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Exploring the Vinylogous Reactivity of Cyclohexenylidene Malononitriles: Switchable Regioselectivity in the Organocatalytic Asymmetric Addition to Enals Giving Highly Enantioenriched Carbabicyclic Structures

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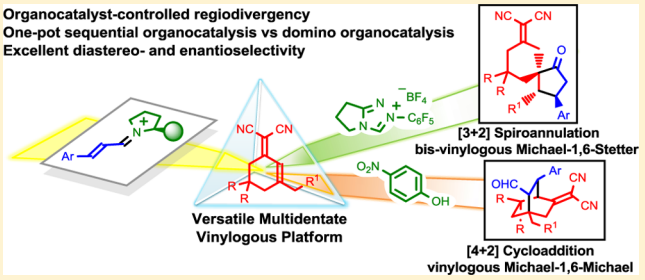
Supporting Information

ABSTRACT: Modulation of the complex reactivity of cyclohexenylidene malononitriles using diverse β-aryl-substituted enals and proper organocatalytic modalities resulted in divergent asymmetric reaction patterns to furnish angularly fused or bridged carbabicyclic frameworks. In particular, use of remotely enolizable dicyanodienes **1**, under one-pot sequential amine/NHC catalysis, led to [3 + 2] cycloaddition to afford ε,δ-bonded spiro[4.5]decanone structures **5**. Alternatively, modifying the standard amine catalysis by adding a suitable chemical stimulus (p-nitrophenol cocatalyst) switched the reactivity decidedly toward a domino [4 + 2] cycloaddition to afford γ',δ-bonded bicyclo[2.2.2]octane carbaldehydes **8**. Products invariably formed in good yields, with rigorous chemo-, regio-, diastereo-, and enantiocontrol. Experimental evidence, including carbon isotope effects measured by ^{13}C NMR, were indicative of the rate (and stereochemistry) determining step of these transformations and suggested a stepwise mechanism for the [4 + 2] cycloadditive pathway.



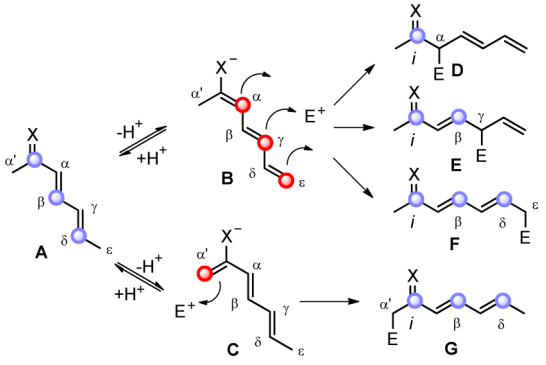
INTRODUCTION

The development of enabling chemical transformations exploiting reaction platforms which embody several orthogonal activation sites with maximum efficiency and chemo-, regio-, and stereocontrol is one of the main challenges at the forefront of organic synthesis. To address those important, often conflicting issues as molecular diversity generation and product selectivity, an ideal protocol would entail the possibility to master a precise reaction itinerary among a wide palette of competing options toward defined, nonrandomized products.

Particularly intriguing in this context are π-extended conjugated electron-poor alkenes of type **A** (Scheme 1), which feature several, alternatively located pro-nucleophilic and electrophilic reaction sites, whose independent and selective activation is desirable. In principle, nucleophilic activation could take place via deprotonation at either remote vinylogous ε- or adjacent α'-positions giving rise to reactive species **B** or **C**.[1] Extended triene **B**, as a multiple $d^2/d^4/d^6$ donor representative, could engage electrophilic addition to either α-, γ-, or ε-positions to ultimate in the corresponding substituted intermediates **D**, **E**, or **F** where the original double-bond sequence of **A** is partially or totally restored.

On the other hand, the cross-conjugated α' enolate **C** could react with competent electrophiles giving rise to dienes **G**. Due to preserved function potentiality, each of these intermediates could then trigger different nucleophilic intermolecular or

Scheme 1. Multisite Reactivity of a Generic Vinylogous Scaffold A[a]



[a]Increasing vinylogy in reagent and products amplifies the reactivity scenario. Blue circles indicate electrophilic sites, and red circles indicate nucleophilic sites; X = O, NR_2^+; *i* = *ipso*

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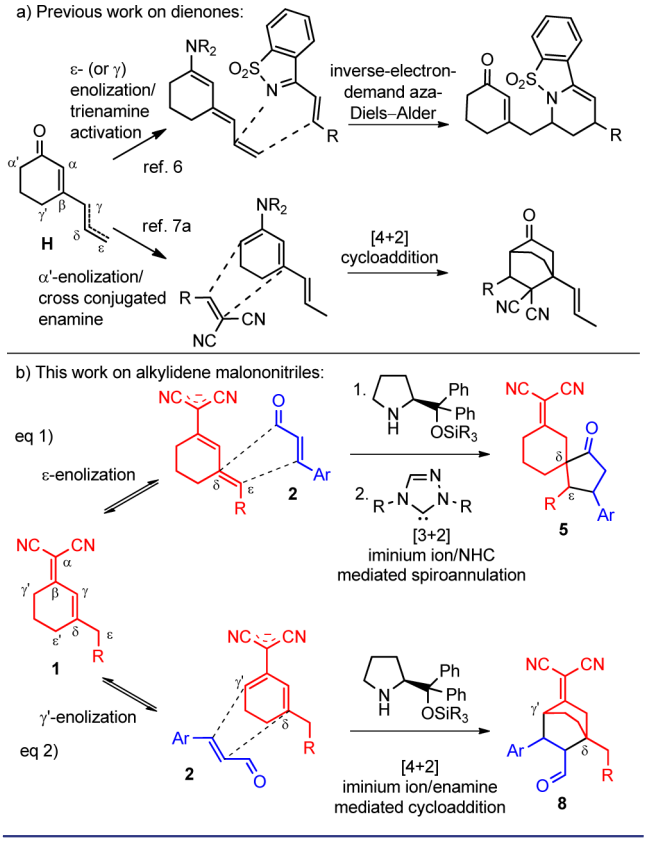
intramolecular captures, with the *ipso*-, *β*-, or *δ*-positions involved, further enlarging the skeleton diversity of the product collection. When, however, lacking in any control, these diverse reaction pathways were concurrently activated, an inextricable scenario might result, involving the installation of a number of carbon−carbon bonds in a random order.

Organocatalytic domino reactions[2] are perceived as possible solutions to circumvent the selectivity problems of mastering multisite reactivity, owing to their intrinsic capability to promote distinct types of processes through combination of orthogonal activation modalities, with significant opportunities for structural and stereochemical diversification.

As a proof of these concepts, we sought to exploit the synthetic potential of a previously uncharted multisite vinylogous platform in the form of cyclic allylidene doubly unsaturated malononitrile **1** (Scheme 2), which represents a substantial advance in the domain of vinylogous *α*,*α*′-dicyanoolefin compounds.[3] *γ*-Enolizable-*α*,*α*′-dicyanoalkenes,[4] in fact, have been known and largely exploited since a decade as vinylogous carbon pro-nucleophiles in catalytic, asymmetric carbon−carbon and carbon−heteroatom bond forming reactions,[3] while their extended counterparts, namely, *α*,*α*′-dicyanodienes of type **1**, have never been used in the context of remotely activatable pro-nucleophilic substrates.[5] Previous works on structurally related 2,4-dienones (or 2,5-dienones) of type **H** (Scheme 2) demonstrated the possibility of engaging either enantioselective inverse-electron-demand aza-Diels−Alder cycloadditions[6] or [4 + 2] cyclizations,[7] involving HOMO-activation of **H** via conjugated trienamine or cross conjugated enamine intermediates, respectively.[8] However, the Michael-type functionalization at the remote *ε*-position[9] and/or the regioselective activation of multiple reaction pathways have never been applied on these substrates.

Scheme 2. Vinylogous Reactivity Space of Extended Cyclic Enones (previous work) and Cyclohexenylidene Malononitriles (this work) by Comparison



We wondered whether the intrinsic manifold reactivity potential of substrate **1** could facilitate the interplay of diverse domino reaction pathways with complementary reactants. Specifically, we herein explore the vinylogous reactivity space of **1** by using diverse enals **2** and modulate their activation using dual iminium ion/*N*-heterocyclic carbene (NHC) or iminium ion/enamine organocatalytic activation modalities. Of the several itineraries departing from diene **1**, we envisioned to plan: (1) a sequential *ε*,*δ*-regioselective bis-vinylogous Michael/1,6-Stetter [3 + 2] spiroannulation delivering spiro[4.5]-decanone structures **5** (Scheme 2, eq 1), and (2) a domino *γ*′,*δ*-vinylogous Michael/1,6-Michael [4 + 2] cycloaddition affording bicyclo[2.2.2]octane structures **8** (eq 2). In this paper, we disclose the successful realization of this plan. Clues unveiling the behavior of the reacting partners and catalyst(s) during the transformations and the key role exerted by the malononitrile handle were especially sought after and are here reported.

RESULTS AND DISCUSSION

Formal [3 + 2] Spiroannulation of Cyclohexenylidene Malononitriles with Enals. An Entry to Enantioenriched Spiro[4.5]decanones 5. According to the projected [3 + 2] spiroannulation pathway delineated in Scheme 2 (eq 1), the synthesis of the title structures **5** from **1** was addressed. A sequence featuring an amine-catalyzed direct bis-vinylogous Michael addition at C-*ε* followed by a NHC-catalyzed intramolecular 1,6-Stetter ring closure at C-*δ* would secure the transformation. Before focusing on a one-pot consecutive execution with all reactants and catalysts involved, we needed to check the two reaction steps individually, searching for optimum reaction conditions. We thus began by examining the reactivity of cyclohexenylidene malononitrile **1a** with cinnamaldehyde **2a** (Table 1). The first trial with 20 mol % prolinol silyl ether catalyst **4a**, using **1a** as the limiting reagent (0.2 M in CH_2Cl_2), gave the desired product **3a** with excellent *ε*-regioselectivity albeit in a poor 26% yield, along with the recovery of significant amounts of **1a** (Table 1, entry 1).

Aware of precedents on amine-catalyzed direct Michael additions to enals where the use of basic additives proved effective in triggering the initial enolization step,[10] catalytic triethylamine was used as an additive (entry 2). Unfortunately, a series of degradation products formed, among which the self-condensation adduct of the starting cyclohexene was identified. By employing an inverted reactant ratio (**1a**:**2a** = 2:1), a gratifying conversion and good enantioselectivity were obtained (entry 3). Addition of catalytic benzoic acid proved detrimental to the overall reaction giving **3a** in low yield accompanied by significant amounts of an unidentified side product (entry 4, vide infra).[11] The best reaction performance was obtained using bulky TBS-protected prolinol catalyst **4b**, affording compound **3a** in a good 83% isolated yield and with optimal 98% enantiomeric excess (entry 5). Changing protected prolinol **4b** for various amine-based catalysts including, among others, L-proline **4c** and squaramide **4d**, resulted in lowered or even totally annihilated efficiency and enantioinduction, emphasizing the crucial role exerted by silyloxy prolinol catalysts in effectively triggering this asymmetric transformation (entries 6 and 7; see also Table S1 in the Supporting Information).

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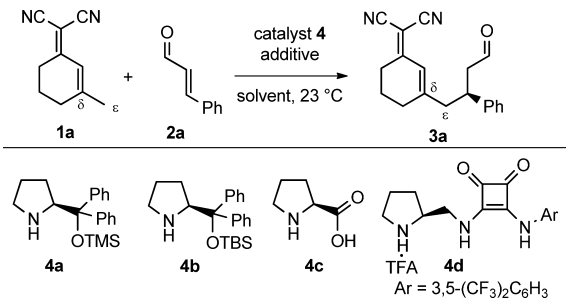
Table 1. Selected Screening Results of the Direct Asymmetric Bis-Vinylogous Michael Addition Involving Cyclohexenylidene Malononitrile 1a and Cinnamaldehyde 2a[a]



entry	4 (mol %)	solvent	add (mol %)	yield (%)[b]	ee (%)[c]
1[d]	**4a** (20)	CH_2Cl_2		26	nd[e]
2[d]	**4a** (20)	CH_2Cl_2	Et_3N (20)		
3	**4a** (20)	CH_2Cl_2		62	90
4[f]	**4a** (20)	CH_2Cl_2	BA (20)	21	nd[e]
5	**4b** (20)	CH_2Cl_2		83	98
6	**4c** (20)	CH_2Cl_2		77	23[g]
7	**4d** (20)	CH_2Cl_2			
8	**4b** (10)	CH_2Cl_2		81	95
9	**4b** (20)	THF		35	nd[e]
10	**4b** (20)	PhMe		19	nd[e]
11	**4b** (20)	$CHCl_3$		33	nd[e]

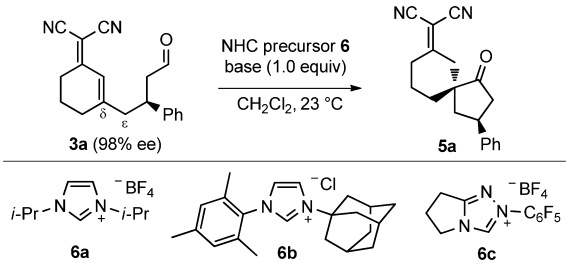
[a]Additional reaction conditions: **2a** (0.05 mmol, 1.0 equiv), **1a** (2.0 equiv), $[\mathbf{2a}]_0$ = 0.2 M in the indicated solvent for 50 h. [b]Yield of isolated product **3a**. [c]Determined by HPLC analysis on a chiral stationary phase. [d]**1a** (0.05 mmol, 1.0 equiv), **2a** (2.0 equiv). [e]nd = not determined. [f]The presence of a byproduct was detected by ^{1}H NMR analysis of the crude reaction mixture (see text). [g]The opposite (*R*) enantiomer was obtained. BA = benzoic acid.

Examination of reaction media revealed that CH_2Cl_2 was the solvent of choice for this transformation with respect to both reactivity and asymmetric induction (entry 5 vs 9−11 and Table S2). Furthermore, when the catalyst loading of **4b** was reduced to 10 mol %, the reaction performed almost equally well, with only a slight reduction in enantioselectivity (entry 8).

With the optimized reaction conditions for the first synthetic step secured (entry 5, Table 1), we turned our attention to the development of the second step, namely, the spiroannulation connecting the aldehyde-carbonyl to the δ-site within compound **3**. A quite challenging *N*-heterocyclic carbene (NHC)-mediated intramolecular vinylogous 1,6-Stetter reaction was thus required, to tether the polarity-reverted acyl anion from the aldehyde group to the remote δ-carbon of the dicyanodiene moiety.[12]

Mindful of our ultimate goal of developing an efficient one-pot procedure, we started our investigation by using the same solvent and substrate molarity of the first optimized step (CH_2Cl_2, 0.2 M). Thus, 98% ee-pure substrate **3a** was treated with different NHC precursor catalysts **6** in the presence of basic reagents (Table 2). While imidazolium salts **6a** and **6b** with sodium or potassium acetate failed in efficiently promoting the desired transformation (Table 2, entries 1−3), reactive triazolium tetrafluoborate catalyst **6c** in combination with KOAc performed the best results, producing the desired spirocyclic product **5a** in a respectable 67% yield, high 98% ee and complete diastereoselectivity (>20:1 dr, entry 4). Lowering the catalyst loading from 30 to 20 mol % resulted in a slight

Table 2. Screening Results of the Asymmetric Intramolecular 1,6-Stetter Reaction Involving Cyclohexenylidene Malononitrile 3a under NHC Activation[a]



entry	6 (mol %)	base	yield (%)[b]	dr[c]	ee (%)[d]
1	**6a** (30)	NaOAc			
2	**6b** (30)	NaOAc	26	>20:1	98
3	**6b** (30)	KOAc	29	>20:1	98
4	**6c** (30)	KOAc	67	>20:1	98
5	**6c** (20)	KOAc	63	>20:1	98

[a]Additional reaction conditions: **3a** (0.05 mmol), $[\mathbf{3a}]_0$ = 0.2 M in CH_2Cl_2, for 2 h. [b]Yield of isolated product **5a**. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis on a chiral stationary phase.

yield deterioration, while maintaining the same levels of stereocontrol (entry 5).

Next, the feasibility of a one-pot procedure was examined, merging the intermolecular bis-vinylogous Michael addition and the intramolecular 1,6-Stetter closure in a consecutive fashion. The model reaction between **1a** and **2a** was carried out, with the NHC-promoter and KOAc base being added after the complete consumption of enal **2a** (Table 3). Remarkably, this strategy worked and spirocyclic [4.5]decanone **5a** was obtained in a 57% yield, which compared well with the alternative, two-step procedure (55%). Complete diastereoselectivity and very high enantioselectivity for **5a** were obtained, which remained intact even when the amount of triazolium precatalyst **6c** was lowered to 25 mol %. Of note, complete regioselectivity of the double transformation was maintained, with no even small traces of regioisomeric compounds detected. At this point, it has to be underlined that a one-pot domino procedure wherein all reagents and substoichiometric promoters were mixed together at the beginning of the reaction was carried out. In this case, however, significant loss of chemical control was witnessed and only trace amount of product **5a** was attained.

To assay the generality of the reaction, structurally varied β-aryl-substituted enal acceptors **2** were used, and the results of this screening are displayed in Table 3. Substituents of different size and electronic nature on the aromatic ring could be tolerated and the reactions consigned the corresponding products **5** in good yields, complete site- and diastereocontrol, and high margins of enantiocontrol. Slightly diminished reactivity and/or enantiocontrol were witnessed in reactions involving heteroaryl- and methoxyphenyl-substituted aldehydes **2d** and **2f**, albeit excellent diastereoselectivity was maintained in these cases. Noticeably, reactions carried out on a 5× scale delivered compounds **5a** and **5b** with comparable productivity and stereocontrol.[13]

The configuration of products **5** was established by single crystal X-ray diffraction analysis of representative compound **5f**[14] (see the Supporting Information). In addition, certification of the absolute configuration of **5** was made by indirect, though reliable assignment of the **5a** structure via $KMnO_4$-promoted

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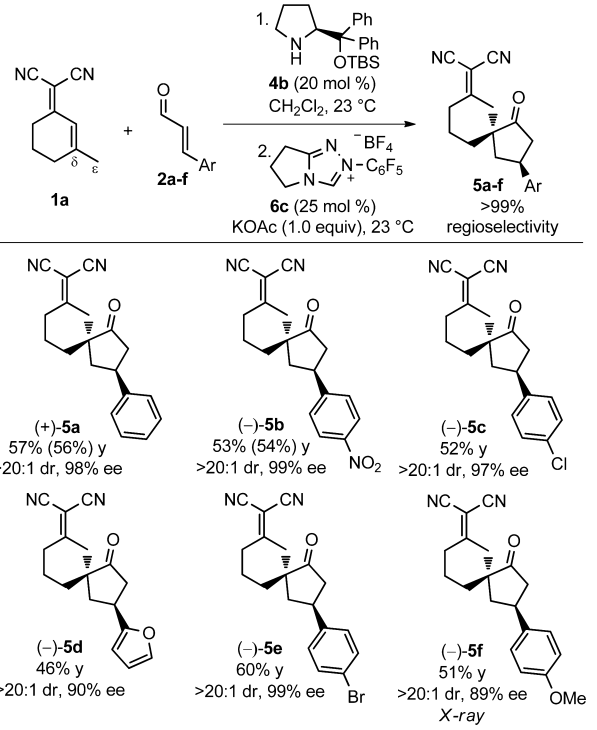
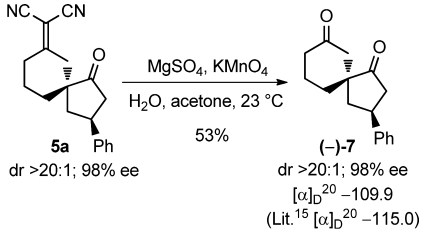
Table 3. Scope of the One-Pot Sequential Asymmetric [3 + 2] Spiroannulation Delivering Enantioenriched Spiro[4.5]decanones 5[a]



[a]Additional reaction conditions: **2** (0.2 mmol), $[2]_0$ = 0.2 M in CH_2Cl_2 for 42−75 h. Yields (y) refer to isolated products **5**. In parentheses, yields of **5** obtained on a 5× scale. Diastereomeric excess determined by ^{1}H NMR analysis of the crude reaction mixture. Enantiomeric excess determined by HPLC analysis on a chiral stationary phase.

oxidative fission of the exocyclic malononitrile double bond to give known diketone product **7**,[15] as detailed in Scheme 3 and in the Supporting Information.

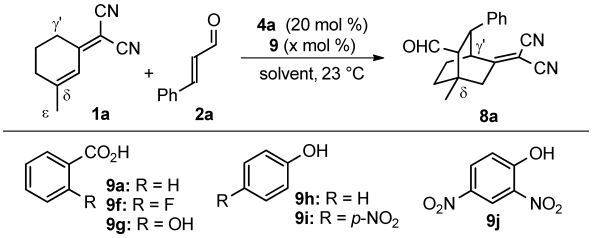
Scheme 3. Elaboration of Spirocyclic Cyclohexenylidene Malononitrile 5a into Known Spirocyclic Diketone 7



This procedure, while confirming the stereodisposition within **5a** and hence that of the other products **5** by analogy, demonstrated the synthetic malleability of such products and highlighted the utility of the malononitrile handle as a surrogate of the carbonyl function.

Formal [4 + 2] Cycloaddition of Cyclohexenylidene Malononitriles with Enals. An Entry to Enantioenriched Bicyclo[2.2.2]octanes 8. To access the title bicyclic structures, a formal [4 + 2] cycloaddition would be addressed, seemingly arising by a domino sequence involving (i) a vinylogous Michael addition of in situ formed γ'-enolate from **1** to iminium ion-activated enal **2** followed by (ii) a δ-regioselective enamine-mediated intramolecular 1,6-Michael addition closure (see infra, mechanistic insights). Closer inspection of the initial optimization studies revealed that reaction of **1a** with **2a** in the presence of **4a** and benzoic acid additive **9a** led to the formation of the ε-Michael adduct **3a** in only 21% yield, accompanied by significant amount (12%) of the [4 + 2] cycloaddition product **8a**, whose structure was unequivocally determined by extensive NMR and mass analyses (Table 1, entry 4 and Table 4, entry 1). And this convinced us

Table 4. Selected Screening Results of the Asymmetric Formal [4 + 2] Cycloaddition Involving Cyclohexenylidene Malononitrile 1a and Cinnamaldehyde 2a[a]



entry	9 (x mol %)	solvent	yield (%)[b]	8a:3a (γ',δ:ε)[c]	dr[c]	ee (%)[d]
1[e]	**9a** (20)	CH_2Cl_2	12	1:2	9:1	nd[f]
2[e]	**9b** (TFA, 20)	CH_2Cl_2				
3[e]	**9f** (20)	CH_2Cl_2	33	1:1	9:1	90
4[e]	**9g** (20)	CH_2Cl_2	58	8:1	10:1	92
5	**9h** (20)	CH_2Cl_2	(50)	4:1	18:1	nd[f]
6[e]	**9i** (20)	CH_2Cl_2	67	12:1	12:1	94
7	**9j** (20)	CH_2Cl_2	(53)	15:1	10:1	nd[f]
8	**9i** (20)	CH_2Cl_2	72	15:1	>20:1	96
9	**9i** (20)	PhMe	65	15:1	>20:1	90
10	**9i** (20)	$CHCl_3$	81	17:1	>20:1	96
11[g]	**9i** (10)	$CHCl_3$	80	17:1	>20:1	96

[a]Additional reaction conditions: **1a** (0.05 mmol, 1.0 equiv), **2a** (2.0 equiv), $[1a]_0$ = 0.5 M in the indicated solvent, for 10 h. [b]Yield of isolated product **8a** (conversion in parentheses). [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis on a chiral stationary phase. [e]**2a** (0.05 mmol, 1.0 equiv), **1a** (2.0 equiv). [f]nd = not determined. [g]10 mol % catalyst **4a** loading.

that addition of a Brønsted acid cocatalyst to the reaction mixture could be beneficial to driving the main reaction pathway toward γ'-activation, diverting it from the ε-addition.

Thus, the model reaction between **1a** and **2a** using substoichiometric quantities of **4a** was carried out in the presence of diverse Brønsted acid additives, and the results are displayed in Table 4 and Table S3 in the Supporting Information. Aliphatic carboxylic acids such as trifluoroacetic acid, acetic acid, and camphorsulfonic acid proved totally incompetent cocatalysts, producing no addition products at all. Using, instead, differently substituted benzoic acids including *o*-fluorobenzoic acid (**9f**) and, better, salicylic acid (**9g**) resulted in a nice ε-to-γ',δ-switching in favor of the desired [4 + 2] addition product **8a**. Reasoning that the beneficial influence of salicylic acid additive on γ',δ reactivity could be due to favorable balance between acidic and structural (aromatic) properties, scrutiny went on using phenolic candidates, that is, phenol itself (**9h**), *p*-nitrophenol (**9i**), and 2,4-dinitrophenol (**9j**). Good results were obtained, with *p*-nitrophenol **9i** behaving best as far as site-, diastereo-, and enantioselectivity are concerned (entry 6). Other acidic additives comprising isatin, imide

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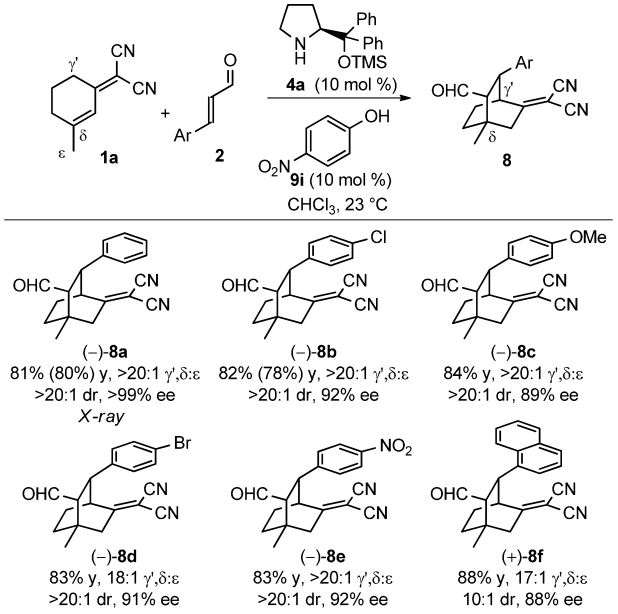
derivatives, and *p*-toluenesulfonic acid gave unsatisfactory, if any, results. With *p*-nitrophenol **9i** fixed as the best acidic additive, screening of the overall reaction conditions (reactants molar ratio, additive and catalyst loading, solvent, and reaction temperature) was carried out and the final optimized conditions are reported in entry 11. Briefly, by simply treating **1a** and **2a** with 10 mol % catalyst **4a**, 10 mol % *p*-nitrophenol **9i** in $CHCl_3$ at room temperature consigned, after 10 h, the desired bicyclooctane structure **8a** in a good 80% yield, remarkable 17:1 site selectivity, complete diastereoselectivity, and as high as 96% enantioselectivity.

Next, the generality and limits of the formal [4 + 2] cycloaddition were tested on a 0.2 mmol (and 1.0 mmol) scale, using diverse *β*-aryl-substituted enals **2**. As shown in Table 5, very good results were obtained in terms of reaction yields and enantioselectivity, with extraordinary levels of regio- and diastereocontrol raised in all instances.

Table 5. Scope of the Asymmetric Formal [4 + 2] Cycloaddition Delivering Enantioenriched Bicyclo[2.2.2]octanes 8[a]

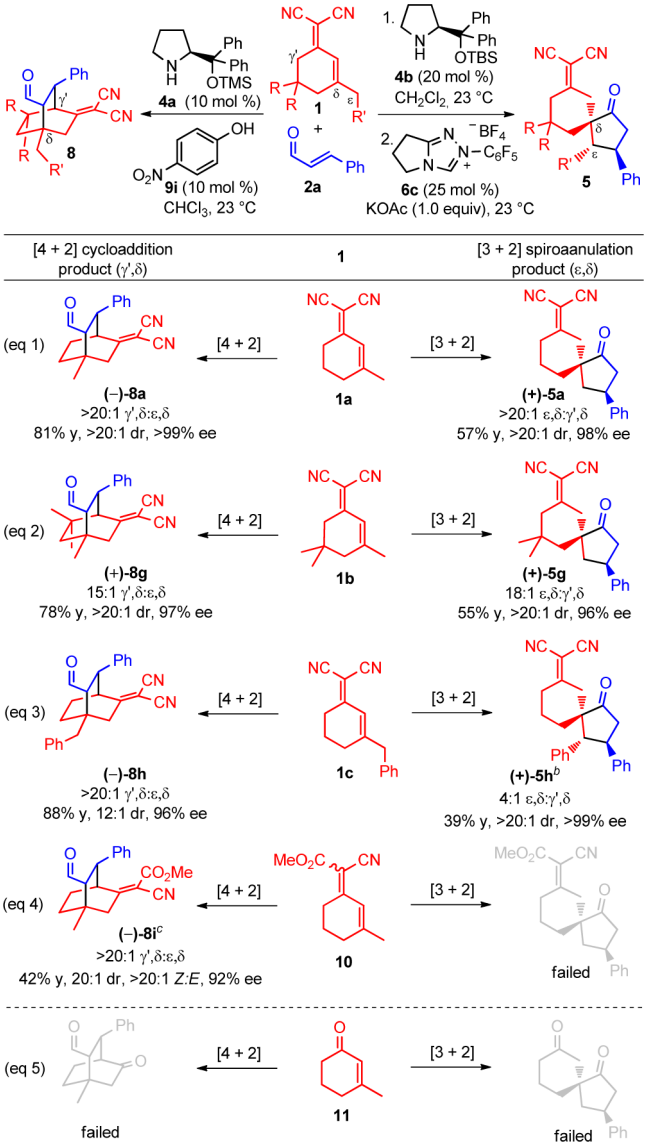


[a]Additional reaction conditions: **1a** (0.2 mmol), $[\mathbf{1a}]_0$ = 0.5 M for 10 h. Yields (y) refer to isolated products **8**. In parentheses, yields of **8** obtained on a 5× scale. Diastereomeric excess and site selectivity determined by ^{1}H NMR analysis of the crude reaction mixture. Enantiomeric excess determined by HPLC analysis on a chiral stationary phase.

Single crystal X-ray analysis of bicyclooctane **8a**[16] certified its three-dimensional assessment (see the Supporting Information), while the configuration of the other products **8** was assigned by analogy.[17]

Further Scope and [3 + 2] Spiroannulation versus [4 + 2] Cycloaddition Regiodivergence. As disclosed in the previous paragraphs, simple experimental conditions were found, according to which organocatalyzed reactions between cyclohexenylidene malononitrile **1a** and *β*-aryl enals **2** could alternatively divert with exceptional regioselectivity toward either [3 + 2] spiroannulation or [4 + 2] cycloaddition pathways, to produce enantioenriched spirocycles of type **5a** or bicyclooctanes of type **8a**, respectively (Table 6, eq 1). To bring this remarkable strategy to fruition, several cyclohexenylidene

Table 6. [3 + 2] Spiroannulation versus [4 + 2] Cycloaddition Pathways: Scope of the Cyclohexenylidene Nitriles 1 and 10[a]



[a]Additional reaction conditions as reported in Table 3 (for the [3 + 2] path) and Table 5 (for the [4 + 2] path). [b]Relative configuration determined by NOESY NMR experiments. [c]Three days reaction time.

malononitrile candidates were assayed in coupling reactions with **2a**, under either experimental conditions. As displayed in Table 6, dimethyl-substituted malononitrile **1b** behaved equally well, diverting to spirocycle **5g** or bicycle **8g** with very high regioselectivity and remarkable levels of reaction efficiency and stereocontrol in both cases (eq 2). Next, *ε*-phenyl-substituted cyclohexenylidene malononitrile **1c** was tested under either optimized procedures (eq 3). The [4 + 2] pathway worked decidedly well, giving **8h** as the exclusive regioisomer in high isolated yield and good margins of diastereo- and enantioselection. Quite unexpectedly, however, the one-pot sequential [3 + 2] spiroannulation occurred with reduced *ε*,*δ*-selectivity (4:1) demonstrating that, notwithstanding the enhanced acidic character of the benzyl *ε*-position facilitating the remote enolization, steric bulkiness within compound **5h** could play a major role in guiding the reaction outcome (see infra). In the

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event, spirocyclic product **5h** was isolated in a modest 39% yield, while complete diastereo- and enantiocontrol were still achieved. Compound **5h** is worthy of note, since it presents three contiguous stereocenters within a quite rare and complex chemical architecture.[18]

Further scope included "mixed" ester-nitrile malonate **10**, whose behavior in these processes would emphasize the actual feasibility of the reaction to malonate-like counterparts, while furnishing clues on the role of the nitrile functionality during such transformations. The results, portrayed in eq 4, are insightful. Under the [3 + 2] spiroannulation conditions, reaction of **10** and **2a** to the corresponding spirocycle was fully inhibited, and recovery of bicyclooctane **8i** was observed after 8-day reaction time (42% yield, 15:1 dr, >99% ee, *Z*:*E* = 10:1). On the other hand, under the [4 + 2] conditions, the reaction rate between **10** and **2a** proved lowered (3 days vs the standard 10 h), giving the expected bicyclic product **8i** as the sole regioisomer (>20:1) in a 42% yield, 20:1 dr, >20:1 *Z*:*E*, and 92% ee. Also, complete reactivity depletion using control ketone **11**, the precursor of malononitriles **1**, was observed under either conditions. Taken altogether these results point to the belief that *the malononitrile moiety is an essential structural prerequisite* for the present method to be efficiently pursued. Attempts to clarify this point were made, as reported in the next paragraph.

Mechanistic Insights. The chemistry disclosed in this paper poses questions about the underlying mechanisms bringing to the observed products and, especially, the subtle reasons responsible for the high regio- and stereoselectivity of these transformations. Several pieces of experimental evidence support the construction of a conceivable reaction rationale.

First, reactions between **1** and **2** do not work in the absence of amine catalysts **4**, supporting the notion that these catalytic asymmetric couplings are initially triggered by LUMO energy-lowering of the electrophilic enal partner.

Second, the direct nature of these coupling reactions implies that the pro-nucleophilic partner **1** is activated by in situ remote enolization. In particular, of the three potentially nucleophilic sites, the γ'-, ε-, and ε'-position, only two enolization paths are operative, namely, the ε-enolization to furnish the Michael products **3** (and hence spirocycles **5** along the [3 + 2] path) and the γ'-deprotonation to afford bicycles **8** (along the [4 + 2] path). Indeed, catalytic amounts of Brønsted bases are present in the reaction vessel, which could be responsible for such deprotonation step, under the guise of hydroxide anion, formed during condensation between prolinol catalyst and enal, as well as prolinol silyl ether itself.[19] Moreover, propensity to enolization (i.e., acidity of the enolizable protons) seems to be heavily dependent upon the dicyano-moiety within **1**, since no reaction at all was observed using ketone control **11**, while pronounced reaction slowdown occurred when mixed ester-nitrile malonate **10** was employed.

Third, the striking regiodivergence in reactions between **1** and **2** is mostly attributable to the key presence (or absence) of the *p*-nitrophenol additive; and this supports the notion that the phenolic cocatalyst plays a strategic role in stabilizing one of the competing transition states (see infra, Figure 2).

Fourth, considering the coupling reaction between **1** and **2** to products **8**, either a concerted [4 + 2] Diels–Alder cycloaddition pathway or a stepwise 1,4-Michael-1,6-Michael addition pathway could be invoked. No monocyclic Michael addition intermediates were indeed isolated during such transformations; on the other hand, when the optimized [4 + 2] conditions were applied to δ-phenyl cyclohexenylidene malononitrile (not shown), exclusive formation of the first Michael adduct was attained, probably due to the bulky phenyl group at δ-position preventing the subsequent 1,6-Michael closure. Therefore, this formal [4 + 2] cycloaddition is more likely to occur by a stepwise Michael–Michael addition pathway.

Fifth, to provide insights into the reaction mechanisms, investigation of the carbon isotope effects for both the ε-Michael addition (**1a** + **2a** → **3a**) and the γ',δ-cycloaddition (**1a** + **2a** → **8a**) was carried out, using Singleton's ^{13}C NMR method at natural abundance.[20]

Considering the **1a** + **2a** → **3a** reaction under the optimized protocol (Table 1, entry 5, 5.0 mmol scale), the ^{13}C ratio of each carbon in the recovered nitrile to the same carbon in virgin nitrile was measured using quantitative ^{13}C NMR. As shown in Figure 1 (left), the only appreciable carbon isotope

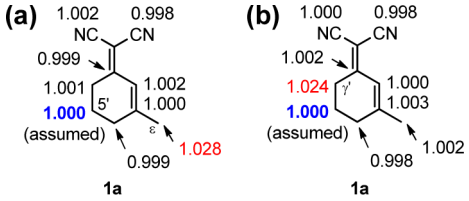

Figure 1. Carbon isotope effects (R/R_0) calculated for cyclohexenylidene malononitrile **1a**. (a) Recovered under conditions of entry 5, Table 1. (b) Recovered under conditions of entry 11, Table 4. The C5′ carbon (value in blue) was taken as the internal standard. For details, see the Supporting Information.

effect was observed at the ε-methyl position [^{13}C-(recovered/^{13}C(virgin) = 1.028, average of three runs), indicating that the C-ε involving Michael addition attack is the rate-determining step. On the other hand, for the **1a** + **2a** → **8a** reaction under the optimized [4 + 2] protocol (Table 4, entry 11, 5.0 mmol scale), the only appreciable carbon isotope effect was observed at the γ'-position (Figure 1, right) [^{13}C(recovered/^{13}C(virgin) = 1.024, average of three runs), indicating that the rate-determining step is the first Michael addition coupling, likely further corroborating that the [4 + 2] cycloadddition proceeds via a stepwise mechanism.

On these grounds, we propose a bifurcated catalytic cycle, which could be operative in either cases, as depicted in Figure 2. After iminium ion activation of enal **2** (LUMO-lowering), pro-nucleophilic malononitrile **1a** is deprotonated by hydroxide ion at both ε- and γ'-sites, giving coexisting extended enolate **II** (a linear trienylidene amide) and cross-conjugated enolate **IV** (a crossed trienylidene amide), respectively (HOMO-raising). In the absence of the phenol cocatalyst, the bis-vinylogous enolate **II** could easily engage enantioselective attack to the *Si*-face of the enal acceptor via a stabilized transition state wherein a favorable Coulombic interaction occurs between the dispersed negatively charged nitrogen atoms of nitrile functions and the positively charged nitrogen atom of **I**.[21] Enamine **III** is then forged, which rapidly hydrolyzes to the final product **3** (and hence **5**) with the recycle of the organocatalyst. When approaching iminium ion **I** along an (aryl)*endo*-Diels–Alder-like trajectory, γ'-enolate **IV** cannot enjoy the same favorable stabilizing interaction until a suitable hydrogen bond donor (e.g., *p*-nitrophenol, ROH in Figure 2) is added. In such a case, the attack of **IV** (from its *Re* face) to the *Si*-face of **I** becomes favorable, and the reaction path drives toward intermediate **V**

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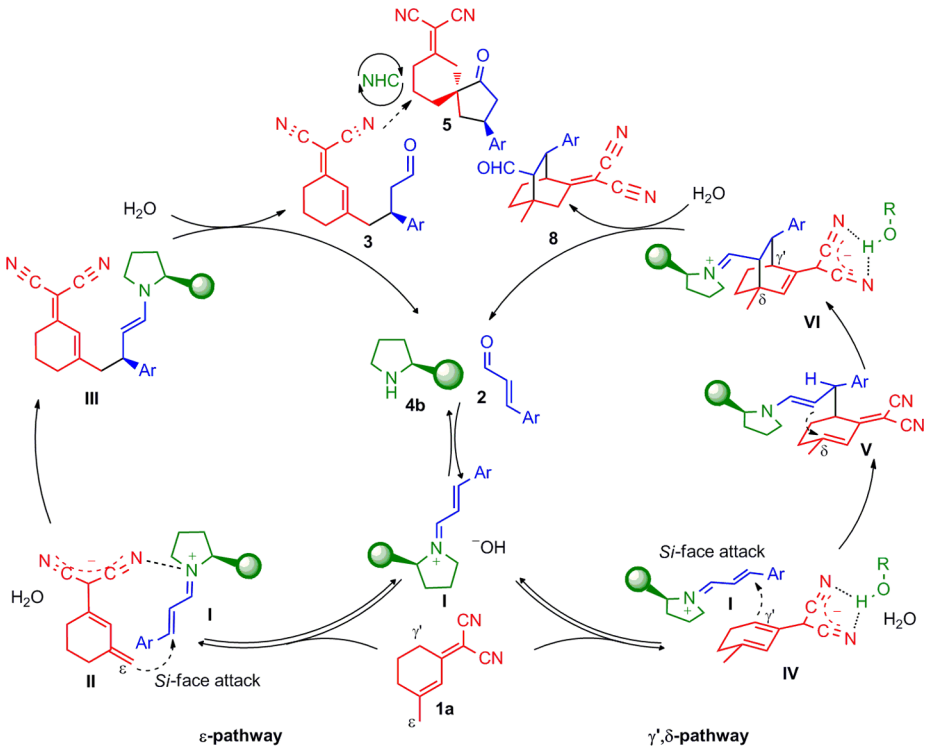

Figure 2. Proposed regiodivergent ε-pathway (left) and γ',δ-pathway (right) for the reaction between **1a** and **2** to afford compounds **3** and **8** (ROH = *p*-nitrophenol).

and then **VI**, which finally releases the target compound **8** and catalyst **4b** upon hydrolysis.[22]

CONCLUSIONS

The direct, remote functionalization of a progeny of orthogonally activatable vinylogous platforms, namely, the cyclohexenylidene malononitriles **1**, has been herein presented for the first time. Focused organocatalytic experimental conditions were searched and found, which enabled the divergent regio- and stereoselective entry to highly enantioenriched spiro[4.5]decanones **5** and bicyclo[2.2.2]octane carbaldehydes **8**, whose synthetic appeal and potential is testified by their functionality-rich skeletons. Remarkably, the regiocontrol of the process could be switched by subtly altering the reaction parameters: use of prolinol catalyst via covalent activation of the enal component was favorable for **3**, while synergistic merger of prolinol catalyst and phenolic additive was the best for **8**. Within this class of polyconjugated and remotely enolizable dicyanoolefins, a key role is attributed to the malononitrile moiety which seems crucial in both facilitating the initial in situ HOMO-raising activation of the multivinylogous carbon nucleophile and dictating the regioselective coupling to enals **2**. Emphasized is also the utility of the malononitrile handle, which can be considered as a masking group for a carbonyl function since it can be conveniently removed by oxidative fission. A plausible mechanistic rationale was proposed, which was also supported by reliable carbon isotope effects measurements. Efforts toward expanding the scope of multiconjugated malononitriles as nucleophic diene surrogates in the catalytic, asymmetric construction of densely functionalized carbocycles are currently underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization of new compounds, chemical correlation studies, X-ray crystallographic analyses of products **5f** and **8a**, carbon isotope effects measurements, HPLC chromatograms, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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(14) CCDC 1004862 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(17) Lacking heavy atoms and using a diffractometer equipped with a molybdenum X-ray source, the assignment of the 1*S*,4*S*,5*R*,6*S* absolute configuration of **8a** is not impeccable, while the relative assignment is attributed without uncertainty. However, the Flack parameter (Parsons' method) calculated from two different data sets, collected first at room temperature and subsequently at low temperature (150 K), passes from −0.038(477) to 0.004(378) and both the closeness to the expected zero value for the correct assignment and the reduction of the standard deviation value seem to corroborate the given assignment. In addition, the observed stereochemical outcome accounts for a facial selectivity in full accordance with results of the above-discussed ε-selective pathway (iminium ion *Si*-face attack), in line with the many literature precedents on nucleophilic additions involving the same acceptors and the same catalyst. See, for example: (a) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (b) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248. (c) Rios, R.; Companyó, X. In *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*; Dalko, P. I., Ed.; Wiley-VCH Verlag: Weinheim, 2013; Part III, Chapter 33, pp 975–1012. See also ref 10.

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