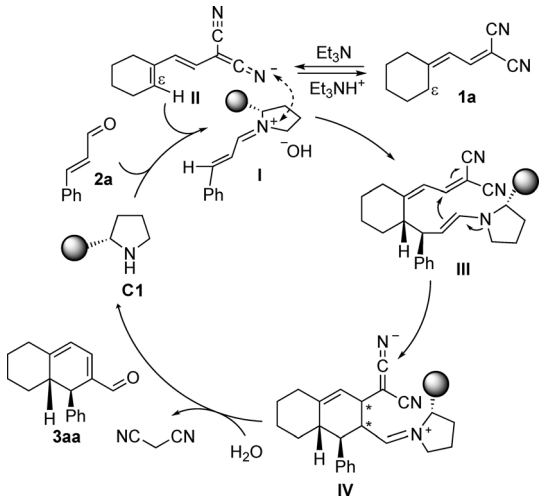

Figure 3. Proposed reaction mechanism for the formal eliminative [4+2] cycloaddition of this study.

In summary, we have developed the chemo-, diastereo-, and enantioselective [4+2] eliminative cycloaddition of extended monocyclic and polycyclic allylidene malononitriles with aromatic and aliphatic enals. The process enables the formation of linear and angular polycycles embedding a cyclohexadiene carbaldehyde frame with uniformly high levels of *trans*-diastereo- and enantioselectivity, even in the case of complex multicyclic steroidal substrates. The proliferative activity of one testosterone-based product towards human smooth muscle cells illustrates the potential of this steroid-transforming technique in a medicinally relevant context. We believe that this catalytic, malononitrile-driven asymmetric strategy may enable further application in structural diversification of other allylidene carbo- and heterocyles bearing remotely enolizable alkyl groups. Additional results will be disclosed in due course.

Keywords: asymmetric catalysis · carbocycles · cycloaddition · organocatalysis · synthetic methods

[1] a) *Dictionary of Natural Products*, Chapmann&Hall, London, **1996**; b) P. M. Dewick *in Medicinal Natural Products. A Biosynthetic Approach*, 2nd ed., Wiley, Chichester, **2002**.
[2] K. J. Hale, *Org. Lett.* **2013**, *15*, 3181.
[3] a) Y. Hayashi in *Cycloaddition Reactions in Organic Synthesis* (Eds.: S. Kobayashi, K. A. Jørgensen), Wiley-VCH, Weinheim, **2001**, chap. 1; b) E. J. Corey, *Angew. Chem. Int. Ed.* **2002**, *41*, 1650; *Angew. Chem.* **2002**, *114*, 1724; c) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem. Int. Ed.* **2002**, *41*, 1668; *Angew. Chem.* **2002**, *114*, 1742.
[4] *Comprehensive Enantioselective Organocatalysis*, *Vol. 1–3* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2013**.
[5] For proline-promoted and/or prolinol silyl ether-catalyzed intermolecular self- and cross-annulations of enals, see: a) B. J. Bench, C. Liu, C. R. Evett, C. M. H. Watanabe, *J. Org. Chem.* **2006**, *71*, 9458; b) B.-C. Hong, M.-F. Wu, H.-C. Tseng, G.-F. Huang, C.-F. Su, J.-H. Liao, *J. Org. Chem.* **2007**, *72*, 8459 (corrigendum: B.-C. Hong, M.-F. Wu, H.-C. Tseng, G.-F. Huang, C.-F. Su, J.-H. Liao, *J. Org. Chem.* **2008**, *73*, 2480); c) B. J. Bench, S. E. Tichy, L. M. Perez, J. Benson, C. M. H. Watanabe, *Bioorg. Med. Chem.* **2008**, *16*, 7573.
[6] For amine-catalyzed intramolecular annulations of α,β-unsaturated dialdehydes, see: R. M. de Figueiredo, R. Fröhlich, M. Christmann, *Angew. Chem. Int. Ed.* **2008**, *47*, 1450; *Angew. Chem.* **2008**, *120*, 1472.
[7] For prolinol silyl ether catalyzed intermolecular [4+2] cycloadditions between α,β-unsaturated aldehydes and ketones en route to steroid compounds, see: K. S. Halskov, B. S. Donslund, S. Barfüsser, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2014**, *53*, 4137; *Angew. Chem.* **2014**, *126*, 4221.
[8] For an example of intermolecular asymmetric [4+2] cycloaddition reaction of enones, see: D. Yang, L. Wang, F. Han, D. Zhao, R. Wang, *Chem. Eur. J.* **2014**, *20*, 8584.
[9] For the use of α,α′-dicyanoalkenes and α,α′-dicyanodienes as vinylogous carbon pronucleophiles, see: a) T.-Y. Liu, H.-L. Cui, J. Long, B.-J. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *J. Am. Chem. Soc.* **2007**, *129*, 1878; b) H.-L. Cui, Y.-C. Chen, *Chem. Commun.* **2009**, 4479; c) L. Dell'Amico, G. Rassu, V. Zambrano, A. Sartori, C. Curti, L. Battistini, G. Pelosi, G. Casiraghi, F. Zanardi, *J. Am. Chem. Soc.* **2014**, *136*, 11107.
[10] For examples of eliminative Michael/Michael/retro-Michael domino reactions, see: a) J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Angew. Chem. Int. Ed.* **2007**, *46*, 389; *Angew. Chem.* **2007**, *119*, 393; b) X. Jiang, B. Tan, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2013**, *52*, 9261; *Angew. Chem.* **2013**, *125*, 9431.
[11] For key references on the use of diphenylprolinol silyl ether catalyst, see: a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794; *Angew. Chem.* **2005**, *117*, 804; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; *Angew. Chem.* **2005**, *117*, 4284; c) H. Hayashi, D. Okamura, T. Yamazaki, Y. Ameda, H. Gotoh, S. Tsuzuki, T. Uchimaru, D. Seebach, *Chem. Eur. J.* **2014**, *20*, 17077.
[12] While the ^{13}C and ^{1}H NMR spectra of **3aa** in our hands are identical to those reported (Ref. [5b]), the optical rotation is rather different in absolute value ($[\alpha]_{22}^{D}=-936.0$ ($c=0.1$ in

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$CHCl_3$, > 99 % *ee*); $[\alpha]_{22}^{D} = -475.9$ ($c = 9.0$ in $CHCl_3$, 98 % *ee*).[5b] Note that the absolute configuration of the product reported in Ref. [5b] was not assigned.

[13] In few instances (e.g. compounds **3da**, **3ea**, **3ia**), scant degradation and/or epimerization occurred during chromatographic purification.

[14] CCDC 1047357 (**4**) 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.

[15] The result is consistent with the stereochemical outcome observed in other reactions in which the catalyst **C1** has been used with α,β-unsaturated aldehydes under iminium ion activation. See, for example: K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248. See also ref. [11c].

[16] For the use of malononitrile as stoichiometric reagent for in situ activation of acceptor components in multicomponent reactions, see for example: V. P. R. Gajulapalli, P. Vinayagam, V. Kesavan, *RCS Adv.* **2015**, *5*, 7370.

[17] For leading references, see: a) G. Casiraghi, L. Battistini, C. Curti, G. Rassu, F. Zanardi, *Chem. Rev.* **2011**, *111*, 3076; b) C. Schneider, F. Abels, *Org. Biomol. Chem.* **2014**, *12*, 3531.

[18] For similar Coulombic interactions see, for example: L. Dell'Amico, Ł. Albrecht, T. Naicker, P. H. Poulsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2013**, *135*, 8063.

[19] For selected reviews on organocatalytic domino/cascade reactions, see: a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; *Angew. Chem.* **2007**, *119*, 1590; b) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167; c) H. Pellissier, *Chem. Rev.* **2013**, *113*, 442; d) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390.

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Communications

Organocatalysis

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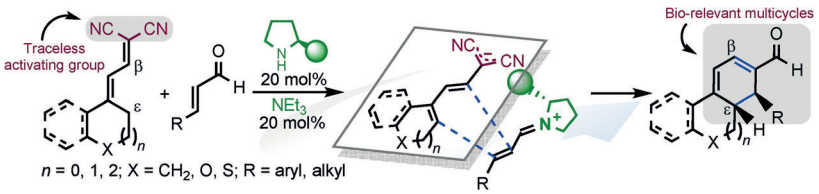

Without a trace: The covalent activation of α,β-unsaturated aldehydes with malononitrile produced remotely enolizable π-extended allylidene malononitriles. Their amine-catalyzed eliminative [4+2] cycloaddition to aromatic and aliphatic enals enabled the construction of cyclohexadiene-containing polycycles with outstanding diastereo- and enantioselectivities. The essential role of the malononitrile handle as a traceless activating moiety was demonstrated.

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