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1-Azadienes as Regio- and Chemoselective Dienophiles in Aminocatalytic Asymmetric Diels–Alder Reaction

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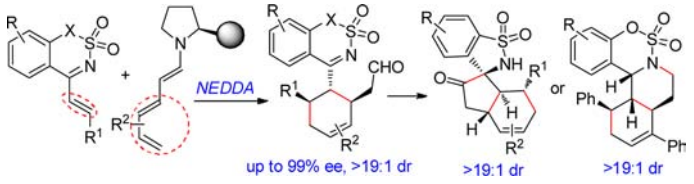
ABSTRACT



Electron-deficient 1-aza-1,3-butadienes containing a 1,2-benzoisothiazole-1,1-dioxide or 1,2,3-benzoxathiazine-2,2-dioxide motif act as regio- and chemoselective dienophiles in normal-electron-demand Diels–Alder reactions with HOMO-raised trienamines, rather than typical 4π-participation in inverse-electron-demand versions. The enantioenriched cycloadducts could be efficiently converted to spiro or fused frameworks with high structural and stereogenic complexity by a sequential aza-benzoin reaction or other transformations.

Electron-deficient 1-aza-1,3-butadienes are versatile synthetic building blocks which have been widely involved in many transformations.[1] They are useful for the preparation of a variety of nitrogen-containing chiral compounds via 1,2- and 1,4-addition reactions or as partners for diverse [4 + 2], [4 + 1], [3 + 2], or [2 + 2] annulations.[2] In particular, since the pioneering and seminal studies of Boger et al., who established the 4π-participation of 1-sulfonyl-1-aza-1,3-butadienes with electron-rich dienophiles in regio- and *endo*-selective inverse-electron-demand (IED) aza-Diels–Alder reactions,[3] a number of stereoselective versions with such 1-azadienes have been developed for the construction of enantioenriched tetrahydropyridines by either chiral auxiliary induction or asymmetric catalysis [Scheme 1, eq (a)].[4,5] In addition, we also presented some asymmetric IED aza-Diels–Alder reactions of 1-sulfonyl-1-aza-1,3-butadienes and enolizable aldehydes via enamine or dienamine activation. All the reactions exhibited

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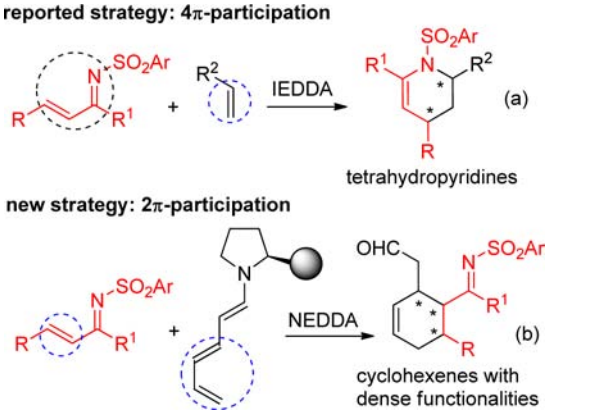
the typical 4π-participation of 1-azadienes as observed in other types of cycloadditions.[6]

However, to the best of our knowledge, there is still no previous report that 1-sulfonyl-1-azadienes could be utilized as dienophiles in normal-electron-demand Diels–Alder (NEDDA) reactions with all carbon based dienes, though they have been identified as good acceptors in Michael additions.[7] This reaction pattern would be highly challenging, probably because of the inherency and tendency of 4π-participation of electron-deficient 1-azadienes with electron-rich alkenes.[3]

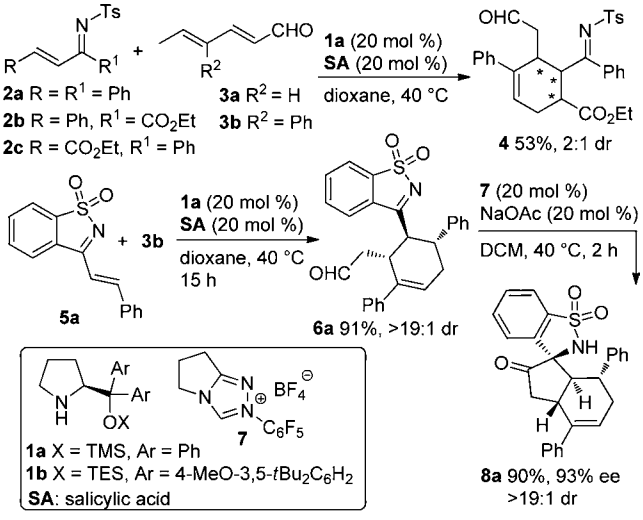
Inspired by our recent studies on asymmetric NEDDA cycloadditions with HOMO-raised trienamines from polyconjugated carbonyl compounds,[8] we are fascinated by the difficult but potential regio- and chemoselective 2π-participation of 1-sulfonyl-1-azadienes in the NEDDA reactions with trienamine intermediates, as outlined in Scheme 1, eq (b). This previously unreported reaction pattern would be extremely attractive and useful since it could efficiently deliver densely functionalized cyclohexene derivatives that allow sequential transformations for the construction of more complex carbo- or heteroring systems.

The initial reactions of diversely substituted acyclic *N*-Ts 1-azadienes[3] **2a**–**2c** with simple 2,4-hexadienal **3a** resulted in no success catalyzed by chiral amine **1a** and salicylic acid, and significant hydrolysis of these relatively unstable 1-azadienes to the corresponding enone compounds was observed. Similar results were observed for the combinations of **2a** or **2b** with more reactive 2,4-dienal **3b**; however, we indeed isolated the ketimine product **4** with **2c** in the desired 2π-participation version but with very poor diastereoselectivity, and the yield was only modest due to other side reactions (Scheme 2). Unfortunately, all attempts to further transformations with **4** produced a complex mixture. Encouraged by our recent study on the asymmetric IEDDA reactions of cyclic 3-vinyl-1,2-benzoisothiazole-1,1-dioxides,[9] we envisaged that these 1-azadienes should be used as more ideal substrates in the above-mentioned reaction, because they are readily accessible and stable and should be more electrophilic owing to the strong electron-withdrawing effect of the 1,2-benzoisothiazole-1,1-dioxide moiety.[10] To our gratification, a styryl-substituted cyclic imine **5a** exhibited much higher reactivity with 2,4-dienal **3b** under the same catalytic conditions, delivering the expected NEDDA cycloadduct **6a** in excellent yield and with exclusive *exo*-selectivity. Moreover, in contrast to acyclic

Scheme 1. Alternative Diels–Alder Cycloaddition Patterns of 1-Sulfonyl-1-aza-1,3-butadienes: Dienes *vs* Dienophiles



Scheme 2. 3-Styryl-1,2-benzoisothiazole-1,1-dioxide as Dual Regio- and Chemoselective Electrophiles in a NEDDA Reaction and a Sequential Aza-benzoin Reaction



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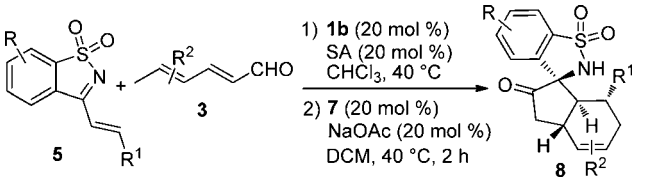
imine **4**, **6a** is a quite stable compound and may allow for sequential diverse transformations. For example, an intramolecular aza-benzoin condensation[11] could proceed efficiently in DCM in the presence of triazolium salt **7** and NaOAc, and a complex spirocyclic product **8a** with four chiral centers was obtained in 90% yield and remarkable diastereo- (>19:1) and enantioselectivity (93% ee).[12] It should be noted that this is also the first time that simple ketimine groups could successfully participate in carbene-catalyzed aza-benzoin reactions with aliphatic aldehydes.[13]

Having established 2π-participation of 3-styryl-1,2-benzoisothiazole-1,1-dioxide **5a** with 2,4-dienal **3b** by trienamine activation, we further screened a number of parameters in order to improve the results. It was found that a bulky chiral amine **1b** gave better enantioselectivity in the DA reaction in chloroform, and product **8a** was attained in 97% ee and with 86% yield after a sequential aza-benzoin reaction. It should be addressed that the cascade catalysis of amine and carbene in a relay version was not successful, and a lower yield (59%) was obtained when two reactions were conducted in a one pot fashion.[12]

Consequently, we explored various reactions of 3-vinyl-1,2-benzoisothiazole-1,1-dioxide **5** and 2,4-dienals **3** in chloroform catalyzed by amine **1b** in combination with salicylic acid. Then the DA cycloadducts were isolated by flash chromatography, and an aza-benzoin reaction was subsequently conducted in DCM. The results are summarized in Table 1. In general, cyclic 1-azadienes bearing a variety of aryl or heteroaryl groups exhibited similar good reactivity, and a spectrum of spirocyclic products **8a**–**8l** were isolated as a single diastereomer in moderate to high yield and with excellent enantioselectivity (Table 1, entries 1–12). 1-Azadienes bearing branched alkyl groups were also prepared and smoothly applied in the DA reactions and aza-benzoin reactions, producing the corresponding products **8m** and **8n** with good results (entries 13 and 14).[14] 1-Azadienes with either electron-withdrawing or -donating groups on the 1,2-benzoisothiazole-1,1-dioxide moiety also gave the desired products **8o** and **8p** in high yield and ee values, respectively (entries 15 and 16). On the other hand, more 2,4-dienals were explored. 4-Phenyl-2,4-heptadienal **3c** showed high reactivity in the reaction with **5a**, and product **8q** with five stereogenic centers was obtained with remarkable results (entry 17). In addition, lower reactivity was observed for 5-methyl-2,4-hexadienal **3d**; the cycloaddition reaction was conducted at 50 °C for 48 h, and the final product **8r** was produced in moderate yield but with outstanding stereoselectivity still (entry 18). Nevertheless, 5-(2′-furyl)-2,4-hexadienal **3e** showed better reactivity, and product **8s** was obtained with good results (entry 19). It should be noted that simple 2,4-hexadienal **3a** still failed to produce the expected DA adduct due to lower reactivity and other side reactions.

Apart from *N*-sulfonyl-1-azadienes containing a 1,2-benzoisothiazole-1,1-dioxide motif, it was pleasing that the analogous 4-styryl-1,2,3-benzoxathiazine-2,2-dioxides[16] **9** could be effectively applied in the regio- and chemoselective NEDDA reaction with 2,4-dienal **3b** via trienamine activation. As summarized in Table 2, the reactions occurred smoothly under the same catalytic conditions, and multifunctional cycloadducts **10a**–**10f** were produced in

Table 1. Substrate Scope and Limitations in Reactions of 3-Vinyl-1,2-benzoisothiazole-1,1-dioxides **5** and 2,4-Dienals **3**[a]



entry	R	R^1	R^2	t (h)[b]	yield (%)[c]	ee (%)[d]
1	H	Ph	4-Ph	17	**8a**, 86	97
2	H	3-FC_6H_4	4-Ph	19	**8b**, 59	97
3	H	4-ClC_6H_4	4-Ph	16	**8c**, 89	96
4	H	4-BrC_6H_4	4-Ph	22	**8d**, 77	97
5	H	4-$CF_3C_6H_4$	4-Ph	19	**8e**, 61	96
6	H	3,4-$Cl_2C_6H_3$	4-Ph	22	**8f**, 73	96
7	H	3-MeC_6H_4	4-Ph	25	**8g**, 84	96
8	H	4-MeC_6H_4	4-Ph	18	**8h**, 81	96[e]
9	H	2-$MeOC_6H_4$	4-Ph	35	**8i**, 79	96
10	H	2-naphthyl	4-Ph	40	**8j**, 86	97
11	H	2-furyl	4-Ph	24	**8k**, 81	97
12	H	2-thienyl	4-Ph	72	**8l**, 78	97
13[f]	H	isopropyl	4-Ph	36	**8m**, 68	96
14[g]	H	cyclohexyl	4-Ph	25	**8n**, 72	94
15	6-Br	Ph	4-Ph	16	**8o**, 88	99
16	5,7-Me_2	Ph	4-Ph	32	**8p**, 83	95
17	H	Ph	4-Ph-6-Me	16	**8q**, 73	96
18	H	4-BrC_6H_4	5-Me	48	**8r**, 46	94
19	H	Ph	5-2′-furyl	36	**8s**, 71	97

[a] Reactions were performed with 1-azadiene **5** (0.1 mmol), 2,4-dienal **3** (0.15 mmol), amine **1b** (20 mol %), and salicylic acid (20 mol %) in $CHCl_3$ (0.5 mL) at 40 °C. After completion, the DA adduct was isolated and salt **7** (20 mol %), NaOAc (20 mol %), and DCM (0.5 mL) were added and stirred at 40 °C for 2 h. [b] For DA reaction step. [c] Yield of isolated pure product **8** for two steps. [d] Determined by chiral HPLC analysis; dr > 19:1 by ^{1}H NMR analysis. [e] The absolute configuration of **8h** was determined by X-ray analysis.[15] The other products were assigned by analogy. [f] dr (6.7:1) was observed in DA reaction step. [g] dr (6.7:1) was observed in DA reaction step.

(11) For aza-benzoin reactions with aldimines, see: (a) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696. (b) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 1654. (c) Mattson, A. E.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 4363. (d) Li, G.-Q.; Dai, L.-X.; You, S.-L. *Chem. Commun.* **2007**, 852. (e) DiRocco, D. A.; Rovis, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 5904.

(12) For more details, see the Supporting Information.

(13) Only activated ketimines have been utilized in aza-benzoin reactions with limited examples; see: (a) Enders, D.; Henseler, A.; Lowins, S. *Synthesis* **2009**, 4125. (b) Sun, L.-H.; Liang, Z.-Q.; Jia, W.-Q.; Ye, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 5803.

(14) The 1-azadienes with a linear alkyl group have not been produced yet.

(15) CCDC-948633 (**8h**) 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.

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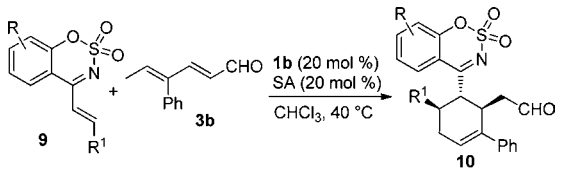
excellent enantioselectivity (entries 1−6), though a small amount of diastereomers were observed in some cases (entries 3−5). Nevertheless, the imine group of products **10** exhibited inert reactivity in carbene-mediated intramolecular aza-benzoin reaction.

Table 2. NEDDA Reactions of 4-Styryl-1,2,3-benzoxathiazine-2,2-dioxides **9**[a]

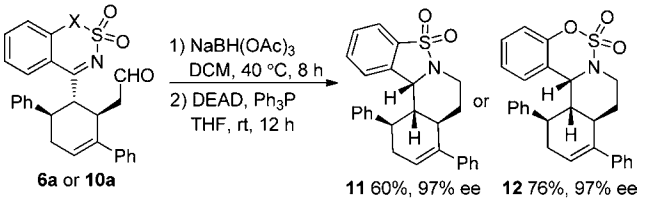


entry	R	R^1	t (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	H	Ph	18	**10a**, 92	>19:1	97
2	H	4-$CF_3C_6H_4$	24	**10b**,86	>19:1	97
3	H	4-MeC_6H_4	24	**10c**, 83	10:1	97
4	H	2-thienyl	40	**10d**, 80	10:1	98
5	7-F	Ph	13	**10e**, 86	10:1	98
6	7-MeO	Ph	24	**10f,** 86	>19:1	90

[a] Reactions were performed with 1-azadiene **9** (0.1 mmol), 2,4-dienal **3b** (0.15 mmol), amine **1b** (20 mol %), and salicylic acid (20 mol %) in $CHCl_3$ (0.5 mL) at 40 °C. [b] Yield of isolated pure product **10**. [c] By ^1H NMR analysis of crude mixture. [d] Determined by chiral HPLC analysis.

On the other hand, the multifunctionalities of DA cycloadducts still enable other transformations to construct frameworks with more structural diversity. The ketimine groups of both **6a** and **10a** could be reduced to the corresponding amines with complete diastereoselectivity with $NaBH(OAc)_3$, along with the simultaneous reaction of the aldehyde group. Moreover, a subsequent intramolecular Mitsunobu reaction could be conducted between *N*-sulfonylamide and alcohol groups, facilely producing the fused piperidine systems **11** and **12**, respectively (Scheme 3). Thus, 2π-participation of these electron-deficient 1-azadienes apparently provides more synthetic versatility to access diverse nitrogen-containing chiral

Scheme 3. Construction of Other Polycyclic Structures



materials in comparison with that of the 4π-participation version reported in early examples.[4,5]

In conclusion, we have developed a previously unreported 2π-participation pattern of electron-deficient 1-azadienes containing a 1,2-benzoisothiazole-1,1-dioxide or 1,2,3-benzoxathiazine-2,2-dioxide motif in normal-electron-demand Diels−Alder cycloadditions with HOMO-raised trienamine species. These 1-azadienes could be utilized as dual regio- and chemoselective electrophiles in asymmetric Diels−Alder and subsequent transformations, giving a spectrum of spirocyclic or fused frameworks with high molecular and stereogenic complexity, which might be useful in medicinal chemistry. We believe that these readily accessible and stable 1-azadienes would find more applications in asymmetric catalysis, and the results will be reported in due course.

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Supporting Information Available. Experimental procedures, structural proofs, NMR spectra and HPLC chromatograms of the products, cif file of enantiopure **8h**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.