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Stereodivergence in Amine-Catalyzed Regioselective [4 + 2] Cycloadditions of β-Substituted Cyclic Enones and Polyconjugated Malononitriles

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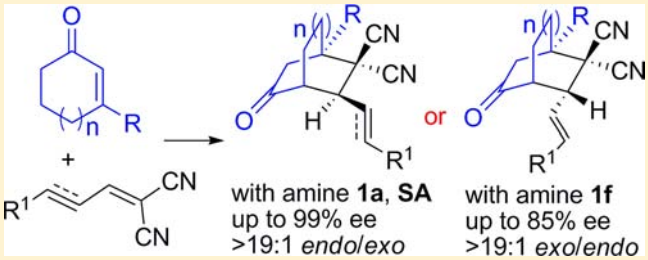
Supporting Information

ABSTRACT: Switchable reaction patterns of β-substituted cyclic enones via amine-based dienamine activation are reported. While γ-regioselective vinylogous Michael addition was observed with alkylidenemalononitriles, a completely different [4 + 2] cycloaddition was obtained with allylidene- or alkynylidenemalononitrile substrates, affording densely substituted bicyclo[2.2.2]octanes or analogous architectures with moderate to excellent diastereo- and enantioselectivity by the catalysis of primary amines from natural quinidine or quinine. Importantly, high diastereodivergence was achieved through unusual hydrogen-bonding interactions of multifunctional primary-amine catalytic systems. Endo cycloadducts were efficiently produced using a combination of 9-amino-9-deoxyepiquinidine and salicylic acid, while exo variants were obtained using 6′-hydroxy-9-amino-9-deoxyepiquinidine. Moreover, we successfully isolated the Michael addition intermediates in some cases, indicating that the above [4 + 2] reaction via dienamine catalysis may proceed by a stepwise Michael−Michael cascade rather than by a concerted Diels−Alder cycloaddition pathway.

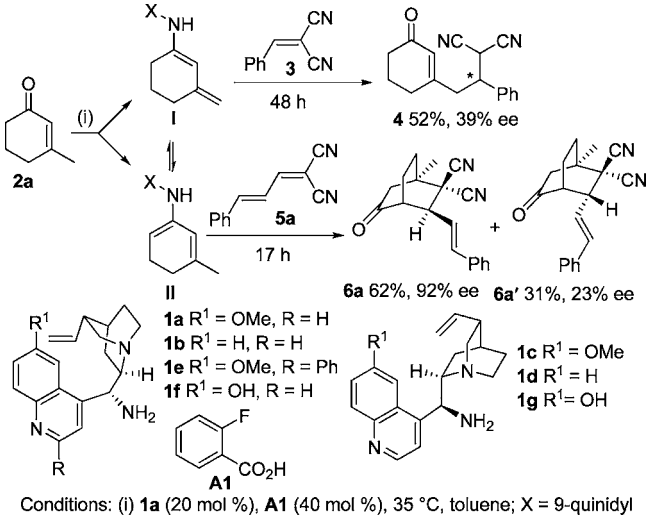


INTRODUCTION

2-Aminobutadienes, the dienamine species of α,β-unsaturated ketones, are valuable intermediates in organic synthesis. In 1992, the Enders group developed a diastereoselective [4 + 2] cycloaddition with nitroalkenes based on a chiral auxiliary strategy.[1] In 2002, Barbas and co-workers had reported the first amine-catalyzed direct [4 + 2] cycloaddition of α,β-unsaturated ketones and nitroalkenes.[2] Since then, several highly stereoselective [4 + 2] cycloadditions of α,β-unsaturated ketones and various electron-deficient dienophiles have been presented.[3] Despite the diversity of these reactions, only a few of them[3d,e] involve β,β-disubstituted enones,[4] probably because these compounds form a highly congested all-carbon quaternary stereocenter.[5] An even more important challenge to expanding these catalytic reactions is to diversify the diastereochemical outcomes of [4 + 2] cycloadditions of α,β-unsaturated ketones using the dienamine pathway.[6] To the best of our knowledge, such diastereodivergent cycloadditions have not been reported to date, although a variety of catalytic protocols have been developed over the past years to achieve stereodivergence in asymmetric synthesis.[7,8]

Dienamine catalysis can be used to expand the reaction diversity based on β-substituted cyclic enones. In fact, the Melchiorre group[9] reported that such substrates can be added to nitroalkenes by highly γ-regioselective Michael addition in the presence of a cinchona alkaloid-derived primary amine[10] via a pathway involving extended dienamine **I** (Scheme 1). The similar vinylogous Michael addition of β-methylcyclohexenone

Scheme 1. Switchable Regioselective Reaction Pathways of β-Methylcyclohexenone via Dienamine Catalysis



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(**2a**) to benzylidenemalononitrile (**3**) was observed to give product **4** under the catalytic action of the chiral primary amine 9-amino-9-deoxyepiquinidine (**1a**) and *o*-fluorobenzoic acid (**A1**), albeit with low enantioselectivity. Unexpectedly, the reaction pathway was switched completely when the electrophile was replaced with related substrate 3-phenylallylidenemalononitrile (**5a**). The crowded bicyclo[2.2.2]octane derivatives **6a** and **6a′**, whose skeleton is ubiquitous in natural products and biologically important compounds,[11] were delivered via cross-dienamine **II** with good enantioselectivity but a low endo/exo ratio.

To expand the usefulness of [4 + 2] cycloadditions involving *β*-substituted cyclic enones, we describe here a systematic study of the stereoselective [4 + 2] reaction of these compounds with polyconjugated malononitriles. Importantly, we achieved significant stereodivergence through unusual hydrogen-bonding interactions involving the identical multifunctional primary-amine catalytic systems derived from quinidine or quinine.

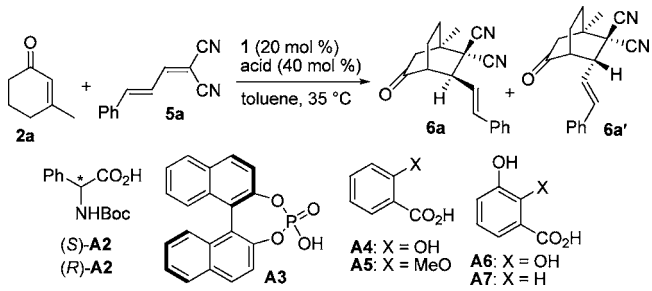
RESULTS AND DISCUSSION

Endo-Selective [4 + 2] Cycloaddition Survey. A variety of chiral primary amines **1a−g** derived from natural cinchona alkaloids (Scheme 1) were initially screened in the [4 + 2] cycloaddition of **2a** and **5a** (Table 1, entries 1−7). An excellent enantiomeric excess (ee) was obtained for the major endo diastereomer **6a** in the presence of catalyst **1e**, a derivative of **1a**,[10k] but the diastereomeric ratio (dr) was still disappointing (entry 5). Surprisingly, the diastereocontrol was switched in the presence of 6′-hydroxy-9-amino-9-deoxyepiquinidine (**1f**),[10e] and good diastereoselectivity with a modest ee was attained for the exo cycloadduct **6a′** (entry 6). The diastereoselectivity was also better for 6′-hydroxy-9-amino-9-deoxyepiquinine (**1g**) (entry 7). Thus, hydrogen bonding involving the 6′-OH group appears to improve the exo diastereoselectivity.

Some acid additives were also tested with amine **1e**. Similarly poor dr values were obtained for chiral *N*-Boc-phenylglycine (**A2**) and phosphoric acid **A3** (Table 1, entries 8−10), and almost no reaction occurred in the presence of *p*-toluenesulfonic acid (entry 11). To our gratification, using salicylic acid (**A4**) dramatically improved the endo selectivity and gave excellent enantioselectivity (entry 12). Similarly good results were obtained for the combination of amine **1a** and acid **A4** on both a small scale (entry 13) and a large scale (entry 14).[12] The *o*-OH group of acid **A4** appears to play a crucial role in this catalytic system,[13] since using *o*-methoxybenzoic acid (**A5**) gave lower diastereoselectivity (entry 15). Introducing another OH group at the meta position (**A6**) also decreased the stereocontrol (entry 16), and using *m*-hydroxybenzoic acid (**A7**) gave very poor results (entry 17). We were pleased to find that for amine **1c**, the diastereoselectivity could be switched using **A4**, producing the endo adduct **6a** having the configuration opposite to that of amine **1a** with excellent ee and a good dr (entry 18 vs entry 3).

Reaction Scope of Endo [4 + 2] Cycloaddition. After optimizing the catalytic conditions, we investigated the reactions of a variety of *β*-substituted cyclic enones **2** and polyconjugated malononitriles in the presence of amine **1a** and acid **A4**. The results are summarized in Table 2. Allylidenemalononitriles **5** bearing diverse aryl groups with either electron-donating or -withdrawing groups were well-tolerated in cycloadditions with **2a**, and most produced the corresponding products **6a−g** with excellent diastereo- and enantioselectivities (entries 1−7). A heteroaryl-substituted diene substrate also

Table 1. Screening of Conditions for the [4 + 2] Cycloaddition Involving *β*-Methylcyclohexenone (2a) and 3-Phenylallylidenemalononitrile (5a)[a]



entry	1	acid	*t* (h)	yield (%)[b]	6a:6a′	ee (%)[c]
1	**1a**	**A1**	17	93	2:1	92/23
2	**1b**	**A1**	18	94	1.2:1	89/35
3	**1c**	**A1**	16	90	1:2	−86/−64
4	**1d**	**A1**	15	94	1:1.5	−80/−67
5	**1e**	**A1**	21	88	2.5:1	97/63
6	**1f**	**A1**	47	88	1:9	−/76
7	**1g**	**A1**	43	83	1:6	−/−80
8	**1e**	(*S*)-**A2**	26	91	2:1	88/51
9	**1e**	(*R*)-**A2**	26	88	2.1:1	91/56
10	**1e**	**A3**	43	80	2.5:1	82/38
11	**1e**	TsOH[d]	24	–	–	–
12	**1e**	**A4**	23	85	8.2:1	97/−
13	**1a**	**A4**	**19**	**83**	**8:1**	**99**/−
14[e]	**1a**	**A4**	41	82	7.6:1	98/−
15	**1a**	**A5**	18	83	3:1	90/−
16	**1a**	**A6**	19	87	4:1	95/−
17	**1a**	**A7**	19	90	1:1.4	77/17
18	**1c**	**A4**	**24**	**91**	**4:1**	**−96**/−

[a]Unless noted otherwise, the reactions were performed with 0.12 mmol of **2a**, 0.1 mmol of **5a**, 20 mol % **1**, and 40 mol % acid in 1 mL of toluene at 35 °C. [b]Combined isolated yields of separable **6a** and **6a′**. [c]ee for **6a**/ee for **6a′**, as determined by chiral HPLC analysis. [d]TsOH = *p*-toluenesulfonic acid. [e]The reaction was run on a 1.0 mmol scale.

gave noteworthy results (entry 8). Comparable stereocontrol was observed in reactions between **5a** and cyclohexenones with larger *β*-alkyl or even alkenyl groups (entries 9−11). In fact, a 2-phenylethynyl-substituted cyclohexenone showed complete diastereocontrol, albeit with lower reactivity (entry 12); this compound also reacted with alkyl-substituted allylidenemalononitriles to give products **6m** and **6n** with good results (entries 13 and 14). Simple 2-cyclohexenone also delivered good data (entry 15). Using *β*-methylcyclopentenone provided product **6p** with exclusive diastereocontrol, though the ee value was moderate (entry 16). In comparison, high enantioselectivity with modest diastereoselectivity was obtained for *β*-methylcycloheptenone (entry 17).[14] On the other hand, additional substrates were used to explore the catalytic efficacy of amine **1c**. An array of cycloadducts were obtained with the opposite configuration to that of catalyst **1a**; the enantioselectivities were excellent, although the dr values were modest (entries 18−22).[15]

Notably, it was found that alkynylidenemalononitrile substrates **7** also exhibited high reactivities in the [4 + 2] cycloadditions with *β*-substituted cyclic enones under the same catalytic conditions. As summarized in Table 3, an array of chiral cycloadducts **8a−i** with different alkynyl groups were

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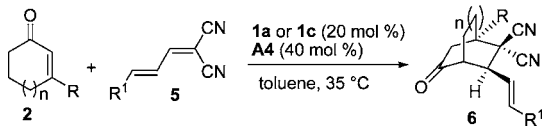
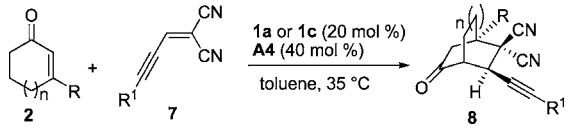
Table 2. Substrate Scope of Endo Cycloadditions with Cyclic Enones and Allylidenemalononitriles[a]



entry	n	R	R^1	t (h)	**6**, yield (%)[b]	dr[c]	ee (%)[d]
1	1	Me	Ph	19	**6a**, 82	8:1	99
2	1	Me	*p*-MeC_6H_4	22	**6b**, 85	11:1	99
3	1	Me	3,4-$(MeO)_2C_6H_3$	19	**6c**, 78	9:1	98
4	1	Me	*m*-ClC_6H_4	16	**6d**, 80	10:1	99
5	1	Me	*p*-ClC_6H_4	22	**6e**, 84	12:1	99[e]
6	1	Me	*o*-BrC_6H_4	74	**6f**, 78	12:1	98
7	1	Me	*p*-BrC_6H_4	22	**6g**, 87	12:1	99
8	1	Me	2-furyl	24	**6h**, 86	11:1	99
9	1	*n*Bu	Ph	23	**6i**, 89	13:1	98
10	1	vinyl	Ph	28	**6j**, 78	10:1	97
11	1	1-propenyl	Ph	36	**6k**, 80	9:1	94
12	1	PhC≡C	Ph	62	**6l**, 91	>19:1	97
13	1	PhC≡C	*n*Pr	72	**6m**, 72	>19:1	97
14	1	PhC≡C	*i*Pr	72	**6n**, 41	>19:1	91
15	1	H	Ph	32	**6o**,76	7.5:1	96
16	0	Me	Ph	29	**6p**, 94	>19:1	75
17	2	Me	Ph	45	**6q**, 66	4:1	92
18[f]	1	Me	*p*-MeC_6H_4	19	**6b**, 65	3.5:1	−96
19[f]	1	Me	*m*-ClC_6H_4	35	**6d**, 70	4:1	−97
20[f]	1	*n*Bu	Ph	33	**6i**, 66	3:1	−95
21[f]	1	vinyl	Ph	29	**6j**, 67	4:1	−96
22[f]	1	PhC≡C	Ph	59	**6l**,71	5:1	−94

[a]Unless noted otherwise, the reactions were performed with 0.12 mmol of **2**, 0.1 mmol of **5**, 20 mol % **1a**, and 40 mol % **A4** in 1 mL of toluene at 35 °C. [b]Isolated yields of the pure endo isomers. [c]Determined by ^{1}H NMR analysis of the crude products. [d]Determined by chiral HPLC analysis. [e]The absolute configuration of **6e** was determined by X-ray analysis. Those of the other products were assigned by analogy. [f]Catalyst **1c** was used.

Table 3. Substrate Scope of Endo Cycloadditions with Cyclic Enones and Alkynylidenemalononitriles[a]



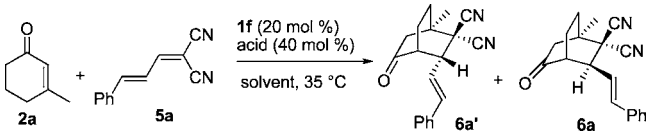
entry	n	R	R^1	t (h)	**8**, yield (%)[b]	dr[c]	ee (%)[d]
1	1	Me	Ph	12	**8a**, 89	>19:1	96
2	1	Ph	Ph	18	**8b**,72	5.5:1	85
3	1	PhC≡C	Ph	15	**8c**, 91	>19:1	97
4	1	Me	*p*-ClC_6H_4	12	**8d**, 86	>19:1	94
5	1	Me	*p*-BrC_6H_4	17	**8e**, 82	>19:1	96
6	1	Me	*m*-CNC_6H_4	22	**8f**, 73	>19:1	96
7	1	Me	*o*-$MeOC_6H_4$	17	**8g**, 83	>19:1	95
8	1	Me	2-thienyl	25	**8h**, 78	>19:1	93
9	2	Me	Ph	28	**8i**, 56	6:1	85
10[e]	1	Me	Ph	18	**8a**, 71	5:1	−95
11[e]	1	PhC≡C	Ph	17	**8c**, 74	4.5:1	−95

[a]Unless noted otherwise, the reactions were performed with 0.12 mmol of **2**, 0.1 mmol of **7**, 20 mol % **1a** and 40 mol % **A4** in 1 mL of toluene at 35 °C. [b]Isolated yields of the pure endo isomers. [c]Determined by ^{1}H NMR analysis of the crude products. [d]Determined by chiral HPLC analysis. [e]Catalyst **1c** was used.

efficiently constructed with good stereoselectivity in the presence of amine **1a** (entries 1−9) or **1c** (entries 10 and 11).

Exo-Selective [4 + 2] Cycloaddition Survey. We also conducted further studies of reactions involving amines **1f** or **1g** with a 6′-OH group, since these amines switch the diastereoselectivity to the exo products, as illustrated in Table 1, entries 6 and 7. Therefore, we further optimized the conditions to improve the results for the exo cycloadditions. The data are summarized in Table 4. At first, more acidic

Table 4. Screening of Conditions for the Exo [4 + 2] Cycloaddition[a]



entry	**1**	acid	solvent	t (h)	yield (%)[b]	**6a′**:**6a**	ee (%)[c]
1	**1f**	(*S*)-**A2**	toluene	46	84	>19:1	79
2	**1f**	(*R*)-**A2**	toluene	46	86	>19:1	78
3	**1f**	**A3**	toluene	46	56	>19:1	61
4	**1f**	**A4**	toluene	46	78	5:1	74
5	**1f**	(*S*)-**A2**	THF	59	78	8:1	30
6	**1f**	(*S*)-**A2**	Et_2O	48	67	8:1	56
7	**1f**	(*S*)-**A2**	DCM	52	88	9:1	63
8	**1f**	(*S*)-**A2**	MeCN	48	72	9:1	−11
9[d]	**1f**	(*S*)-**A2**	**toluene**	**46**	**79**	**>19:1**	**85**

[a]Unless noted otherwise, the reactions were performed with 0.12 mmol of **2a**, 0.1 mmol of **5a**, 20 mol % **1f**, and 40 mol % acid in 1 mL of toluene at 35 °C. [b]Combined isolated yields of **6a** and **6a′**. [c]ee of **6a′** as determined by chiral HPLC analysis. [d]The reaction was run at room temperature.

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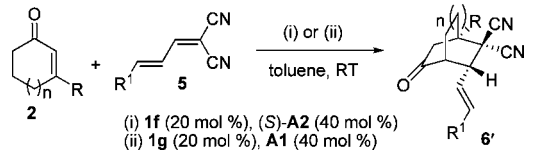
additives were screened (entries 1–4). Exclusive exo control was observed in the presence of amine **1f** and chiral acid **A2**, while the enantioselectivity was slightly improved (entries 1 and 2). It should be noted that the exo selectivity was decreased when acid **A4** was used (entry 4), indicating that the hydrogen-bonding interaction of the OH group of **A4** would affect that of chiral amine **1f**. A few solvents were investigated using the combination of **1f** and (*S*)-**A2** but generally provided inferior results (entries 5–8). Even the enantioselectivity was inverted in MeCN (entry 8). Finally, it was found that the reaction still proceeded smoothly in toluene at ambient temperature, leading to the exo cycloadduct with better enantioselectivity (entry 9).

Reaction Scope of the Exo [4 + 2] Cycloaddition. Consequently, a number of cyclic enones and allylidenemalononitriles **5** in toluene at ambient temperature were explored in toluene at ambient temperature. The results are summarized in Table 5. Good enantioselectivity with moderate to excellent diastereoselectivity was obtained for the reactions of various cyclohexenones and allylidenemalononitriles by the catalysis of amine **1f** and (*S*)-**A2** (entries 1–7), and similar data were obtained with β-methylcycloheptenone (entry 8). Nevertheless, *o*-fluorobenzoic acid **A1** was found to be a superior additive when used in combination with amine **1g**. Exo enantiomers with the opposite configuration to that of amine **1f** were produced with comparable stereoselectivities (entries 9–14).

Table 5. Substrate Scope of the Exo Cycloaddition[a]



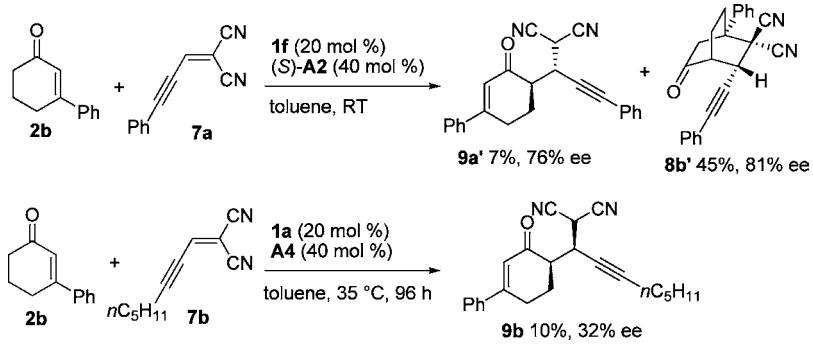
entry	*n*	R	R^1	*t* (h)	6′, yield (%)[b]	dr[c]	ee (%)[d]
1	1	Me	Ph	46	**6a′**, 76	>19:1	85
2	1	Me	*p*-MeC_6H_4	71	**6b′**, 65	>19:1	82
3	1	Me	*p*-ClC_6H_4	49	**6e′**, 66	8:1	84[e]
4	1	Me	2-furyl	48	**6h′**, 73	>19:1	81
5	1	*n*Bu	Ph	72	**6i′**, 55	6:1	68
6	1	PhC≡C	Ph	58	**6l′**, 53	4:1	71
7	1	H	Ph	58	**6o′**, 64	9:1	80
8	2	Me	Ph	96	**6q′**, 63	8:1	82
9	1	Me	Ph	61	**6a′**, 62	6:1	−82
10	1	Me	*p*-MeC_6H_4	52	**6b′**, 55	8:1	−81
11	1	Me	*p*-ClC_6H_4	56	**6e′**, 60	7:1	−82
12	1	Me	2-furyl	68	**6h′**, 62	9:1	−79
13	1	*n*Bu	Ph	70	**6i′**, 54	6:1	−65
14	1	PhC≡C	Ph	47	**6l′**, 55	3.8:1	−71

[a]The reactions were performed with 0.12 mmol of **2** and 0.1 mmol of **5** in 1 mL of toluene at room temperature [entries 1–8, conditions (i); entries 9–14, conditions (ii)]. [b]Isolated yields of the pure exo isomers. [c]Determined by ^1H NMR analysis of the crude products. [d]Determined by chiral HPLC analysis. [e]The absolute configuration of **6e′** was determined by X-ray analysis. Those of the other products were assigned by analogy.

Preliminary Mechanism Studies with Experimental Observations. Although the early investigations of amine-catalyzed direct [4 + 2] cycloadditions of α,β-unsaturated ketones with electron-deficient dienophiles involving the in situ generation of 2-amino-1,3-butadienes suggested that such reactions proceed via a concerted Diels–Alder reaction pathway, no affirmative evidence has been provided by either experimental or computational results to date.[2,3,16] In addition, a stepwise mechanism involving double Michael addition has also been proposed for the amine-catalyzed [4 + 2] processes of α,β-unsaturated ketones, but still without authoritative proof.[17] In contrast, we fortunately isolated a low yield of the Michael addition intermediate **9a′** in the reaction of β-phenylcyclohexenone **2b** and alkynylidenemalononitrile **7a** in the presence of amine **1f** and acid (*S*)-**A2**, along with the expected exo cycloadduct **8b′**. Compound **9a′** could be converted to cycloadduct **8b′** under the same catalytic conditions, verifying that **9a′** is the reaction intermediate. Moreover, the Michael addition product **9b** was dominantly generated in the reaction of enone **2b** and alkynylidenemalononitrile **7b** bearing an δ-alkyl group by the catalysis of amine **1a** and salicylic acid **A4**, albeit in low yield (Scheme 2). Therefore, this amine-catalyzed [4 + 2] cycloaddition reaction is more likely to occur by a stepwise Michael–Michael addition pathway.[18]

On the other hand, in contrast to the vinylogous Michael addition reported by Melchiorre,[9] the same [4 + 2] cycloaddition as for polyconjugated malononitriles also occurred in the reaction of 1-nitrodiene **10** and β-methylcyclohexenone **2a** through the catalytic action of amine **1a** and acid **A4**. Product **11a** was obtained with exclusive endo selectivity in fair yield as a result of lower reactivity (Scheme 3). Interestingly, the Michael addition intermediate **12** was isolated as a major product in the reaction of diene **10** and simple cyclohexenone **2c** under the same catalytic conditions, which also supports a stepwise Michael–Michael addition cascade. It should be noted that exo-**11a** and exo-**11b** were produced for the same substrate combinations catalyzed by supramolecular self-assemblies formed from chiral amines and poly(alkene glycol)s, through a proposed Diels–Alder reaction pathway.[19]

Scheme 2. Isolation of Michael Addition Intermediates



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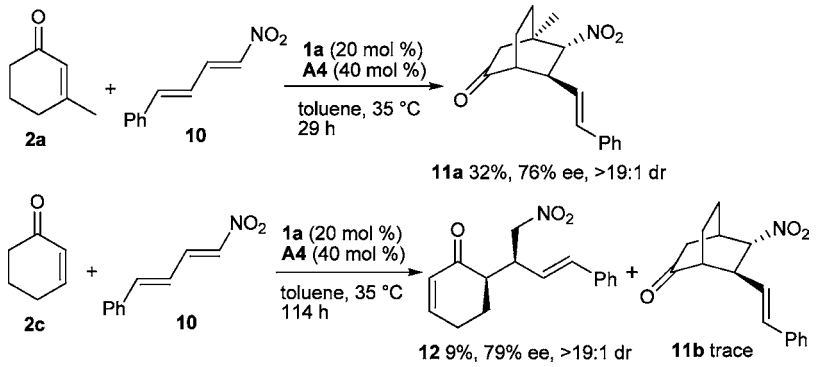
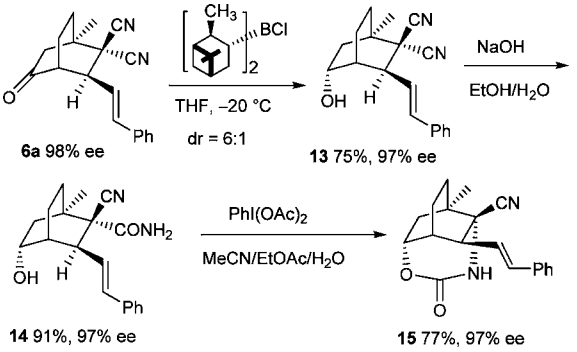
Scheme 3. Reactions of 1-Nitrodiene Substrate 10 via Dienamine Catalysis



Synthetic Transformations of Cycloadduct 6a. The multifunctionality of the cycloadducts allows certain highly chemoselective transformations. We could diastereoselectively reduce the carbonyl group of cycloadduct **6a** using (−)-DIP-chloride, giving separable alcohol **13** in good yield (Scheme 4).

Scheme 4. Synthetic Transformations of Cycloadduct 6a



Notably, the endo cyano group could be selectively hydrolyzed to an amide group without affecting the exo one, probably because of steric hindrance. We further carried out an efficient Hoffman degradation reaction with the corresponding amide **14**, affording complex caged carbamate product **15**.

CONCLUSION

We have developed aminocatalytic asymmetric and regioselective [4 + 2] cycloadditions of β-substituted cyclic enones with polyconjugated malononitriles. High stereodivergence has been achieved by relying on different hydrogen-bonding interactions. Endo cycloadducts were efficiently produced using the combined catalytic system of 9-amino-9-deoxyepiquinidine and salicylic acid, while exo variants were produced using 6′-hydroxy-9-amino-9-deoxyepiquinidine. Moreover, the corresponding products with the opposite configuration could be obtained using catalytic chiral amines derived from natural quinine, further improving the stereodivergent outcomes with the same substrates. A broad spectrum of densely substituted bicyclo[2.2.2]octanes and related architectures have been constructed with moderate to excellent enantioselectivities. Moreover, we have provided direct experimental proofs that the above [4 + 2] process via dienamine catalysis may occur in a stepwise Michael−Michael cascade rather than via a concerted Diels−Alder cycloaddition. We hope that such multifunctional catalytic systems will be applicable to more stereodivergent reactions involving dienamine or other types of amine catalysis.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, characterization data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Enders, D.; Meyer, O.; Raabe, G. *Synthesis* **1992**, 1242 and references therein.

(2) Thayumanavan, R.; Dhevalapally, B.; Sakthivel, K.; Tanaka, F.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 3817.

(3) For selected examples, see: (a) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2003**, *42*, 4233. (b) Ramachary, D. B.; Barbas, C. F., III. *Chem.—Eur. J.* **2004**, *10*, 5323. (c) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2003**, *5*, 4301. (d) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962. (e) Xu, D.-Q.; Xia, A.-B.; Luo, S.-P.; Tang, J.; Zhang, S.; Jiang, J.-R.; Xu, Z.-Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 3821. (f) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200. (g) Wu, L.-Y.; Bencivenni, G.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7196.

(4) For selected examples involving iminium activation, see: (a) Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662. (b) Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070. (c) Li, P.; Wang, Y.; Liang, X.; Ye, J. *Chem. Commun.* **2008**, 3302. (d) De Vincentiis, F.; Bencivenni, G.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Galzerano, P.; Melchiorre, P. *Chem.—Asian J.* **2010**, *5*, 1652. (e) Kwiatkowski, P.; Dudziński, K.; Łyżwa, D. *Org. Lett.* **2011**, *13*, 3624.

(5) For recent reviews of the construction of quaternary chiral centers, see: (a) Prakash Das, J.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593. (b) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295. (c) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583.

(6) For a review of dienamine catalysis, see: Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865.

(7) For reviews, see: (a) Bartók, M. *Chem. Rev.* **2010**, *110*, 1663. (b) Hatano, M.; Ishihara, K. *Chem. Commun.* **2012**, *48*, 4273.
(8) For selected examples of diastereodivergent catalysis, see: (a) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2327. (b) Huang, Z.-Z.; Kang, Y.-B.; Zhou, J.; Ye, M.-C.; Tang, Y. *Org. Lett.* **2004**, *6*, 1677. (c) Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 9630. (d) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979. (e) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768. (f) Yan, X.-X.; Peng, Q.; Li, Q.; Zhang, K.; Yao, J.; Hou, X.-L.; Wu, Y.-D. *J. Am. Chem. Soc.* **2008**, *130*, 14362. (g) Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3779. (h) Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2009**, *11*, 677. (i) Tian, X.; Cassani, C.; Liu, Y.; Moran, A.; Urakawa, A.; Galzerano, P.; Arceo, E.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 17934. (j) Kim, H. Y.; Li, J.-Y.; Kim, S.; Oh, K. *J. Am. Chem. Soc.* **2011**, *133*, 20750. (k) Lu, G.; Yoshino, T.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4382. (l) Maroto, E. E.; Filippone, S.; Martín-Domenech, A.; Suarez, M.; Martín, N. *J. Am. Chem. Soc.* **2012**, *134*, 12936.
(9) Bencivenni, G.; Galzerano, P.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20642.
(10) For reviews of cinchona-based primary aminocatalysis, see: (a) Chen, Y.-C. *Synlett* **2008**, 1919. (b) Jiang, L.; Chen, Y.-C. *Catal. Sci. Technol.* **2011**, *1*, 354. (c) Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748. For selected examples, see: (d) Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 389. (e) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667. (f) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422. (g) Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 8134. (h) Zhou, J.; Wakchaure, V.; Kraft, P.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7656. (i) Zhang, E.; Fan, C.-A.; Tu, Y.-Q.; Zhang, F.-M.; Song, Y.-L. *J. Am. Chem. Soc.* **2009**, *131*, 14626. (j) Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 9685. (k) Lifchits, O.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 10227. (l) Lee, A.; Michrowska, A.; Sulzer-Mosse, S.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 1707. (m) Cai, Q.; Zheng, C.; Zhang, J.-W.; You, S.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8665. (n) Xiong, X.-F.; Zhou, Q.; Gu, J.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2012**, *51*, 4401. (o) Tian, X.; Liu, Y.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 6439. (p) Lee, J. H.; Deng, L. *J. Am. Chem. Soc.* **2012**, *134*, 18209.
(11) For selected examples, see: (a) Toyota, M.; Yokota, M.; Ihara, M. *Org. Lett.* **1999**, *1*, 1627. (b) Li, S.-H.; Wang, J.; Niu, X.-M.; Shen, Y.-H.; Zhang, H.-J.; Sun, H.-D.; Li, M.-L.; Tian, Q.-E.; Lu, Y.; Cao, P.; Zheng, Q.-T. *Org. Lett.* **2004**, *6*, 4327. (c) Jayasuriya, H.; Herath, K. B.; Zhang, C.; Zink, D. L.; Basilio, A.; Genilloud, O.; Diez, M. T.; Vicente, F.; Gonzalez, I.; Salazar, O.; Pelaez, F.; Cummings, R.; Ha, S.; Wang, J.; Singh, S. B. *Angew. Chem., Int. Ed.* **2007**, *46*, 4684. (d) Lim, S.-H.; Sim, K.-M.; Abdullah, Z.; Hiraku, O.; Hayashi, M.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1380. (e) Spangler, J. E.; Sorensen, E. J. *Tetrahedron* **2009**, *65*, 6739. (f) Sacher, J. R.; Weinreb, S. M. *Org. Lett.* **2012**, *14*, 2172. (g) Abdelkafi, H.; Herson, P.; Nay, B. *Org. Lett.* **2012**, *14*, 1270.
(12) (a) Jadhav, M. S.; Righi, P.; Marcantoni, E.; Bencivenni, G. *J. Org. Chem.* **2012**, *77*, 2667. (b) Also see refs 9 and 10n.
(13) (a) Mandal, T.; Zhao, C.-G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7714. (b) Xia, A.-B.; Xu, D.-Q.; Luo, S.-P.; Jiang, J.-R.; Tang, J.; Wang, Y.-F.; Xu, Z.-Y. *Chem.—Eur. J.* **2010**, *16*, 801. (c) Ramachary, D. B.; Sakthidevi, R.; Shruthi, K. S. *Chem.—Eur. J.* **2012**, *18*, 8008. (d) Nugent, T. C.; Sadiq, A.; Bibi, A.; Heine, T.; Zeonjuk, L. L.; Vankova, N.; Bassil, B. S. *Chem.—Eur. J.* **2012**, *18*, 4088.
(14) Linear enones did not participate in such [4 + 2] cycloadditions.
(15) For an exploration of more polyconjugated substrates, see the Supporting Information.
(16) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580.
(17) Westermann, B.; Ayaz, M.; van Berkel, S. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 846.
(18) We still cannot rule out the possibility that the reactions reported in Tables 2 and 3 proceed via a concerted cycloaddition pattern because the corresponding Michael addition intermediates have not yet been detected.
(19) Xia, A.-B.; Xu, D.-Q.; Wu, C.; Zhao, L.; Xu, Z.-Y. *Chem.—Eur. J.* **2012**, *18*, 1055.