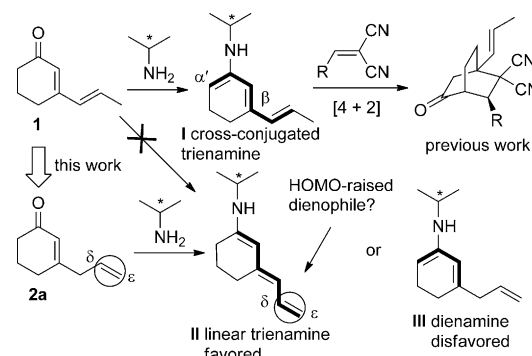


Trienamines Derived from Interrupted Cyclic 2,5-Dienones: Remote δ,ϵ -C=C Bond Activation for Asymmetric Inverse-Electron-Demand Aza-Diels–Alder Reaction**

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A special challenge in the field of asymmetric catalysis is the realization of remote stereocontrol.^[1] The problem can be extended to remote sites which must be activated to ensure better reactivity. While most early examples of remote asymmetric inductions rely on enzyme catalysis or intramolecular relay of chiral information through the substrate,^[2] current studies have demonstrated that chiral catalysts can facilitate enantioselectivity in variety of reactions.^[3] In particular, our group and the group of Jørgensen found that the well-established enamine chemistry of saturated carbonyl compounds could be expanded to polyconjugated 2,4-dienals based on the principle of vinylogy,^[4] thus leading to the remote ϵ -site activation and still allowing highly stereoselective cycloadditions at β,ϵ -sites of in situ formed linear trienamine intermediates.^[5] Moreover, such an activation mode was successfully applied to 2,4-dienone analogues. Unfortunately, it was not possible to utilize 2,4-dienones with an enolizable α' -alkyl substitution because the cross-conjugated trienamine species were preferably generated.^[6]

In fact, we also found that the cyclic 2,4-dienone **1** would predominantly generate the cross-conjugated trienamine **I**, catalyzed by a primary amine, and then react with a dienophile by a α',β -regioselective [4+2] annulation pathway (Scheme 1).^[7] To overcome the inherent preference for the formation of cross-conjugated trienamines from 2,4-dienones bearing an enolizable α' -alkyl group, we envisaged that an appropriately positioned δ,ϵ -C=C bond, as shown for the interrupted 3-allyl cyclohexen-2-one **2a** (Scheme 1), would induce the generation of the desired polyconjugated linear trienamine **II**, rather than the dienamine^[8] **III** which has a higher energy.^[9] Thus, the electron-donating effects of the amine could be transmitted through the conjugated π system,



Scheme 1. Strategy for the formation of linear trienamine intermediate.

and raise the HOMO energy of the remote δ,ϵ -C=C group to participate in asymmetric reactions.

Based on the above considerations, we initially investigated the reaction of the 2,5-dienone **2a** and the 1-azadiene **3a**, containing a 1,2-benzisothiazole-1,1-dioxide moiety,^[10] in the presence of 9-amino-9-deoxyepiquinidine (**C1**) and benzoic acid (**A1**).^[11] To our gratification, the reaction proceeded smoothly in toluene at 35 °C, and the inverse-electron-demand aza-Diels–Alder cycloaddition product **4a** was isolated in 63% yield with exclusive δ,ϵ -regioselectivity.^[12–14] More pleasingly, both diastereo- (*endo*, >19:1) and enantioselectivity (98% *ee*) are remarkable, even though the δ,ϵ -C=C bond is quite remote from chiral amine catalyst (Table 1, entry 1).^[15] It should be addressed that almost no reaction occurred for the reaction of the conjugated 2,4-dienone **1** and **3a** under the same catalytic conditions, thus further verifying that the appropriately positioned δ,ϵ -C=C bond is crucial for inducing the formation of the required linear trienamine intermediate. 9-Amino-9-deoxyepiquinine (**C2**) afforded the product with the opposite configuration in excellent stereoselectivity (Table 1, entry 2), but **C3**, having with a free OH group, failed to catalyze the reaction (Table 1, entry 3). The acid additives had significant effects on the reaction. Salicylic acid (**A2**) produced better reactivity (Table 1, entry 4), and a slower reaction and even poor conversion was observed by using either **A3** or **A4** (Table 1, entries 5 and 6). Other solvents were tolerated though lower yields were obtained (Table 1, entries 7–10). Notably, the reaction still proceeded smoothly with a decreased amount (10 mol % or 5 mol %) of **C1** in combination with **A2**, and better results were obtained after a longer reaction time (Table 1, entries 11 and 12).

Consequently, a number of cyclic 2,5-dienones and electron-deficient 1-azadienes were investigated (Table 2). For the reactions of **2a**, a variety of 3-vinyl-1,2-benzisothia-

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Table 1: Screening of reaction conditions for the inverse-electron-demand aza-Diels–Alder reaction of **2a** and **3a**.^[a]

Entry	Cat	Acid	Solvent	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	C1	A1	toluene	16	63	98
2	C2	A1	toluene	24	56	–95
3	C3	A1	toluene	24	–	–
4	C1	A2	toluene	13	92	> 99.5
5	C1	A3	toluene	22	77	99
6	C1	A4	toluene	48	< 20	–
7	C1	A2	CH ₂ Cl ₂	19	84	99
8	C1	A2	THF	24	70	99
9	C1	A2	EtOAc	36	73	99
10	C1	A2	CH ₃ CN	17	77	99
11 ^[d]	C1	A2	toluene	26	85	> 99
12 ^[e]	C1	A2	toluene	38	80	> 99

[a] Unless noted otherwise, reactions were performed with 2,5-dienone **2a** (0.15 mmol), 1-azadiene **3a** (0.1 mmol), amine **C** (20 mol %) and acid (40 mol %) in solvent (1.0 mL) at 35 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase; d.r. > 19:1 by ¹H NMR analysis. [d] With 10 mol % of **C1** and 20 mol % of **A2**. [e] With 5 mol % of **C1** and 10 mol % of **A2**. THF = tetrahydrofuran.

zole-1,1-dioxides (**3**) having a variety of aryl or heteroaryl groups were well tolerated, thus giving the corresponding tetrahydropyridines in excellent yields (Table 2, entries 1–13). 1-Azadienes (**3**) with branched alkyl groups exhibited a similar reactivity (Table 2, entries 14 and 15),^[16] and those with either electron-withdrawing or electron-donating groups on the 1,2-benzisothiazole-1,1-dioxide moiety also result in high yields and *ee* values (Table 2, entries 16 and 17). In contrast, a few substituted cyclic 2,5-dienones were tested in the reactions with **3a**. Excellent results were attained for the 2,5-dienone **2b** having 5',5'-dimethyl groups (entry 18). The 2,5-dienones **2c** and **2d**, having an ϵ -aryl and alkyl group, respectively, delivered cycloadducts having three contiguous stereogenic centers (Table 2, entries 19 and 20). Even the 2,5-dienone **2e**, having an electron-withdrawing ethoxycarbonyl group at the ϵ -site, showed comparable reactivity (Table 2, entry 21). In addition, the analogous cyclic 1-azadienes **5** with a 1,2,3-benzoxathiazine-2,2-dioxide motif^[17] reacted smoothly, thus delivering another type of heterocycles (**6**) in high yield and with excellent enantioselectivity (Table 2, entries 22–25). Furthermore, the reactions of some 1-azadienes with **2a** catalyzed by **C2** were explored. The cycloadducts having an opposite configuration to those obtained with **C1** were generally produced with excellent *ee* values and with moderate yields (Table 2, data within parentheses).^[18]

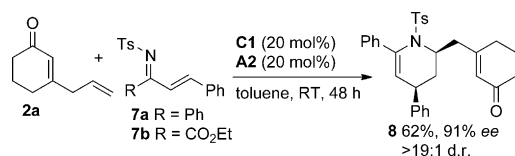
Table 2: Substrate scope and limitations.^[a]

Entry	2	R ²	R ³	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	2a	H	Ph	13 (39)	4a , 92 (69)	> 99.5 (–95)
2	2a	H	3-MeC ₆ H ₄	15	4b , 88	> 99.5
3	2a	H	3-MeOC ₆ H ₄	13 (48)	4c , 90 (73)	99 (–95)
4	2a	H		16	4d , 89	99
5	2a	H	3-FC ₆ H ₄	16	4e , 93	> 99
6	2a	H	2-ClC ₆ H ₄	16 (37)	4f , 90 (71)	> 99 (–96)
7	2a	H	4-BrC ₆ H ₄	15	4g , 94	> 99.5
8	2a	H	4-CF ₃ C ₆ H ₄	17 (42)	4h , 89 (77)	> 99.5 (–96)
9	2a	H	2-F-4-BrC ₆ H ₃	14	4i , 92	> 99.5
10	2a	H	1-naphthyl	14	4j , 90	> 99.5
11	2a	H	2-naphthyl	13	4k , 93	> 99.5
12	2a	H	2-furyl	14	4l , 93	> 99
13	2a	H	2-thienyl	17	4m , 91	> 99.5
14	2a	H	<i>i</i> Propyl	12	4n , 89	> 99.5
15	2a	H	<i>c</i> Hexyl	12	4o , 85	> 99.5
16	2a	6-Br	Ph	12	4p , 87	> 99.5
17	2a	5,7-Me ₂	Ph	17	4q , 91	> 99 ^[d]
18	2b	H	Ph	12	4r , 87	> 99.5
19	2c	H	Ph	12	4s , 87	> 99.5
20	2d	H	Ph	46	4t , 61	99
21	2e	H	Ph	44	4u , 73	96
22	2a	H	Ph	21 (17)	6a , 83 (72)	96 (–95)
23	2a	H	4-MeC ₆ H ₄	23	6b , 85	97
24	2a	H	4-CF ₃ C ₆ H ₄	21	6c , 80	94
25	2a	H	2-thienyl	22	6d , 89	96

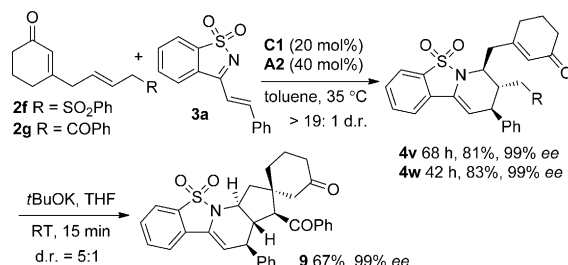
[a] Unless noted otherwise, reactions were performed with 2,5-dienone **2** (0.15 mmol), 1-azadiene **3** or **5** (0.1 mmol), amine **C1** (20 mol %) and acid **A2** (40 mol %) in toluene (1.0 mL) at 35 °C. Data in parentheses obtained with amine **C2**. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase; d.r. > 19:1 by ¹H NMR analysis. [d] The absolute configuration of **4q** was determined by X-ray analysis. See the Supporting Information.^[19] The other products were assigned by analogy.

Apart from the cyclic 1-azadienes **3** and **5**, we also investigated the asymmetric cycloadditions of acyclic *N*-tosyl-1-azadienes which have been widely used for aza-Diels–Alder reactions.^[13] The substrate **7a**, derived from chalcone, exhibited acceptable reactivity in the presence of **C1** and **A2**. The cycloadduct **8** was obtained with high diastereo- and enantioselectivity, albeit in moderate yield. A reduced amount of the acid additive slowed the hydrolysis of the imine group of **7a**, but the more labile 1-azadiene **7b**, having an α -ethoxycarbonyl group, failed to deliver the aza-cycloadduct because of rapid decomposition of the ketimine group under the catalytic conditions (Scheme 2).

The remaining cyclic enone motif of the cycloadducts encouraged us to design appropriately functionalized sub-



Scheme 2. Asymmetric aza-Diels-Alder reaction with acyclic *N*-tosyl-1-azadienes.

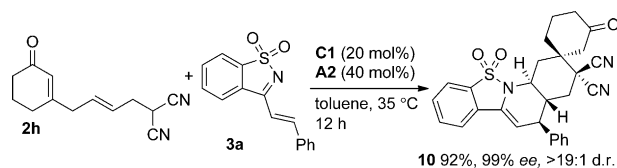


Scheme 3. Sequential reactions with multifunctional 2,5-dienones.

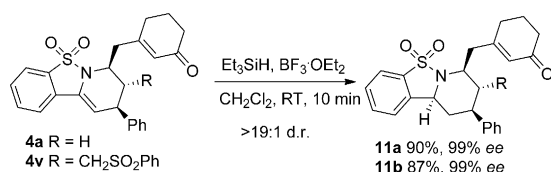
strates to access more complex frameworks. As outlined in Scheme 3, both **2f** and **2g**, bearing an activated methylene group at the ω -site, enabled a highly δ,ϵ -regioselective inverse-electron-demand aza-Diels-Alder reaction with **3a** to give the cycloadducts **4v** and **4w**, respectively. A diastereoselective cyclization with **4w** was efficiently promoted by adding *t*BuOK,^[20] thus producing **9** as a separable single enantiomer, which possesses five fused and spirocyclic rings and five stereogenic centers.

Based on the above results, the 2,5-dienone **2h**, having a more reactive malononitrile moiety, was designed. Thus, the first cascade-induced trienamine-iminium catalysis with **2h** and **3a** could be realized,^[21] directly producing the polycyclic compound **10** in excellent yield and with almost enantiomeric purity (Scheme 4).

As illustrated in Scheme 5, the enamide functionality of the aza-cycloadducts **4** could be chemoselectively reduced with Et_3SiH and $\text{BF}_3\cdot\text{OEt}_2$ without affecting the enone or other groups.^[11] The piperidine derivatives **11a** and **11b** were efficiently obtained in high yield and with exclusive diaste-



Scheme 4. Cascade induced trienamine-iminium catalysis.



Scheme 5. Chemoselective reduction of enamide group.

reoselectivity from **4a** and **4v**, respectively. More structural diversity and complexity might be introduced from the cyclic enone moiety based on previously established methodologies.^[22]

In conclusion, we have developed an unprecedented asymmetric inverse-electron-demand aza-Diels-Alder reaction with interrupted cyclic 2,5-dienones and electron-deficient 1-azadienes under the catalysis of chiral amines derived from quinidine or quinine. The success of this novel catalytic mode relies on the rational design of the polyunsaturated ketone substrates, which contain an appropriately positioned $\delta,\epsilon\text{-C=C}$ bond to induce the in situ generation of HOMO-raised linear trienamine species. In contrast to early examples of trienamine catalysis,^[5,6] the current cycloaddition exhibits exclusive remote δ,ϵ -regioselectivity, and excellent catalytic efficacy and stereocontrol were observed for the reactions of a variety of substrates with substantial scope. Moreover, an aza-Diels-Alder reaction/Michael addition process was developed by introducing a functional group to the 2,5-dienone substrates. The cascade reaction efficiently constructed frameworks having high structural and stereogenic complexity. We believe that this strategy would help overcome the limitations of more types of unsaturated ketone substrates bearing α' -enolizable alkyl groups in other aminocatalytic asymmetric reactions. More results will be reported in due course.

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