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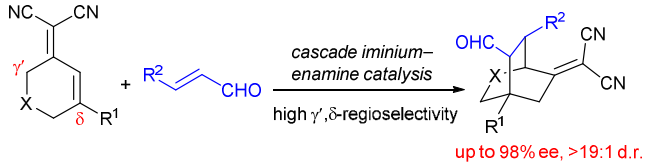
Graphical Abstract

A regio- and stereoselective [4+2] formal cycloaddition process of cyclohexenylidenemalononitriles and α,β-unsaturated aldehydes was developed via cascade iminium-enamine catalysis, generating chiral bridged bicyclo[2.2.2]octanes with high molecular complexity



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ARTICLE TYPE

Organocatalytic Asymmetric [4+2] Formal Cycloadditions of Cyclohexenylidenemalononitriles and Enals to Construct Chiral Bicyclo[2.2.2]octanes

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A highly regio- and stereoselective [4+2] formal cycloaddition process of cyclohexenylidenemalononitriles and *α,β*-unsaturated aldehydes has been developed by the catalysis of a chiral secondary amine, affording a range of bridged bicyclo[2.2.2]octane architectures with high molecular complexity (up to 98% ee, >19:1 d.r.).

There has been a continuing interest in the chemistry of functionalized bridged bicyclo[2.2.2]octanes that exist in a vast array of natural products and drug candidates as outlined in Figure 1.[1] Since such skeletons have vital applications in the total syntheses of natural products,[2] developing concise methods to access diversely structured bicyclo[2.2.2]octanes have always triggered much attention in organic chemistry.[3] Among them, the [4+2] cycloaddition reactions of cyclohexadienes with olefinic dienophiles have provides one of the most straightforward protocols to access these skeletons.[4] In particular, the in situ generated cross-conjugated dienamine species between 2-cyclohexenones and an amine catalyst, pioneered by Barbas and co-workers,[5] could perform as HOMO-raised dienes in [4+2] cycloadditions with various electron-deficient dienophiles, furnishing bicyclo[2.2.2]octanes in a highly enantioenriched manner (Scheme 1).[6] However, such catalytic strategy still suffer from relatively narrow substrate scope, and highly reactive dienophiles are generally required.

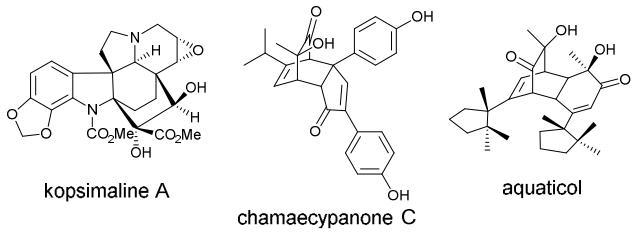
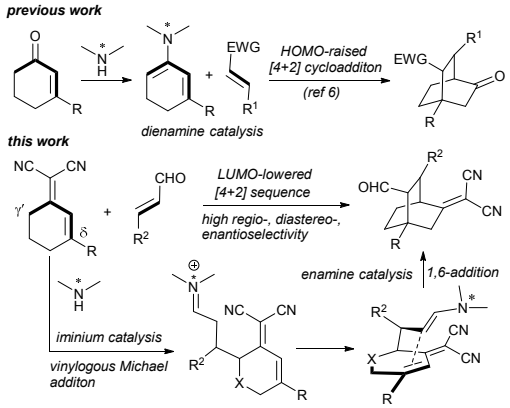


Fig 1. Selected natural products containing bicyclo[2.2.2]octane core

The iminium-promoted direct *γ*-regioselective vinylogous additions of alkylidenemalononitriles to *α,β*-unsaturated carbonyl compounds have been well established in our previous work.[7] Inspired by this success, we envisaged that the analogous cyclohexenylidenemalononitriles might act as *γ′*-regioselective vinylogous donors in the reactions with iminium-activated *α,β*-unsaturated aldehydes, thus a sequential intramolecular *δ*-regioselective 1,6-addition[8] via cascade enamine catalysis would efficiently afford chiral bicyclo[2.2.2]octanes with densely adored substitutions (Scheme 1).[9]

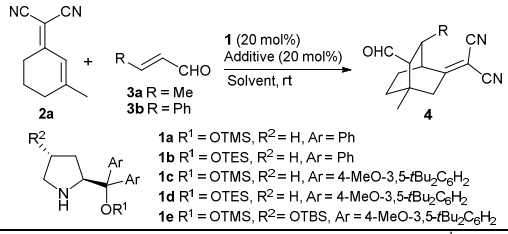


Scheme 1 Organocatalytic asymmetric [4+2]-type cycloadditions to access bicyclo[2.2.2]octane frameworks

The initial attempts to the potential [4+2]-type cycloaddition of cyclohexenylidenemalononitrile **2a** and crotonaldehyde **3a** by the well-established iminium catalysis of *α,α*-diphenylprolinol *O*-TMS ether **1a**[10] (Table 1) and benzoic acid (BA) were unfortunately unsuccessful at ambient temperature in diverse solvents (Table 1, entry 1). Replacing benzoic acid with basic *N,N*-diisopropylethylamine (DIPEA) also resulted in no reactions in a spectrum of solvents (entry 2). To our delight, it was found that the desired reaction proceeded very smoothly catalyzed by amine **1a** and DIPEA by using MeCN as the solvent. A multifunctional bicyclo[2.2.2]octane **4a** was isolated in 87% yield after 12 h and with excellent stereoselectivity (entry 3, 93% ee, >19:1 d.r.). It should be noted that almost no reaction occurred in the absence of DIPEA, indicating that DIPEA is important to the activation of nucleophile **2a**. Subsequently, a few chiral secondary amine catalysts were investigated (entries 4–7), and the studies revealed that *α,α*-diphenylprolinol *O*-TES ether **1b** was the best choice in term of yield and enantioselectivity. Nevertheless, the reaction of **2a** and cinnamaldehyde **3b** bearing a *β*-phenyl group occurred more slowly under the above optimized catalytic conditions, and a significantly decreased enantio-selectivity was detected (entry 8). Consequently, we further screened the reaction of donor **2a** and cinnamaldehyde **3b** with

diverse amine catalysts (entries 9–12), and **1a** was found to give better enantiocontrol (entry 9). Interestingly, benzoic acid was found to be a superior additive for iminium catalysis, and phenyl substituted bicyclic product **4b** was obtained in a high yield after 12 h and with remarkable enantioselectivity (entry 13). It should be noted that acetonitrile was still crucial for the reaction, as almost no conversion was observed in other solvents (entry 14).

Table 1. Screening studies on the [4+2] formal cycloadditions of cyclohexenylidenemalononitrile **2a** with *a*,*β*-unsaturated aldehydes **3**[a]

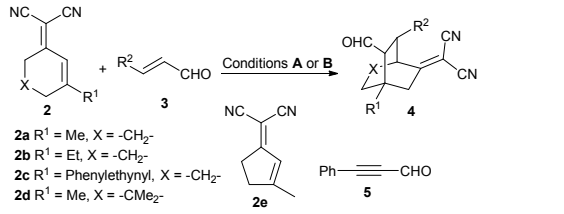


Entry	**1**	**3**	Additives	Solvents	Time (h)	Yield[b] (%)	Ee[c] (%)
1	**1a**	**3a**	BA	Solvent[d]	12	–	–
2	**1a**	**3a**	DIPEA	Solvent[e]	12	–	–
3	**1a**	**3a**	DIPEA	MeCN	12	**4a**, 87	93
4	**1b**	**3a**	**DIPEA**	**MeCN**	**12**	**4a, 84**	**97**
5	**1c**	**3a**	DIPEA	MeCN	12	**4a**, 72	96
6	**1d**	**3a**	DIPEA	MeCN	12	**4a**, 84	95
7	**1e**	**3a**	DIPEA	MeCN	12	**4a**, 79	95
8	**1b**	**3b**	DIPEA	MeCN	24	**4b**, 68	84
9	**1a**	**3b**	DIPEA	MeCN	24	**4b**, 75	90
10	**1c**	**3b**	DIPEA	MeCN	24	**4b**, 68	5
11	**1d**	**3b**	DIPEA	MeCN	24	**4b**, 61	42
12	**1e**	**3b**	DIPEA	MeCN	24	**4b**, 75	86
13	**1a**	**3b**	**BA**	**MeCN**	**12**	**4b**, **90**	**98**
14	**1a**	**3b**	BA	Solvent[e]	12	–	–

[a] Reactions were performed with vinylogous donor **2a** (0.1 mmol), *a*,*β*-unsaturated aldehyde **3** (0.15 mmol), amine **1** (0.02 mmol), and additive (0.02 mmol) in 1.0 mL of solvent at rt. [b] Isolated yield. [c] Determined by chiral HPLC analysis after reduction to the corresponding alcohol with $NaBH(OAc)_3$; d.r. > 19:1 by ^1H NMR analysis. [d] Toluene, $CHCl_3$, MeCN or THF were screened. [e] Toluene, $CHCl_3$ or THF were screened.

With the screened catalytic conditions in hand, the substrate scope and limitations for the [4+2] formal cycloadditions of a variety of cyclohexenylidenemalononitriles **2** and *a*,*β*-unsaturated aldehydes **3** were explored. The results are summarized in Table 2. At first, a few alkyl group substituted acroleins were tested under the catalysis of amine **1b** and DIPEA in MeCN at ambient temperature. Both 2-pentenal and 2-hexenal smoothly delivered the desired bridged products with good results in reactions with donor **2a** (Table 2, entries 2–3). Nevertheless, 4-methyl-2-pentenal, bearing a branched *β*-alkyl group, failed to produce the cycloadduct probably due to steric reason (entry 4). On the other hand, an array of *a*,*β*-unsaturated aldehydes with diverse aryl or heteroaryl groups were investigated in reactions with donor **2a** under the catalysis of amine **1a** and benzoic acid, generally affording the cycloadducts in high yields and with outstanding enantioselectivity (entries 5–13). In addition, enals substituted by a *β*-2-styryl or phenylethynyl group exhibited high *a*,*β*-regioselectivity, and the bicyclo[2.2.2]octanes **4m** and **4n** with more functional groups were obtained in good data (entries 14 and 15). Unfortunately, a complex reaction was observed when phenylpropiolaldehyde **5** was applied (entry 16). Moreover, a few cyclic *α*,*α*-dicyanodienes were prepared and tested in the reactions with cinnamaldehyde **3b**. A *δ*-ethyl substrate **2b** gave product **4o** in similar stereocontrol (entry 17). Notably, *δ*-phenylethynyl-substituted donor **2c** showed even higher reactivity, while the enantioselectivity was slightly decreased (entry 18). Inversely, the reaction of substrate **2d** with *δ′*,*δ′*-dimethyl groups proceeded sluggishly, but good data could be produced after a longer time (entry 19). To our disappointment, the application of cyclopentylidenemalononitrile **2e** to construct bicyclo[2.2.1] heptane architecture was not successful, and a complex mixture was generated (entry 20).

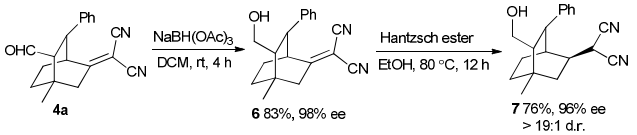
Table 2. [4+2] formal cycloadditions of cyclic *α*,*α*-dicyanodienes **2** with *a*,*β*-unsaturated aldehydes **3**[a]



Entry	**2**	R^2	Conditions	Time (h)	Yield[b] (%)	Ee[c] (%)
1	**2a**	Me	**A**	12	**4a**, 84	97
2	**2a**	Et	**A**	12	**4c**, 73	91
3	**2a**	*n*Pr	**A**	16	**4d**, 76	93
4	**2a**	*i*Pr	**A**	24	–	–
5	**2a**	Ph	**B**	12	**4b**, 90	98
6	**2a**	4-MeOPh	**B**	12	**4e**, 94	95
7	**2a**	4-MePh	**B**	12	**4f**, 83	95
8	**2a**	3-ClPh	**B**	12	**4g**, 91	94[d]
9	**2a**	2-BrPh	**B**	12	**4h**, 87	94
10	**2a**	3,4-Cl_2Ph	**B**	12	**4i**, 85	96
11	**2a**	4-NO_2Ph	**B**	12	**4j**, 90	92
12	**2a**	2-Pyridinyl	**B**	12	**4k**, 94	84
13	**2a**	2-Furyl	**B**	12	**4l**, 93	94
14	**2a**	2-Styryl	**B**	18	**4m**, 79	92
15	**2a**	Phenylethynyl	**B**	18	**4n**, 83	94
16	**2a**	**5**	**B**	12	–	–
17	**2b**	Ph	**B**	16	**4o**, 84	91
18	**2c**	Ph	**B**	6	**4p**, 82	86
19	**2d**	Ph	**B**	36	**4q**, 78	92
20	**2e**	Ph	**B**	12	–	–

[a] Reactions were performed with vinylogous donor **2** (0.1 mmol), *a*,*β*-unsaturated aldehyde **3** (0.15 mmol) either in conditions **A** [amine **1b** (0.02 mmol) DIPEA (0.02 mmol), in MeCN (1.0 mL)] or conditions **B** [amine **1a** (0.02 mmol), benzoic acid (0.02 mmol), in MeCN (1.0 mL)] at rt. [b] Isolated yield. [c] Determined by chiral HPLC analysis after reduction to the corresponding alcohol with $NaBH(OAc)_3$; d.r. > 19:1 by ^1H NMR analysis. [d] The absolute configuration of the alcohol of **4g** was determined by X-ray analysis. The other products were assigned by analogy.

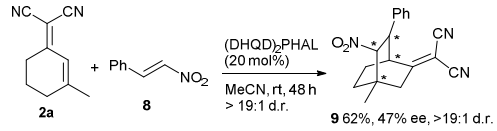
As illustrated in Scheme 2, the aldehyde functionality of cycloadduct **4a** could be selectively reduced to give alcohol **6** without affecting the unsaturated double bond by using $NaBH(OAc)_3$ as the reductant. Nevertheless, the activated alkene group of **6** could be smoothly reduced with Hantzsch ester,[11] producing product **7** as a single diastereomer.



Scheme 2. Regio- and diastereoselective reduction of **4a**

On the other hand, we found another electron-deficient alkene, nitroolefin **8**, could also be applied in the [4+2] formal

cycloaddition with cyclohexenylidenemalononitrile **2a** by the catalysis of a modified cinchona catalyst $(DHQD)_2PHAL$ (hydroquinidine 1,4-phthalazinediyl diether).[12] The reaction was conducted in MeCN at ambient temperature, while a nitro-containing bicyclo[2.2.2]octane **9** was obtained in a moderate yield after 2 days and with fair enantioselectivity.



Scheme 3. Asymmetric [4+2] formal cycloaddition of vinylogous donor **2a** and nitroolefin **8**.

Conclusions

We have investigated the application of a new type of multifunctional substrates, cyclohexenylidenemalononitriles, which have been successfully utilized in γ',δ-regioselective [4+2] formal cycloadditions with diversely structured α,β-unsaturated aldehydes by the catalysis of a chiral secondary amine. These reactions proceed in a γ'-regioselecitve vinylogous Michael addition via iminium catalysis, followed by an intramolecular 1,6-addition process via a cascade enamine catalysis.[13] A spectrum of bicyclo[2.2.2]octane frameworks with dense substitutions were efficiently constructed in excellent yields and stereoselectivity, which might find further application in organic synthesis.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, structural proofs, CIF file of enantiopure alcohol of **4g** (CCDC 1009387). See http://dx.doi.org/10.1039/b000000x/

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