Organocatalysis

International Edition: DOI: 10.1002/anie.201501894
German Edition: DOI: 10.1002/ange.201501894

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

Nicoletta Brindani, Gloria Rassu, Luca Dell'Amico, Vincenzo Zambrano, Luigi Pinna, Claudio Curti, Andrea Sartori, Lucia Battistini, Giovanni Casiraghi, Giorgio Pelosi, Daniela Greco, and Franca Zanardi**

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 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.

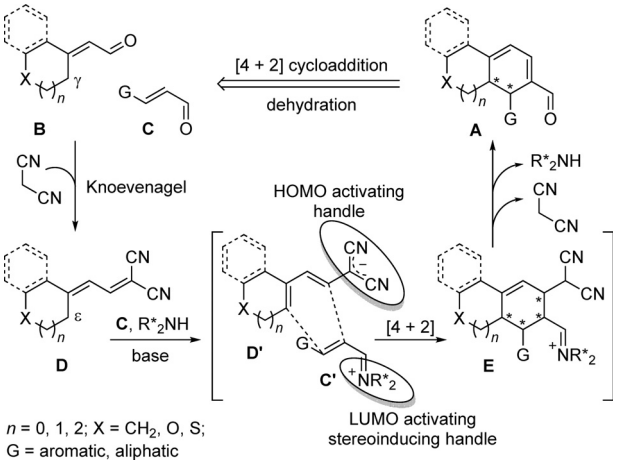


Figure 1. Retrosynthetic analysis of the prototypical cyclohexadiene-containing structures **A** (top) and the allylidene malononitrile-based strategy to access them (bottom, this work).

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

[*] Dr. N. Brindani, Dr. L. Dell'Amico, Dr. C. Curti, Dr. A. Sartori, Prof. Dr. L. Battistini, Prof. Dr. G. Casiraghi, Dr. D. Greco, Prof. Dr. F. Zanardi
Dipartimento di Farmacia, Università degli Studi di Parma
Parco Area delle Scienze 27A, 43124 Parma (Italy)
E-mail: franca.zanardi@unipr.it
Dr. N. Brindani
Dipartimento di Scienze degli Alimenti
Università degli Studi di Parma, Parma (Italy)
Dr. G. Rassu, Dr. V. Zambrano
Istituto di Chimica Biomolecolare
Consiglio Nazionale delle Ricerche
Traversa La Crucca 3, 07100 Li Punti Sassari (Italy)
E-mail: gloria.rassu@icb.cnr.it
Dr. L. Dell'Amico
Institute of Chemical Research of Catalonia, Tarragona (Spain)
Dr. L. Pinna
Dipartimento di Chimica e Farmacia
Università degli Studi di Sassari, Sassari (Italy)
Prof. Dr. G. Pelosi
Dipartimento di Chimica
Università degli Studi di Parma, Parma (Italy)

[**] Financial support provided by the Università degli Studi di Parma is gratefully acknowledged.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201501894.

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

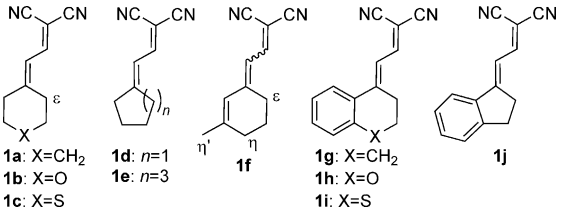
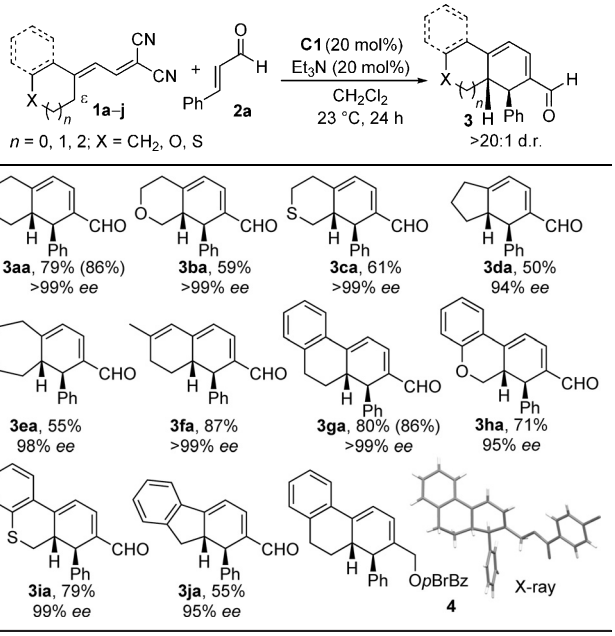


Figure 2. Structures of the pro-diene dicyano substrates **1** of this study.

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]

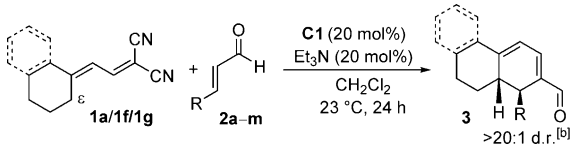


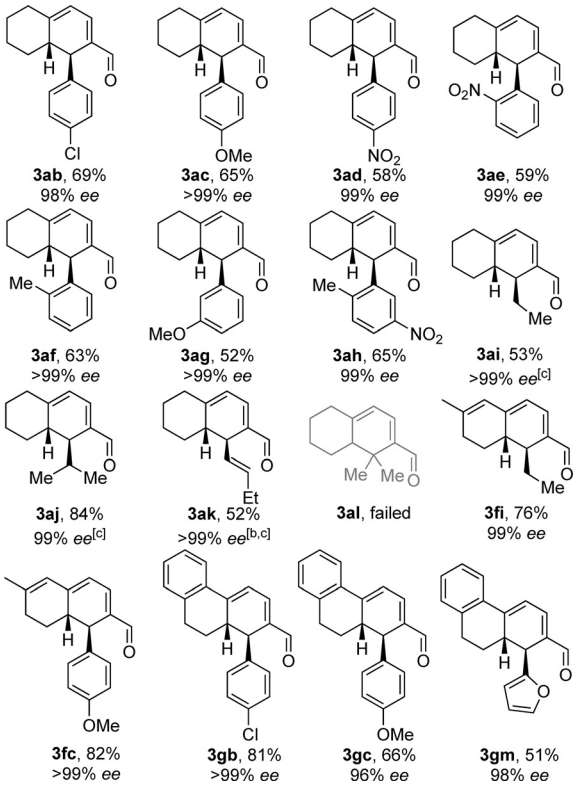
[a] Additional reaction conditions: **1a** (0.25 mmol, 1.0 equiv), **2a** (1.8 equiv), $[\mathbf{1a}]_0 = 0.2$ M, in air. [b] Yields refer to the isolated products **3**. Yield of **3** obtained on a 5× scale is reported within parentheses. [c] Diastereomeric ratio (d.r.) determined by ^{1}H NMR analysis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

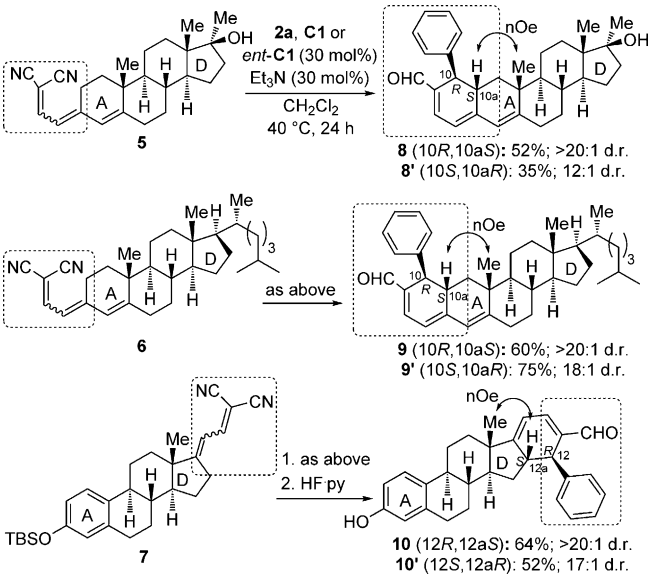
The relative and absolute configuration of the products **3** was assigned as shown in Tables 1 and 2 on the basis of a X-ray crystallographic analysis of the *p*-bromobenzoate ester **4** derived from **3ga** (see Table 1 and Figure S1 in the Supporting Information).[14,15]

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).



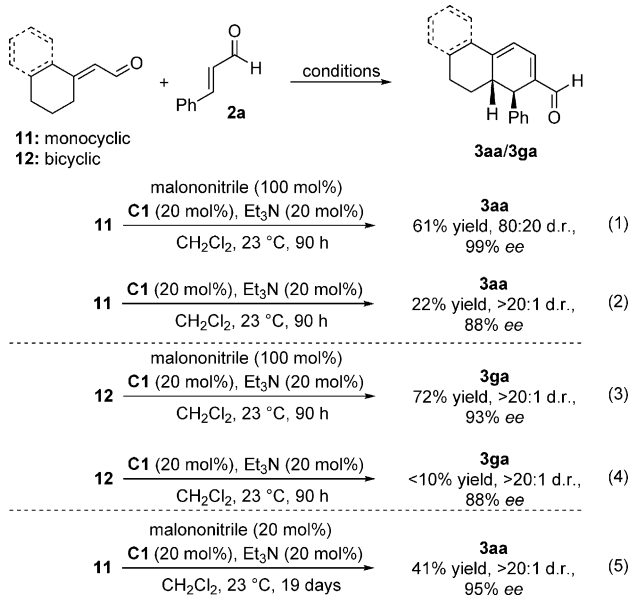
Scheme 1. The amine-catalyzed vinylogous [4+2] cycloaddition as applied to steroid-based allylidene malononitriles.

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]



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

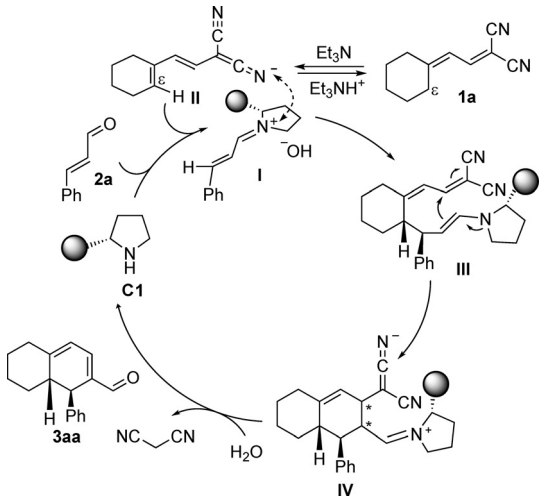


Figure 3. Proposed reaction mechanism for the formal eliminative [4+2] cycloaddition of this study.

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

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 7386–7390
Angew. Chem. **2015**, *127*, 7494–7498

[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

$CHCl_3$, > 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.

Received: February 27, 2015
Revised: March 31, 2015
Published online: May 7, 2015

