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A diene-transmissive Diels–Alder reaction involving inverse electron-demand hetero-Diels–Alder cycloaddition of cross-conjugated azatrienes

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ABSTRACT

The initial inverse electron-demand hetero-Diels–Alder reaction of *N*-sulfonyldivinylmethanimine with electron-rich dienophiles (ethyl vinyl ether and ethyl vinyl sulfide) affords [4+2] cycloadducts with high *endo* selectivity. The monocycloadducts then undergo a second Diels–Alder reaction on the newly formed diene unit with electron-deficient dienophiles (tetracyanoethylene, 4-phenyl-1,2,4-triazoline-3,5-dione, and *N*-phenylmaleimide) to give highly stereoselectively the crossed biscycloadducts, hexa- and octahydroquinolines, and octahydropyridopyridazines.

The diene-transmissive Diels–Alder (DTDA) reaction is a useful and attractive method for constructing polyring-fused cyclic compounds, consisting of two sequential (tandem) Diels–Alder (DA) reactions that involve an initial DA reaction of a cross-conjugated triene (or its equivalent), followed by a second DA reaction of the monoadduct using the newly formed diene unit. Many advances and applications of this DTDA methodology of carbotrienes have been reported.[1] However, only a few examples of the diene-transmissive hetero-Diels–Alder (DTHDA) reaction involving one or more hetero-DA reactions in the tandem sequence have been reported, despite its high potential for straightforward and efficient construction of polyring-fused heterocyclic compounds with high regio- and stereoselectivity.[2–5]

The first reported examples of the DTHDA reaction included that of cross-conjugated thiatrienes.[2,3] Tsuge et al.[4] and Spino et al.[5] demonstrated the DTHDA reaction of cross-conjugated oxatrienes. Our group previously reported the first DTHDA reaction of cross-conjugated azatrienes to produce hexa- and octahydroquinazolinones with high regio- and stereoselectivities, which included the initial aza-Diels–Alder reaction with tosyl isocyanate.[6] We also succeeded in a stereoselective synthesis of hexahydroquinolinones by a DTHDA methodology using ketenes as a dienophile in the initial aza-DA reaction.[7] To extend this azatriene–DTHDA methodology, we were prompted to use cross-conjugated azatrienes bearing an electron-withdrawing sulfonyl group on the nitrogen atom,[8] which involved an inverse electron-demand aza-DA reaction in the initial cycloaddition. We report the preliminary results here.

The cross-conjugated azatrienes **1** were prepared by condensation between di-β-styryl ketone and corresponding sulfonamides using $TiCl_4$ and Et_3N; and they were stable enough to allow isolation after aqueous workup and/or column chromatography. First, the initial DA reaction of the azatrienes **1** with ethyl vinyl ether was performed (Scheme 1, Table 1). When *N*-methanesulfonyl azatriene **1a** was heated in the presence of excess ethyl vinyl ether in toluene for 23 h, the corresponding [4+2] cycloadduct **2a**[9] was obtained in 68% yield with an *endo*:*exo* ratio of 90:10 (entry 1). Azatrienes **1b** and **1c** also reacted with ethyl vinyl ether under the same reaction conditions to give highly *endo* selectively **2b** and **2c** in 86% and 88% yields, respectively; no *exo*-isomers were detected in the crude mixture (entries 2 and 3). Similarly, the reactions of **1a** and **1b** with ethyl vinyl sulfide proceeded in refluxing toluene to produce the monoadducts **3a** and **3b** in fair to good yields with high *endo* selectivity (entries 4 and 5).

Because the obtained monoadducts **2** and **3** possess an electron-rich aminodiene moiety, a second DA reaction could be performed with electron-deficient dienophiles. First, the reactions of **2** and **3** with tetracyanoethylene (TCNE) were carried out to examine diastereo-π-facial selectivity (Scheme 2 and Table 2). The reaction of **2a**–**c** with TCNE proceeded at room temperature for 10 min to produce [4+2] cycloadducts **4a**–**c**[10] in 93–99% yields with complete diastereo-π-facial selectivity (Table 2, entries 1–3). Similarly, the reaction of **3a**,**b** proceeded smoothly in refluxing dichloromethane to give **5a**,**b** in high yields (entries 4 and 5). A one-pot procedure **1b**→**2b**→**4b** proved the DTHDA methodology to be even more effective and viable (entry 6). In all cases, the dienophile added from the less-hindered bottom H-4-side of the diene moiety, a conclusion that was supported by the fact that the large vicinal coupling constant (ca. 12 Hz) between H-4 and H-4a in the bisadducts (**4** and **5**) indicated a trans diaxial relationship. In the

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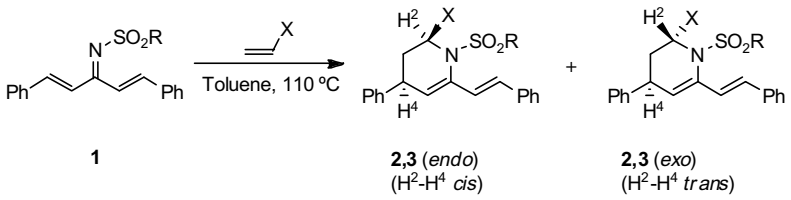
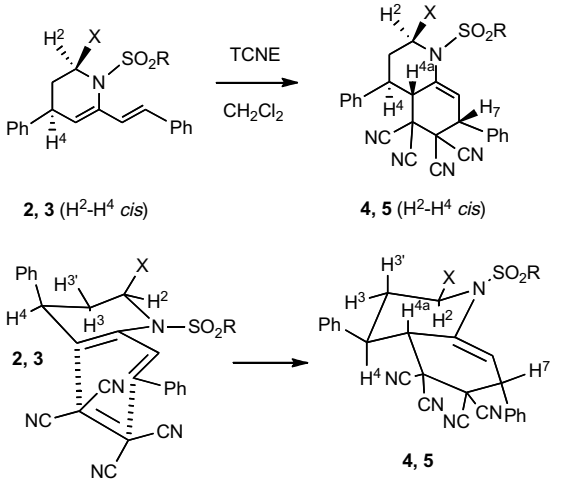


Scheme 1.

Table 1
Initial cycloaddition of cross-conjugated azatrienes **1**

Entry	Azatriene	R	X	Time (h)	Adduct	Yield (%)	*endo*:*exo*[a]
1	**1a**	Me	OEt	23	**2a**	68	90:10
2	**1b**	*p*-Tol	OEt	15	**2b**	86	>95:5
3	**1c**	Ph	OEt	13	**2c**	88	>95:5
4	**1a**	Me	SEt	48	**3a**	68	>95:5
5	**1b**	*p*-Tol	SEt	37	**3b**	51	>95:5

[a] *Endo*:*exo* ratio determined based on ^{1}H NMR integration of the *endo*cyclic olefinic proton of **2** and **3**. Ratio >95:5 denotes that no minor *exo*-isomer was detected.



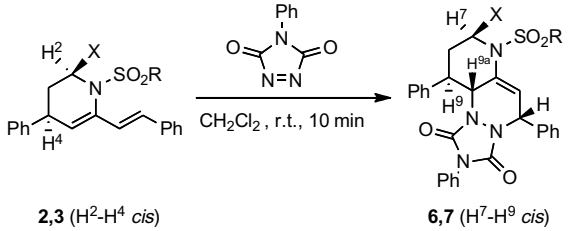
Scheme 2.

Table 2
Second cycloaddition with TCNE

Entry	R	X	Diene	Conditions	Adduct	Yield (%)
1	Me	EtO	**2a**	rt, 10 min	**4a**	93
2	*p*-Tol	EtO	**2b**	rt, 10 min	**4b**	95
3	Ph	EtO	**2c**	rt, 10 min	**4c**	99
4	Me	EtS	**3a**	40 °C, 30 min	**5a**	76
5	*p*-Tol	EtS	**3b**	40 °C, 60 min	**5b**	93
6	*p*-Tol	EtO	**2b**	110 °C, 15 h→rt, 2 d	**4b**	76

endo-monoadduct, the vicinal coupling constants between H-3′ and H-4 and between H-3 and H-4 were observed to be ca. 8 Hz and 5–6 Hz, respectively, suggesting that H-4 orients in a quasi-equatorial position, and hence the phenyl substituent takes a quasi-axial position. Therefore, the top side of the tetrahydropyridine ring was blocked by the more bulky phenyl group from attack by the dienophile.

The reactions of **2** and **3** with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) were also examined to confirm diastereo-π-facial selectivity (Scheme 3, Table 3). Dienes **2a**–**c** and **3a**,**b** reacted rapidly within 10 min at room temperature to produce the



Scheme 3.

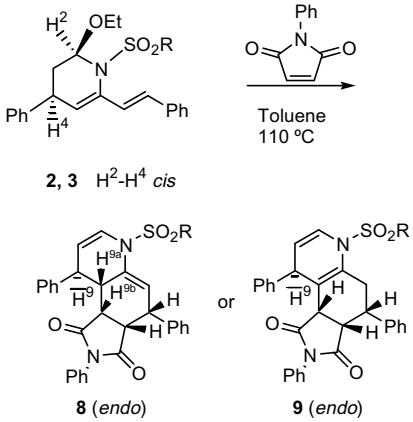
Table 3
Second cycloaddition with PTAD

Entry	R	X	Diene	Adduct	Yield (%)
1	Me	EtO	**2a**	**6a**	99
2	*p*-Tol	EtO	**2b**	**6b**	99
3	Ph	EtO	**2c**	**6c**	99
4	Me	EtS	**3a**	**7a**	99
5	*p*-Tol	EtS	**3b**	**7b**	92

cycloadducts **6a**–**c** and **7a**,**b**, respectively, in quantitative yields. The reaction was highly diastereo-π-face selective, the same as the reaction with TCNE.

The second DA reaction with *N*-phenylmaleimide (*N*-PhMI) was carried out to examine *endo*/*exo* selectivity in addition to diastereo-π-facial selectivity (Scheme 4, Table 4). The monoadducts **2a**–**c** reacted with *N*-PhMI in refluxing toluene to produce cycloadducts **9a** or **8b**,**c** as final products. The reaction proceeded with high *endo* and π-facial selectivities to give initially the 1:1-cycloadduct, from which elimination of ethanol occurred to furnish compounds **8b**,**c** or, in the case of entry 1, **9a** after H-migration from **8a**.

In conclusion, the diene-transmissive hetero-Diels–Alder reaction of N-sulfonylated cross-conjugated azatrienes including an inverse electron-demand aza-Diels–Alder reaction in the initial



Scheme 4.

Table 4
Second cycloaddition with *N*-PhMI

Entry	R	Diene	Time (h)	Adduct	Yield (%)
1	Me	**2a**	3	**9a**	34
2	*p*-Tol	**2b**	18	**8b**	22
3	Ph	**2c**	18	**8c**	21

cycloaddition step has been developed. The protocol provides a new entry to the highly stereoselective synthesis of octahydroquinolines and pyridopyridazines. Further work to extend the scope of this methodology is currently under way.

References and notes

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9. Compound **2a** (*endo*, H^2–H^4 *cis*): Colorless crystals; mp 111–113 °C; IR (KBr): 2970, 1335, 1157, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.22 (ddd, J = 3.5, 4.5, 14.2 Hz, 1H, H-3), 2.51 (ddd, J = 4.8, 8.3, 14.2 Hz, 1 H, H-3′), 3.02 (s, 3H, Ms), 3.50 (dq, J = 7.1, 9.3 Hz, 1H, OCH_2CH_3), 3.54 (ddd, J = 3.7, 4.5, 8.3 Hz, 1H, H-4), 3.78 (dq, J = 7.1, 9.3 Hz, 1H, OCH_2CH_3), 5.54 (dd, J = 3.5, 4.8 Hz, 1H, H-2), 6.02 (d, J = 3.7 Hz, 1H, H-5), 6.88 (s, 2H, H-7, H-8), 7.18–7.36 (m, 8H, Ar), 7.42–7.45 (m, 2H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.8 (CH_3), 30.9 (CH_3), 37.2 (CH), 37.6 (CH_2), 40.6 (CH_2), 63.4 (CH), 83.9 (CH), 122.0 (CH), 126.5 (2CH), 126.7 (2CH), 127.9 (CH), 128.2 (2CH), 128.3 (2CH), 128.6 (CH), 129.9 (CH), 134.8 (C), 136.6 (C), 144.5 (C). HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{25}NNaO_3S$: 406.1447, found: 406.1461. Anal. Calcd for $C_{22}H_{25}NO_3S$: C, 68.90; H, 6.57; N, 3.65. Found: C, 69.11; H, 6.79; N, 3.67. Compound **2a** (*exo*, H^2–H^4 *trans*): Yellow oil; IR (neat): 1335, 1157, 1119 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.77 (ddd, J = 2.4, 12.6, 13.9 Hz, 1H, H-3), 2.37 (dddd, J = 1.5, 2.4, 6.6, 13.9 Hz, 1H, H-3′), 3.01 (s, 3H, Ms), 3.68 (dq, J = 7.1, 9.6 Hz, 1H, OCH_2CH_3), 3.86 (dq, J = 7.1, 9.6 Hz, 1H, OCH_2CH_3), 3.88 (m, J = 1.5, 6.6, 12.6 Hz, 1H, H-4), 5.54 (dd, J = 2.4, 2.4 Hz, 1H, H-2), 5.67 (dd, J = 1.5, 1.5 Hz, 1H, H-5), 6.81 (d, J = 15.6 Hz, 1H, H-8), 7.01 (d, J = 15.6 Hz, 1H, H-7), 7.23–7.44 (m, 10H, Ar); ^{13}C NMR (151 MHz, $CDCl_3$) δ 15.0 (CH_3), 36.1 (CH_2), 36.3 (CH), 40.5 (CH), 63.5 (CH_2), 84.3 (CH_3), 116.6 (CH), 126.6 (CH), 126.8 (2CH), 126.9 (CH), 127.5 (2CH), 127.9 (CH), 128.6 (2CH), 128.9 (2CH), 129.9 (CH), 134.1 (C), 136.6 (C), 143.7 (C). HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{25}NNaO_3S$: 406.1447, found: 406.1465.
10. Compound **4a**: Colorless crystals; mp 176–177 °C; IR (KBr): 1350, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.31 (ddd, J = 2.9, 2.9, 15.1 Hz, 1H, H-3), 2.56 (ddd, J = 2.9, 9.7, 15.1 Hz, 1H, H-3′), 3.19 (s, 3H, Ms), 3.38 (dq, J = 7.1, 8.9 Hz, 1H, OCH_2CH_3), 3.53 (dq, J = 7.1, 8.9 Hz, 1H, OCH_2CH_3), 3.9 (ddd, J = 2.9, 9.7, 11.5 Hz, 1H, H-4), 4.19 (ddd, J = 1.8, 1.8, 11.5 Hz, 1H, H-4a), 4.5 (dd, J = 1.8, 2.8 Hz, 1H, H-7), 5.44 (dd, J = 2.9, 2.9 Hz, 1H, H-2), 6.50 (dd, J = 1.8, 2.8 Hz, 1H, H-8), 7.26–7.53 (m, 10H, Ar); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.9 (CH_3), 35.1 (CH_2), 40.2 (CH), 40.9 (CH_3), 41.3 (C), 43.2 (CH), 43.8 (C), 46.8 (CH), 64.7 (CH_2), 85.3 (CH), 108.3 (C), 109.7 (C), 111.1 (C), 111.3 (C), 114.2 (CH), 128.4 (CH), 128.6 (CH), 129.2 (2CH), 129.3 (3CH), 130.0 (2CH), 130.4 (CH), 132.1 (C), 132.5 (C), 139.7 (C). HRMS-ESI *m/z*: $[M+Na]^+$ calcd for $C_{28}H_{25}N_5NaO_3S$: 534.1570, found: 534.1546.