# β,γ-Regioselective Inverse-Electron-Demand Aza−Diels−Alder Reactions with α,β-Unsaturated Aldehydes via Dienamine Catalysis

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ABSTRACT: A stereoselective inverse-electron-demand aza-Diels−Alder cycloaddition process of cyclic 1-aza-1,3-buta-dienes and α,β-unsaturated aldehydes has been developed via dienamine catalysis. This reaction exhibits excellent β,γ-regioselectivity for enal substrates with substantial structural diversity and broad functionalities, readily producing highly enantioenriched fused piperidine derivatives and enabling efficient sequential construction of complex polycyclic frameworks.
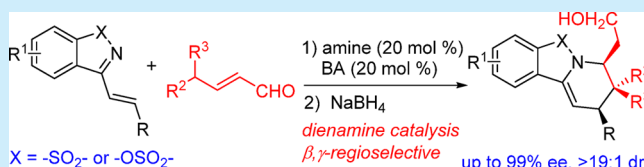
The [4 + 2] cycloaddition between an electron-poor diene and an electron-rich dienophile, namely, the inverse-electron-demand Diels−Alder reaction (IED DA), has been extensively explored since being disclosed.[1] This type of cycloaddition is extremely useful for the construction of *O*-, *N*-, and *S*-centered heterocycles, such as dihydropyrans and piperidines that are privileged frameworks in both organic and medicinal fields,[2] and a diversity of catalytic stereoselective processes have been exploited.[3]

The HOMO-raised enamine[4,5] or dienamine[6,7] species derived from an amine catalyst and aliphatic aldehydes or α,β-unsaturated aldehydes, respectively, have performed as good dienophiles or dienes in various DA reactions with electron-deficient partners. As far as dienamine intermediates are concerned, different regioselectivity was observed in aza-DA cycloadditions with acyclic *N*-Ts 1-azadienes, and the reactions commonly occurred at the proximal *ipso,α*-double bond. In contrast, only one example of remoter β,γ-regioselective aza-DA reaction with simple crotonaldehyde was obtained but with poor enantioselectivity (Scheme 1).[7] Although the Jørgensen group developed highly β,γ-regioselective and stereoselective IED oxo-DA reactions of enals through *H*-bond-directing dienamine catalysis,[8] the corresponding asymmetric aza-version, occurring at the distal C═C bond of dienamines with broader structural diversity, has not been well developed yet. Recently, we reported that cyclic 3-vinyl-1,2-benzoisothia-zole-1,1-dioxides[9] could regio- and chemoselectively act as either 4π-electron-participation dienes[10] or unlettered 2π-electron-participation dienophiles[11] with properly structured trienamine species, or even biselectrophilic C3 partners in formal [5 + 3] cycloadditions via cascade dienamine-dienamine catalysis,[12] we are encouraged to investigate their asymmetric IED aza-DA cycloadditions with α,β-unsaturated aldehydes. Such cyclic 1-azadienes might be more applicable substrates favoring the distal β,γ-regioselectivity owing to the better rigid

Scheme 1. Dienamine Catalysis in Inverse-Electron-Demand Aza-Diels−Alder Reactions
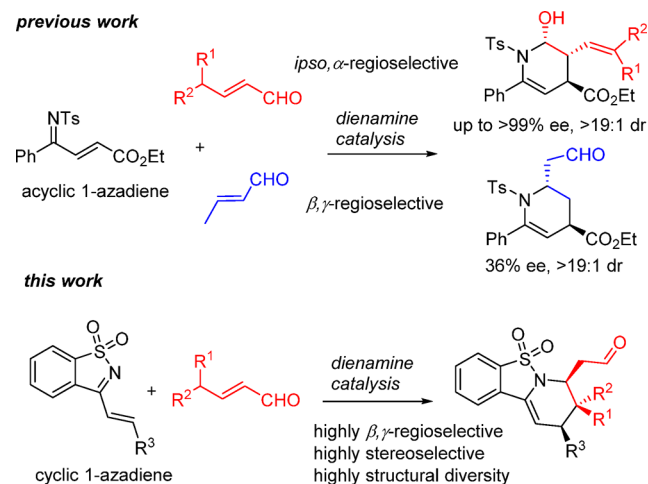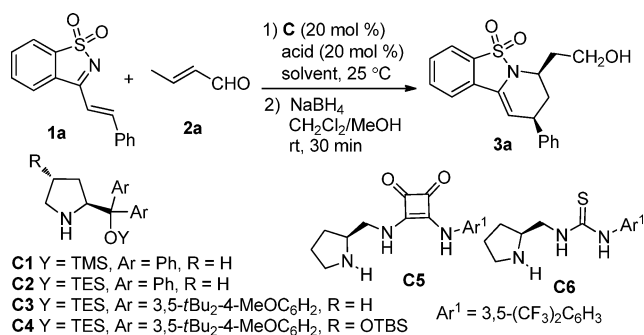

structures in comparison with the previously applied acyclic 1-azadienes.[13]

The initial study was performed with 3-styryl-1,2-benzoiso-thiazole-1,1-dioxide **1a** and crotonaldehyde **2a**, catalyzed by chiral secondary amine α,α-diphenylprolinol *O*-TMS ether **C1** (20 mol %) and benzoic acid (BA, 20 mol %) in CHCl₃.[14] To our delight, the cycloaddition proceeded smoothly with excellent β,γ-regioselectivity at room temperature, and the corresponding alcohol **3a** was isolated in a high yield after sequential in situ reduction with NaBH₄. Pleasingly, the enantioselectivity was quite promising (Table 1, entry 1, 81% ee). Subsequently, a few solvents were screened, none of which

Table 1. Screening Studies of Aza-Diels–Alder Cycloaddition with 1a and Crotonaldehyde 2a[a]

C1 Y = TMS, Ar = Ph, R = H
C2 Y = TES, Ar = Ph, R = H
C3 Y = TES, Ar = 3,5-tBu$_2$-4-MeOC$_6$H$_2$, R = H
C4 Y = TES, Ar = 3,5-tBu$_2$-4-MeOC$_6$H$_2$, R = OTBS

Ar^1 = 3,5-(CF$_3$)$_2$C$_6$H$_3$

entry	C	acid	solvent	t (h)	yield[b] (%)	ee[c] (%)
1	C1	BA	CHCl$_3$	12	81	81
2	C1	BA	CCl$_4$	18	78	82
3	C1	BA	DCM	12	78	79
4	C1	BA	DCE	12	82	71
5	C1	BA	toluene	24	78	61
6	C1	BA	THF	24	78	59
7	C1	BA	MeCN	24	–	–
8	C2	BA	CHCl$_3$	12	83	33
9	C3	BA	CHCl$_3$	12	81	59
10	C4	BA	CHCl$_3$	12	79	51
11	C1	OFBA	CHCl$_3$	12	79	39
12	C1	AcOH	CHCl$_3$	12	80	65
13	C1	SA	CHCl$_3$	12	79	81
14[d]	C1	BA	CHCl$_3$	18	79	84
15[e]	C1	BA	CHCl$_3$	18	80	88
16[f]	C5	BA	CHCl$_3$	72	45	55
17	C6	BA	CHCl$_3$	72	–	–

[a]Unless noted otherwise, reactions were performed with 1-azadiene **1a** (0.05 mmol), crotonaldehyde **2a** (0.075 mmol), amine **C** (0.01 mmol) and acid (0.01 mmol) in solvent (0.5 mL) at 25 °C. [b]Isolated yield for two steps. [c]Determined by chiral HPLC analysis; dr > 19:1. [d]At 0 °C. [e]At −10 °C. [f]Adding DEA (diethylacetamide, 1 equiv).[8]

provided better results unfortunately (entries 2–5), while no reaction occurred in acetonitrile (entry 6). The attempts to improve the enantioselectivity by using more bulky amine catalysts[15] **C2**–**C4** were not successful, and significantly decreased ee values were observed (entries 8–10). Using o-fluorobenzoic (OFBA) and acetic acid also resulted in much poorer enantiocontrol (entries 11 and 12), while the similar good enantioselectivity was obtained in the presence of salicylic acid (SA) (entry 13). Pleasingly, the reaction was carried out efficiently at lower temperature, and the enantioselectivity could be slightly improved without effect on the yield (entries 14 and 15). In contrast to what observed in IED oxo-DA cycloadditions with H-bond-directing aminocatalysis,[8] poor reactivity and fair enantioselectivity was attained by using bifunctional catalyst **C5** (entry 16). Even thiourea **C6** exhibited no catalytic activity (entry 17).

With the optimal catalytic conditions in hand, we consequently investigated the substrate scope and limitations of 3-vinyl-1,2-benzoisothiazole-1,1-dioxides **1** and α,β-unsaturated aldehydes **2**. The resulting aldehyde cycloadducts were directly reduced with NaBH$_4$ to give the corresponding alcohols **3**. The results are summarized in Table 2. At first, a variety of α,β-unsaturated aldehydes were explored in reactions with 1-azadiene **1a**. In comparison with the results of crotonaldehyde **2a** (Table 2, entry 1), excellent enantioselec-

Table 2. Substrate Scope and Limitations in Reactions of Electron-Deficient 1-Azadienes and α,β-Unsaturated Aldehydes 2[a]


1 X = -SO$_2$-
4 X = -OSO$_2$-

2a R^2 = R^3 = H
2b R^2 = H, R^3 = Me
2c R^2 = H, R^3 = Et
2d R^2 = H, R^3 = Ph

2e R^2 = R^3 = Me
2f R^2 = R^3 = (CH$_2$)$_5$
2g R^2 = H, R^3 = CH$_2$OTBS
2h R^2 = H, R^3 = (CH$_2$)$_2$SO$_2$BT

3 X = -SO$_2$-
5 X = -OSO$_2$-

BT = (benzothiazol-2-yl)

TBS = $tert$-Butyldimethylsilyl
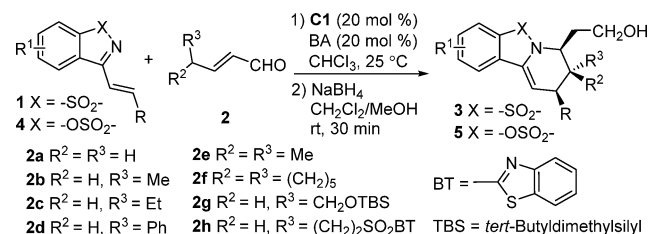
entry	2	R	R^1	t (h)	yield[b] (%)	ee[c] (%)
1[d]	2a	Ph	H	18	3a, 80	88
2[d,e]	2b	Ph	H	18	3b, 81	94[f]
3[d]	2c	Ph	H	18	3c, 81	81[g]
4[d]	2d	Ph	H	12	3d, 80	76
5	2e	Ph	H	36	3e, 75	96
6	2f	Ph	H	12	3f, 70	96
7	2g	Ph	H	24	3g, 78[h]	87
8	2h	Ph	H	48	3h, 60	90
9	2e	3-FC$_6$H$_4$	H	24	3i, 72	96
10	2e	4-ClC$_6$H$_4$	H	24	3j, 77	96[i]
11	2e	2-ClC$_6$H$_4$	H	48	3k, 70	95
12	2e	4-BrC$_6$H$_4$	H	24	3l 77	98
13	2e	4-CF$_3$C$_6$H$_4$	H	24	3m, 70	96
14	2e	3,4-Cl$_2$C$_6$H$_3$	H	24	3n, 75	97
15	2e	3-MeC$_6$H$_4$	H	48	3o, 74	96
16	2e	4-MeC$_6$H$_4$	H	36	3p, 78	96
17	2e	4-MeOC$_6$H$_4$	H	36	3q, 74	94
18	2e	(3,4-methylenedioxyphenyl)	H	48	3r, 70	97
19	2e	2-thienyl	H	48	3s, 62	98
20	2e	Ph	6-Br	24	3t, 74	99
21	2e	Ph	5,7-Me$_2$	32	3u, 74	89
22	2a	$i$propyl	H	18	3v, 66	80
23	2a	$c$hexyl	H	18	3w, 60	82
24[j]	2e	Ph	H	24	5a, 73	84
25[j]	2e	4-CF$_3$C$_6$H$_4$	H	18	5b, 78	85
26[j]	2e	4-MeC$_6$H$_4$	H	18	5c, 79	90
27[j]	2e	Ph	7-F	24	5d, 73	81

[a]Unless noted otherwise, reactions were performed with 1-azadiene **1** (0.1 mmol), enal **2** (0.12 mmol), amine **C1** (0.02 mmol) and benzoic acid (0.02 mmol) in CHCl$_3$ (1.0 mL) at 25 °C. [b]Isolated yield for two steps. [c]ee was determined by chiral HPLC analysis; unless noted otherwise, dr > 19:1 by ^{1}H NMR analysis. [d]At −10 °C. [e]**C4** was used. [f]dr (6:1) in DA step. [g]dr (7:1) in DA step. [h]The aldehyde product was obtained. [i]The absolute configuration of **3j** was determined by X-ray analysis after derivation. The other products were assigned by analogy. [j]1-Azadiene **4** was used.

tivity with moderate diastereoselectivity (6:1) could be obtained for linear 2-pentenal **2b** in the presence of a bulky amine **C4** (entry 2), while using amine **C1** still produced better data for the reaction of 2-hexenal **2c** (entry 3). A modest ee value with excellent diastereoselectivity was attained for 3-phenylbut-2-enal **2d** (entry 4). Importantly, γ,γ-disubstituted enals **2e** and **2f** also exhibited high β,γ-regioselectivity though a quaternary center must be generated, and remarkable stereoselectivity was gained even at room temperature (entries 5 and 6). In addition, α,β-unsaturated aldehydes **2g** and **2h** bearing functional groups could be well tolerated, providing the desired products in high stereoselectivity and with moderate yields (entries 7 and 8). On the other hand, an array of 1-azadienes **1** bearing diverse aryl and heteroaryl groups were explored in reactions with 4-methyl-2-pentenal **2e**, and the corresponding products were efficiently furnished in moderate to high yields and with excellent stereoselectivity (entries 9−21). 1-Azadienes bearing branched alkyl groups were compatible in reactions with crotonaldehyde **2a** catalyzed by amine **C1**, producing products **3t** and **3u** in modest data (entries 22 and 23). Furthermore, the analogous 1-azadienes **4** containing a 1,2,3-benzoxathiazine-2,2-dioxide motif[16] also were effectively applied in reactions with enal **2e** under the same aminocatalytic conditions, affording cycloadducts **5a−5d** in good yields and stereocontrol (entries 24−27).

As the current β,γ-regioselective aza-DA reaction via dienamine catalysis could tolerate diverse functional group, we are inspired to utilize some functionalized α,β-unsaturated aldehydes, which might enable the sequential assembly with aldehyde group to construct complex polycyclic frameworks. As illustrated in Scheme 2, α,β-unsaturated aldehydes **2i** bearing a

Scheme 2. Employing Functionalized Enal Substrates to Construct Heterocycles with Higher Molecular Complexity
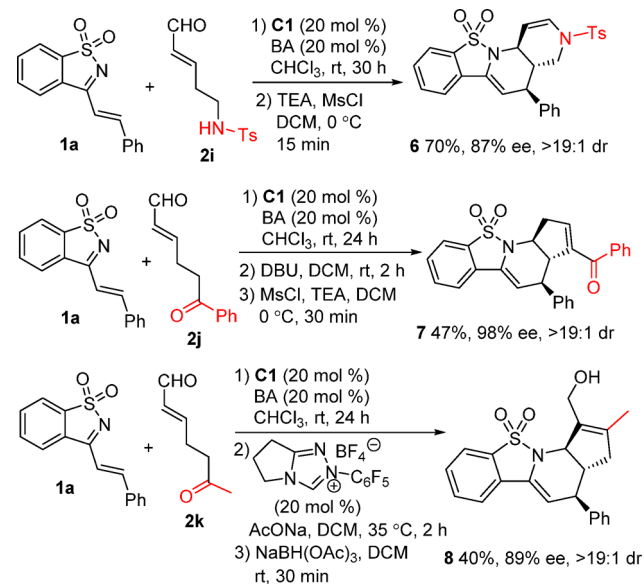

sulfonamide group[17] smoothly reacted with 1-azadiene **1a** under the established catalytic conditions, and a fused polyhydro-1,6-naphthyridine derivative[18] **6** was produced in a good yield and stereoselectivity after subsequent elimination process with methanesulfonyl chloride (MsCl) and triethylamine (TEA). In addition, enal **2j** having a benzoyl group[19] also was successfully employed in the aza-DA reaction, and a

sequential intramolecular aldol and dehydration process was conducted to deliver a polyhydrocyclopenta[*b*]pyridine[20] **7** in a modest yield but with excellent stereoselectivity. Moreover, a different transformation strategy could be developed when substrate **2k** with an acetyl group was used. Interestingly, the attempt to conduct intramolecular benzoin condensation with aldehyde precursor under *N*-heterocyclic carbene catalysis was not successful, but furnished a tetracyclic product **8** after reducing the unexpected regioselective adol product with NaBH(OAc)$_3$,[21] albeit the overall yield is fair. Such drug-like materials might find application in medicinal chemistry.

As outlined in Scheme 3, the reduction of the enamide group of adducts **3e** with Et$_3$SiH and BF$_3$·OEt$_2$ proceeded

Scheme 3. Reduction of Enamide Group
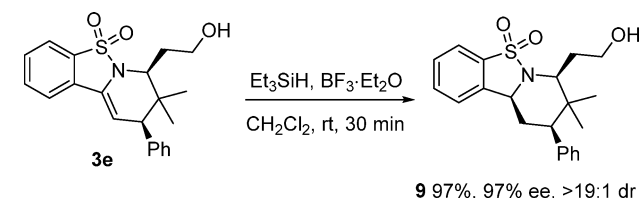
uneventfully,[5a] and piperidine derivative **9** was efficiently obtained in a high yield and with exclusive diastereoselectivity.

In conclusion, we have investigated the asymmetric inverse-electron-demand aza-Diels−Alder cycloadditions of cyclic 1-azadienes containing a 1,2-benzoisothiazole-1,1-dioxide or 1,2,3-benzoxathiazine-2,2-dioxide motif with α,β-unsaturated aldehydes. Excellent distal β,γ-regioselectivity and high stereoselectivity were obtained by employing dienamine catalysis of a chiral secondary amine. The substrate scope for both partners is substantial, and some sequential transformations could be effectively carried out with the multifunctional cycloadducts to furnish frameworks with higher degrees of structural complexity. Further studies would find more valuable applications, and the results will be reported in due course.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Complete experimental procedures and characterization of new products, CIF file of enantiopure derivative of **3j**, NMR spectra and HPLC chromatograms. 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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