Organocatalysis

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Asymmetric [5+3] Formal Cycloadditions with Cyclic Enones through Cascade Dienamine–Dienamine Catalysis**

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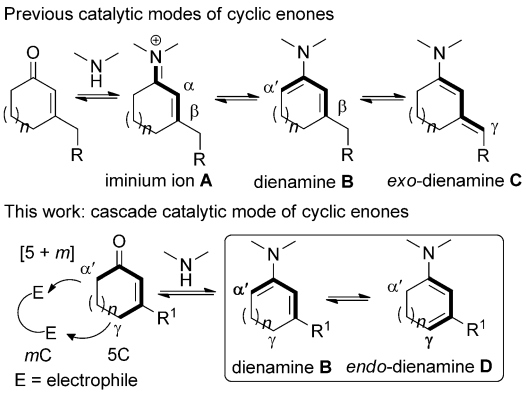
Abstract: *A few aminocatalytic modes, such as iminium ions and different dienamines, have provided versatile tools for the functionalization of cyclic enones at various sites. Described here is a previously unreported cascade dienamine/dienamine catalytic pathway for β-substituted 2-cyclopentenones, and even 2-cyclohexenone. It involves domino α′-regioselective Michael addition and a γ-regioselective Mannich reaction with 3-vinyl-1,2-benzoisothiazole-1,1-dioxides to give fused or bridged architectures, which incorporate a spirocyclic skeleton, in excellent stereocontrol, thus furnishing unusual [5+3] formal cycloaddition reactions. Moreover, preliminary biological assays showed that some of the chiral products exhibited promising activity against some cancer cell lines, thus indicating that such skeletons might serve as leads in drug discovery.*

The α,β-unsaturated cyclic ketones are versatile reactants in organic chemistry. They have been extensively applied in asymmetric catalysis by the covalent activation of a chiral amine. The most common aminocatalytic mode for cyclic enones, pioneered by Yamaguchi et al. and MacMillan et al., involves the generation of the LUMO-lowered iminium ion intermediates **A**, thus enabling β- or α,β-functionalizations by either Michael addition or cycloaddition reactions (Scheme 1).[1,2] In contrast, the HOMO-raised cross-conjugated dienamine species **B** from cyclic enones and an amine catalyst, based on an alternative strategy developed by Barbas and co-workers,[3] could react with electron-deficient dienophiles in an α′,β-regioselective [4+2] cycloaddition manner.[4] In addition, the group of Melchiorre further developed γ-regioselective vinylogous Michael additions or aldol reactions with β-substituted 2-cyclohexenones by the formation of the linear *exo*-dienamines **C**.[5]

Recently, we also developed diastereodivergent [4+2] cycloadditions of a variety of β-substituted cyclic enones and polyconjugated malononitriles to construct chiral bridged



Scheme 1. Different aminocatalytic modes of cyclic enones.

architectures through the dienamines **B**.[6] We were fascinated by the unprecedented catalytic pathway of a cyclic enone substrate, a pathway wherein formation of the cross-conjugated dienamine[3] **B** is followed by formation of the linear *endo*-type dienamine **D**.[7] As a result, chiral fused or even bridged frameworks would be delivered from domino α′- and γ-regioselective additions to suitable reactants, containing two electrophilic groups, in a formal [5+*m*] cycloaddition (Scheme 1).[8]

The initial screening using a variety of multifunctional electrophiles[9] showed that 3-styryl-1,2-benzoisothiazole-1,1-dioxide[10] (**3a**) was a good bis(electrophilic) partner in the reaction with β-phenyl 2-cyclopentenone (**2a**). The [5+3] formal cycloaddition product **4a**,[11] which possesses four contiguous chiral centers, including a quaternary spiro one, was obtained under the catalysis of 9-amino-9-deoxyepiquinine (**1a**) and benzoic acid (**A1**) in toluene at 35 °C (Table 1).[12] The reaction exhibited high chemoselectivity, thus proceeding in the above-mentioned α′-regioselective Michael addition with a subsequent γ-regioselective intramolecular Mannich reaction. Moreover, the stereoselectivity was quite promising (80 % *ee*, > 19:1 d.r.), while the yield was only fair because of incomplete conversion after 84 hours (Table 1, entry 1). Subsequently, a number of reaction parameters were investigated. While almost no reaction or inferior results were observed in $PhCF_3$, THF, and CH_2Cl_2 (Table 1, entries 2–4), the use of the catalyst system of **1a** and **A1** led to higher enantioselectivity in $CHCl_3$, albeit with a poorer yield (Table 1, entry 5). A few acid additives were then screened in $CHCl_3$ (Table 1, entries 6–8), and the enantiopure **4a** could be obtained by using 5-nitrosalicylic acid (**A4**), albeit with an unsatisfactory yield (Table 1, entry 8). Inferior results were observed under the catalysis of 6′-OH-9-amino-9-deoxyepi-

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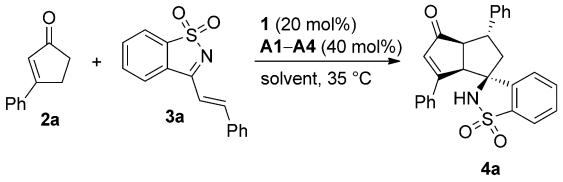
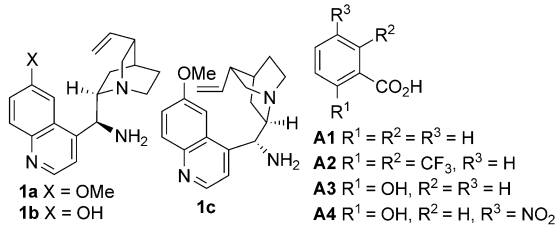
Table 1: Screening studies of [5+3] formal cycloaddition of β-phenyl-2-cyclopentenone (**2a**) and the 1-azadiene **3a**.[a]

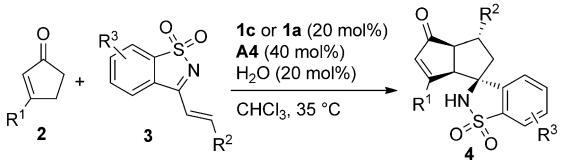


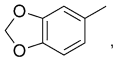


Nr.	1	Solvent	Acid	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	toluene	**A1**	84	42	−80
2	**1a**	$PhCF_3$	**A1**	84	trace	–
3	**1a**	THF	**A1**	84	trace	–
4	**1a**	CH_2Cl_2	**A1**	84	23	−77
5	**1a**	$CHCl_3$	**A1**	84	38	−86
6	**1a**	$CHCl_3$	**A2**	84	33	−90
7	**1a**	$CHCl_3$	**A3**	84	55	−95
8	**1a**	$CHCl_3$	**A4**	72	62	−99
9	**1b**	$CHCl_3$	**A4**	72	48	−84
10	**1c**	$CHCl_3$	**A4**	72	66	99
11[d]	**1c**	$CHCl_3$	**A4**	72	71	99
12[d,e]	**1c**	$CHCl_3$	**A4**	60	85	99

[a] Unless noted otherwise, reactions were performed with the enone **2a** (0.2 mmol), **3a** (0.1 mmol), amine **1** (20 mol%), and acid (40 mol%) in solvent (1 mL) at 35°C. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral column; d.r. > 19:1 as determined by ^{1}H NMR analysis. [d] Adding 20 mol% of H_2O. [e] **3a** was added in three portions. THF = tetrahydrofuran.

Table 2: Substrate scope and limitations of [5+3] formal cycloadditions.[a]



Nr.	R^1	R^2, R^3	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	Ph, H	60	**44a**, 85	>99
			(72)	(80)	(>99)
2	*p*-$MeOC_6H_4$	Ph, H	60	**4b**, 85	>99
			(72)	(82)	(>99)
3	3,5-$(CF_3)_2C_6H_3$	Ph, H	60	**4c**, 88	>99
			(72)	(85)	(>99)
4	*p*-FC_6H_4	Ph, H	60	**4d**, 79	>99
5	1-naphthyl	Ph, H	60	**4e**, 84	>99
6	2-thienyl	Ph, H	60	**4f**, 65	99
7	2-furyl	Ph, H	60	**4g**, 58	98
8	2-benzofuryl	Ph, H	60	**4h**, 75	97
9	Me	Ph, H	84	**4i** 73	>99[d]
10[f]	Me	Ph, H	84	**4i**, 87	>99
11	*n*Bu	Ph, H	84	**4j**, 84	98
12	*c*Hex	Ph, H	84	**4k**, 74	>99
13	*t*Bu	Ph, H	84	**4l**, 71	97
14	H	Ph, H	84	–	–
15	1-Propenyl	Ph, H	84	**4m**, 46	>99
16	$MeO_2CCH{=}CH$-	Ph, H	84	**4n**, 53	>99
17	Ph	*p*-ClC_6H_4, H	72	**4o**, 87	>99
18	Ph	2-F-4-BrC_6H_3, H	60	**4p**, 82	95
19	Ph	2-furyl, H	60	**4q**, 67	>99
20	Ph	2-styryl, H	60	**4r**, 78	>99
21	Ph	*c*Hex, H	84	–	–
22	*n*Bu	*m*-$MeOC_6H_4$, H	84	**4s**, 77	>99
23	*n*Bu	 , H	84	**4t**, 80	97
24	*n*Bu	*p*-BrC_6H_4, H	72	**4u**, 93	97
25	*n*Bu	2-thienyl, H	84	**4v**, 63	98
26	*n*Bu	Ph, 5,7-Me_2	72	**4w**, 90	98
27	*n*Bu	Ph, 6-Cl	84	**4x**, 95	99

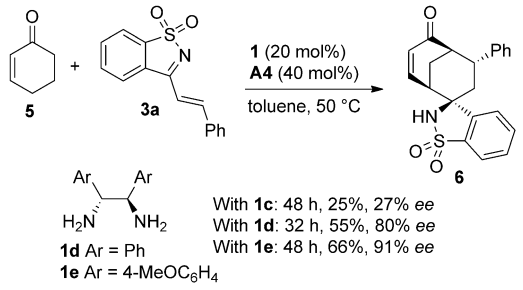
[a] Unless noted otherwise, reactions were performed with the enone **2** (0.2 mmol), **3** (0.1 mmol), **1c** (20 mol%), **A4** (40 mol%), and H_2O (20 mol%) in $CHCl_3$ (1 mL) at 35°C. The substrate **3** was added in three portions. Data within parentheses were obtained with **1a**. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral column; d.r. > 19:1 as determined by by ^{1}H NMR analysis. [d] The absolute configuration of **4i** was determined by X-ray analysis. See the Supporting Information.[13] The other products were assigned by analogy. [f] With 1 mmol of **3a**.

quinine (**1b**) and **A4** (Table 1, entry 9), whereas using 9-amino-9-deoxyepiquinidine (**1c**) provided the product having the opposite configuration but with the same enantiocontrol and with a slightly higher yield (Table 1, entry 10). It was pleasing that better yield could be obtained by adding some H_2O without affecting the enantioselectivity (Table 1, entry 11). Given that **3a** has low solubility in $CHCl_3$, the yield was further improved by adding **3a** in three portions (Table 1, entry 12).

With the optimal reaction conditions in hand, we then investigated a variety of 2-cyclopentenones and 3-vinyl-1,2-benzoisothiazole-1,1-dioxides under the catalysis of either **1c** or **1a** in combination with **A4**. The results are summarized in Table 2. In general, the 2-cyclopentenones **2**, having a variety of β-aryl groups (Table 2, entries 1–5), including a strongly electron-withdrawing group (Table 2, entry 4), were well tolerated in the reactions with **3a**, thus producing the corresponding [5+3] cycloadducts in high yields and with almost enantiomerical purity. A few heteroaryl-substituted 2-cyclopentenones also provided the products with remarkable enantioselectivity, though slightly lower yields were obtained (Table 2, entries 6–8). It was pleasing that 2-cyclopentenones with various linear or branched β-alkyl groups exhibited the same reaction pattern, and the desired products were attained with excellent enantiocontrol (Table 2, entries 9, and 11–13). Even a higher yield with the same *ee* value was obtained on a larger scale (Table 2, entry 10). However, simple 2-cyclopentenone showed no reactivity under the current catalytic conditions (Table 2, entry 14). Importantly, the 2-cyclopentenones **2** bearing β-alkenyl groups, could be smoothly utilized, thus providing densely functionalized products in outstanding enantioselectivity, albeit with lower yields because of side reactions (Table 2, entries 15 and 16). In contrast, an array of 3-vinyl-1,2-benzoisothiazole-1,1-dioxides (**3**) with different

substitutions were investigated in combination with the 2-cyclopentenones. The expected products were generally obtained with outstanding enantioselectivity and with good to high yields (Table 2, entries 17–27), while a cyclohexyl-substituted substrate showed much lower reactivity (Table 2, entry 21). In addition, products with the opposite configuration were produced with excellent results under the catalysis of **1a** (data within parentheses in Table 2).

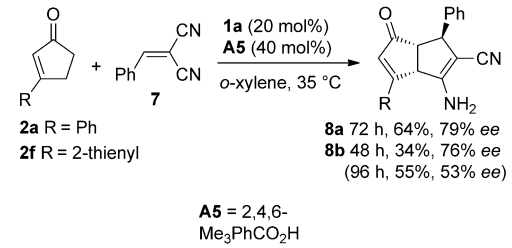
Although simple 2-cyclopentenone did not give the cycloadduct when using **3a**, it was pleasing that a more challenging bridged [5+3] product (**6**) was detected in the reaction of 2-cyclohexenone **5** and **3a** under the catalysis of **1c** and **A4** in toluene at 50 °C (Scheme 2). The yield was very low



Scheme 2. Construction of bridged [5+3] product with 2-cyclohexenone.

as a result of side reactions, and the enantioselectivity was also disappointing. Fortunately, it was found that the amine catalyst could play a significant role in the reaction outcome.[9] A commercially available chiral amine, (*R*,*R*)-1,2-diphenylethanediamine (**1d**), predominantly produced the desired product **6** with much higher enantioselectivity.[14] An excellent *ee* value (91%) with a moderate yield for **6** was finally obtained by employing **1e** as the catalyst.[15]

The bis(electrophilic) partners are not limited to 3-vinyl-1,2-benzoisothiazole-1,1-dioxides. Benzylidenemalononitrile (**7**) was successfully employed, though lower reactivity was observed. As outlined in Scheme 3, the densely substituted



Scheme 3. Benzylidenemalononitrile as the bis(electrophilic) reagent.

bicyclic products **8** were produced with exclusive diastereoselectivity, but only moderate enantioselectivity could be obtained after extensively optimizing the catalytic conditions.[9] The newly generated primary amino group in the product was noticed to have some catalytic activity and could affect the enantiocontrol in the catalytic process, as evidenced by the significantly deteriorated *ee* value observed after a longer reaction time (for product **8b**; data within parenthesis).

These products, which feature highly structural and stereogenic complexity, encouraged us to explore their potential application in chemical biology and medicinal chemistry.[16] A number of compounds were investigated by using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay in vitro.[9] It was pleasing to find that some of them exhibited promising anticancer activity. As summarized in Table 3, the lung adenocarcinoma epithelial

Table 3: Cellular evaluation of the cycloadducts against diverse cancer cell-lines (IC_{50} in μM).[a]

Entry	1	A549	DU145	MDA-MB-231	Eca109	U937
1	(+)-**4a**	9.6	15.3	9.4	31.4	13.6
2	(+)-**4c**	6.2	13.5	21.6	38.8	26.1
3	(+)-**4d**	8.2	7.6	8.0	11.6	20.1
4	(+)-**4f**	10.6	11.1	10.6	15.4	26.4
5	(+)-**4u**	2.3	2.5	13.0	21.8	18.0
6	(+)-**4w**	10.0	9.0	24.9	27.1	30.5
7	(−)-**4a**	>200	>200	>200	>200	>200
8	(±)-**8a**	>200	n.a.[b]	196.3	>200	>200

[a] For the detailed experiments, please see the Supporting Information. [b] n.a. = not available.

cell line A549, prostate cancer cell line DU145, esophageal squamous carcinoma cell line Eca109, breast cancer cell line MDA-MB-231, and leukemic monocyte lymphoma cell line U937, were evaluated. Compounds (+)**4a**, (+)**4c**, (+)**4d**, (+)**4f**, (+)**4u**, and (+)**4w** significantly inhibited proliferation of these five cancer cells in a dose-dependent manner (Table 3, entries 1–6). The compound (+)**4u** showed high potency in inhibiting the growth of A549 and DU145 cell lines, with IC50 (half maximal inhibitory concentration) values of 2.3 and 2.5 μM, respectively (Table 3, entry 5). Importantly, it was noted that the biological effect was highly stereospecific, as very poor activity was observed for the enantiomer of **4a** (Table 3, entry 7 versus entry 1). In addition, the compound (±)-**8a** (79% *ee*) exhibited a very limited effect on inhibiting the proliferation of diverse cancer cell lines (Table 3, entry 8). Such preliminary results suggested that the promising cytotoxic activity of the [5+3] cycloadducts is not related to the electrophilicity of the enone moiety. Using these observations to design better inhibitors is under investigation.

In conclusion, we have developed a previously unreported cross-conjugated dienamine/*endo*-dienamine catalysis with β-substituted 2-cyclopentenones and 2-cyclohexenone in the presence of chiral primary amines. By using 3-vinyl-1,2-benzoisothiazole-1,1-dioxides as bis(electrophilic) partners, the unprecedented formal [5+3] cycloadditions were accomplished to give fused or bridged frameworks, incorporating a spirocyclic skeleton, in excellent enantiomeric purity and with highly structural and stereogenic complexity. Moreover, some of the chiral products showed promising biological activity in some cancer cell lines, thus indicating that such

skeletons might serve as leads in drug discovery. We also believe that this new reaction will lead to the development of a variety of formal [5+*m*] cycloadditions with cyclic enone substrates. More results will be reported in the future.

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Keywords: cancer · cycloaddition · organocatalysis · regioselectivity · synthetic metehods

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[13] CCDC 995792 (**4i**) 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.

[14] For catalytic application of chiral 1,2-diphenylethanediamine, see: a) H. Kim, C. Yen, P. Preston, J. Chin, *Org. Lett.* **2006**, *8*, 5239; b) W. Wu, X. Li, H. Huang, X. Yuan, J. Lu, K. Zhu, J. Ye, *Angew. Chem.* **2013**, *125*, 1787; *Angew. Chem. Int. Ed.* **2013**, *52*, 1743.

[15] β-Substituted 2-cyclohexenones did not give the desired [5+3] cycloadducts with 3-vinyl-1,2-benzoisothiazole-1,1-dioxides under the catalysis of various chiral amines. The reactions proceeded primarily through a [4+2] reaction mode via the dienamine **B**. More results will be reported elsewhere.

[16] a) S. Wetzel, R. S. Bon, K. Kumar, H. Waldmann, *Angew. Chem.* **2011**, *123*, 10990; *Angew. Chem. Int. Ed.* **2011**, *50*, 10800; b) H. Waldmann, *Angew. Chem.* **2012**, *124*, 6388; *Angew. Chem. Int. Ed.* **2012**, *51*, 6284; c) R. Narayan, M. Potowski, Z.-J. Jia, A. P. Antonchick, H. Waldmann, *Acc. Chem. Res.* **2014**, *47*, 1296.