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On the Stereochemistry of the Dihydropyrone Diels–Alder Reaction

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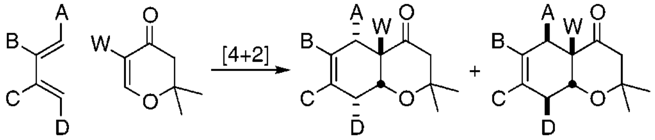
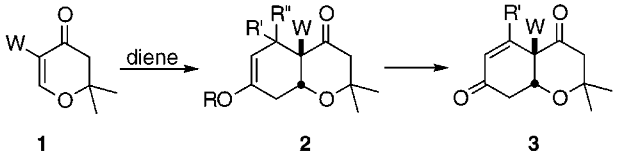
ABSTRACT



The Diels–Alder reaction of activated dihydropyrones with electron-rich dienes proceeds with synthetically useful levels of diastereoselectivity. Product ratios vary with the nature and location of substituents on diene and dienophile, as well as with reaction conditions. Lewis acid catalyzed reactions of related pyrone and benzopyrone dienophiles are also diastereoselective.

We recently reported the Diels−Alder reaction of substituted 2,3-dihydro-4-pyrones (e.g. **1**) with electron-rich dienes (Scheme 1).[1] Application of this method allows for the facile preparation of highly functionalized 1-oxadecalin derivatives **3**, which can serve as potential intermediates for the synthesis of a variety of complex natural products. Though this work demonstrated for the first time that dihydropyrones can serve effectively as dienophiles in this application, the stereoselectivity of this process remained to be elucidated. As the utility of the dihydropyrone Diels−Alder reaction would be enhanced by a reliable expectation of stereochemical control, we initiated a study geared toward illuminating the diastereoselectivity of this process. Herein we report our preliminary findings.

Scheme 1



Our previous studies had demonstrated the need for an electron-withdrawing substituent at C5 to augment the reactivity of the dihydropyrone dienophile toward cycloaddition. As systems of this type contain two functional groups that can potentially orient an incoming diene, the projected stereochemical outcome of these reactions was less than straightforward. Indeed, literature reports indicated that the Diels−Alder reactions of related benzopyrone dienophiles under thermal conditions proceed with a complete lack of diastereoselectivity with electron-rich dienes,[2] while those of 2-carbomethoxy-2-cyclohexenone derivatives under Lewis acid catalyzed conditions are strongly exo selective.[3]

In the present application, diastereoselectivity was evaluated for a series of dihydropyrones **1** in their Diels−Alder reactions with electron-rich dienes under both thermal and Lewis acid catalyzed conditions (Table 1). These reactions generally proceed in good to excellent yields in reasonable reaction times and under relatively mild conditions.

We first evaluated the effect of changing functionality at C5 of the dihydropyrone. Under thermal conditions, reaction of the 5-carbethoxydihydropyrone derivative **1a** with (*tert*-butyldimethylsilyl)oxy Danishefsky's diene **4** gave a 4:1 mixture of cycloadducts **10a** with the endo isomer predominating (entry 1).[4] Enhanced levels of endo selectivity were observed with the C5 nitrile **1b** (16:1) and sulfone **1c**

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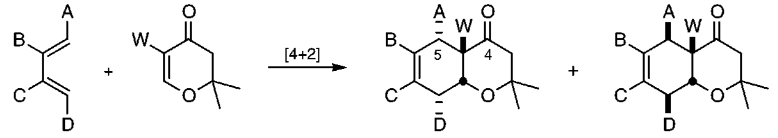
[1] (a) Chen, D.; Wang, J.; Totah, N. I. *J. Org. Chem.* **1999**, *64*, 1776. (b) Seth, P. P.; Totah, N. I. *J. Org. Chem.*, in press.

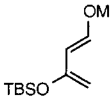
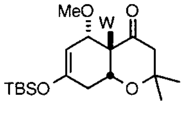
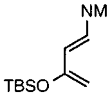
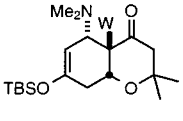
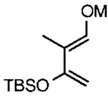
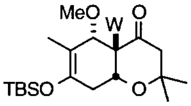
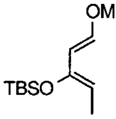
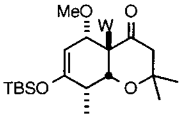
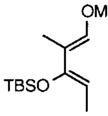
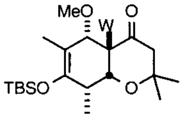
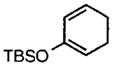
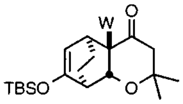
[2] (a) Cremins, P. J.; Saengchantara, S. T.; Wallace, T. W. *Tetrahedron* **1987**, *43*, 3075. (b) Hsung, R. P. *J. Org. Chem.* **1997**, *62*, 7904.

[3] (a) Liu, H. J.; Ngooi, T. K.; Browne, E. N. C. *Can. J. Chem.* **1988**, *66*, 3143. (b) Liu, H. J.; Chew, S. Y.; Browne, E. N. C. *Tetrahedron Lett.* **1991**, *56*, 2005. (c) Fringuelli, F.; Taticchi, A.; Wenkert, E. *Org. Prep. Proced. Int.* **1990**, *22*, 131.

10.1021/ol9909637 CCC: $18.00

Table 1. The Dihydropyrone Diels−Alder Reaction: Effect of Functionality and Substitution on Diastereoselectivity



entry	diene	W[a]	major product		Δ			ZnCl$_2$		
					temp/time	yield[b]	endo:exo[c]	temp/time	yield[b]	endo:exo[c]
1	 **4**	CO$_2$Et		**10a**	110°C, 24h	93%	4 : 1	0°C, 2h	85%	8 : 1
2		CN		**10b**	110°C, 24h	92%	16 : 1	25°C, 16h	trace	---
3	**4**	SO$_2$Ph		**10c**	110°C, 24h	92%	10 : 1	---	---	---
4		COCH$_3$		**10d**	110°C, 24h	93%	1.2 : 1	0°C, 2h	85%	2 : 1
5	 **5**	CO$_2$Et		**11**	25°C, 45min	94%[d]	20 : 1	---	---	---
6	 **6**	CO$_2$Et		**12a**	110°C, 24h	89%	3.4 : 1	0°C, 2h	94%	2.6 : 1
7		CN		**12b**	110°C, 24h	93%	>16 : 1	---	---	---
8	 **7**	CO$_2$Et		**13**	110°C, 24h	89%	4 : 1	25°C, 2h	89%	1.9 : 1
9	 **8**	CO$_2$Et		**14**	110°C, 24h	64%	4 : 1	25°C, 4h	76%	2 : 1
10	 **9**	CO$_2$Et		**15**	110°C, 24h	NR	---	25°C, 2h	85%	1 : 1.4[e]

[a] **1a**, W = CO$_2$Et; **1b**, W = CN; **1c**, W = SO$_2$Ph; **1d**, W = COCH$_3$. [b] Isolated yields. [c] Ratios were obtained by ^{1}H NMR of the crude reaction mixtures. Stereochemical assignments are based on NOE experiments. [d] NMR yield of crude cycloadduct using di-*tert*-butylpyridine as an internal standard. After reduction with LiAlH$_4$ the corresponding diol is isolated in 70% overall yield. [e] Ratio determined after hydrolysis of the enol ether.

(10:1) derivatives (entries 2 and 3), though the presence of a C5 ketone resulted in a complete loss of diastereoselectivity (entry 4). Diastereoselectivity in the reaction of the 5-carbethoxy derivative **1a** could be further enhanced by use of 1-(dimethylamino)-3-((*tert*-butyldimethylsilyl)oxy)-1,3-butadiene **5**[5] (entry 5). In this case, reaction proceeds at 25 °C in 45 min to provide a 20:1 mixture of stereoisomers. Though the instability of the initially formed Diels−Alder adduct **11** precludes its isolation, reduction of the crude keto ester with LiAlH$_4$ provides the corresponding diol, which is stable to silica gel chromatography.

In this sequence, the effect of Lewis acid catalysis on diastereoselectivity was also evaluated for several of the dihydropyrone derivatives.[6] Thus, in the presence of ZnCl$_2$ endo selectivity in the reaction of the 5-carbethoxy derivative **1a** increased to 8:1 (entry 1), and a comparable increase in selectivity (1.2:1 to 2:1) was observed for the C5 ketone **1d** (entry 4). No further enhancement in selectivity was observed when the reaction of dihydropyrone **1a** was conducted at −30 °C. We were unable to evaluate the combined effect of Lewis acid catalysis and a C5 nitrile (entry 2). Though we have found ZnCl$_2$ to be an effective catalyst in the Diels−Alder reactions of the cyano derivative **1b**,[1b] in the present application, only trace amounts of the desired cycloadduct

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(4) For our purposes, the endo isomer is defined as that in which approach of the diene is directed by the 4-keto substituent of the dihydropyrone ring.[3c] Thus, the methoxy substituent at C5 and the W substituent at C4a will be trans in the endo cycloadduct.

(5) (a) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252. (b) Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039.

(6) A variety of Lewis acids (e.g. TiCl$_4$, EtAlCl$_2$, Et$_2$AlCl, BF$_3$·OEt$_2$, ZnCl$_2$) were screened in this application.[1b] Optimized conditions are used in the present studies.

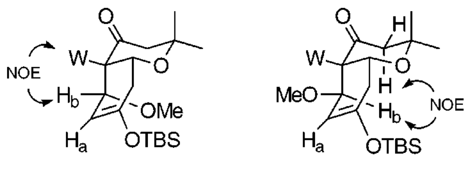
could be isolated due to decomposition of this product under the conditions of the reaction.

Several 1-methoxy-3-silyloxy dienes **6**−**8** were next examined to evaluate the effect of diene substitution on diastereoselectivity. Under thermal conditions, little variation in selectivity was observed with the addition of substituents at the 2- and 4-positions (entries 6, 8, and 9). Stereoselectivity was also maintained relative to that of the parent system (entry 1). Indeed, in each of these cases, the cycloaddition proceeds to give a ca. 4:1 ratio of diastereomers that favor the endo product. A slight decrease in selectivity (3.4:1) is observed with the 2-methyl derivative **6** (entry 6). In this example, use of the C5 nitrile **1b** in place of the ester **1a** (entry 7) results in a significant increase in diastereoselectivity, providing the cycloadduct as a >16:1 mixture of endo to exo isomers.[7]

When the same sequence of reactions was carried out under Lewis acid catalyzed conditions, we were surprised to find that not only did the level of selectivity observed decrease significantly relative to that obtained with Danishefsky's diene **4** in the presence of $ZnCl_2$ (entry 1) but selectivity also decreased relative to that obtained with the same dienes under thermal conditions. Indeed, under Lewis acid catalyzed conditions Diels−Alder reactions of the more highly substituted dienes **6**−**8** proceed to give only a ca. 2:1 mixture of diastereomers (entries 6, 8, and 9). Again, a subtle variation is observed in the reaction of diene **6** (entry 6). Here too, the stereochemical course of the reaction is unaffected by a decrease in reaction temperature.[8]

A further erosion in selectivity is observed in the Diels−Alder reaction of the unrelated cyclic diene **9** with pyrone **1a** (entry 10). In this case, cycloaddition proceeds to give a 1:1:4 mixture of diastereomers **15**, now favoring formation of the exo adduct. Presumably this change in selectivity is steric in nature.

For the above experiments, relative stereochemistry of the cycloaddition products was determined by NOE experiments on the individual diastereomers. Key enhancements are generalized in Figure 1.[9] The pseudoaxial orientation of the C5 methoxy substitutent in the endo isomer is supported by the observation of a large coupling constant between protons H_a and H_b ($J_{a,b} \approx 5$ Hz) relative to that of the exo isomer ($J_{a,b} \approx 2$ Hz) in relevant systems.



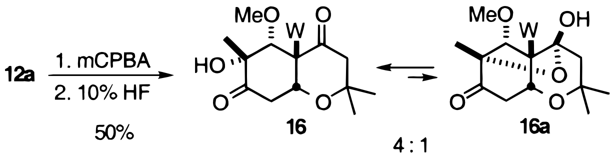
endo **exo**

Figure 1. Determination of cycloadduct stereochemistry.

At present, the factors which influence diastereoselectivity in the dihydropyrone Diels−Alder reaction remain unclear. As the dihydropyrone **1** contains two dienophilic functions, selectivity will, in part, be a function of the secondary orbital overlap of these groups with the incoming diene,[10] and such issues may account for the differences in diastereoselectivity encountered with changes in the C5 substituent on the dihydropyrone under thermal conditions. In the presence of Lewis acid, a situation in which complexation with the Lewis acid enhances the secondary orbital interaction of the diene with the "endo" (ketone) substituent relative to that in the uncatalyzed case is expected to result in an increase in endo selectivity, whereas enhancement of the secondary orbital interactions with the "exo" (ester) substituent would result in a decrease in endo selectivity. One might also consider that, at lower reaction temperatures, steric factors will play a larger role in controlling the reaction pathway. Thus, a decrease in diastereoselectivity might well be expected under the conditions of the Lewis acid catalyzed cycloaddition reaction, though such factors do not explain the differential sense of selectivity observed between the substituted and parent 1-methoxy-3-silyloxy dienes under these conditions.[11]

Further manipulation of Diels−Alder adducts of these types generally involves hydrolysis of the resulting enol ether to provide the corresponding α,*β*-unsaturated ketone (e.g. **3**, Scheme 1). However, the stereochemical benefits of the cycloaddition reaction can be maximized via selective manipulation of the enol ether under conditions that leave the *β*-methoxy function intact. For example, Rubottom oxidation[12] of the cycloadduct **12a** (mCPBA, CH_2Cl_2, 0 °C) provides the α-hydroxy ketone **16** (W = CO_2Et) as a single diastereomer that exists as an inseparable mixture of C4 ketone (**16**) and hemiketal (**16a**) isomers (Scheme 2).[13] The relative stereochemistry of compound **16** follows from the presence of the hemiketal **16a**, as the other diastereomer **17** would be unable to cyclize in this manner.

Scheme 2



The Diels−Alder reactions of related pyrone dienophiles with Danishefsky's diene are reported to proceed with low

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[7] Upon purification, a single diastereomer was isolated.

[8] That the ratios obtained in the above experiments reflect a kinetic process is supported by a lack of equilibration when individual isomers of **10a** and **12a** are resubjected to either thermal or Lewis acid catalyzed reaction conditions.

[9] For endo isomers (W = CO_2Et, CN), NOE experiments are generally conducted on the products obtained upon reduction of the cycloadducts with $LiAlH_4$.

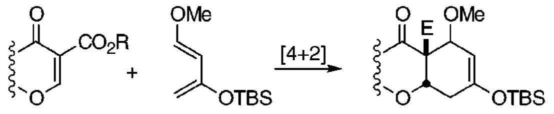
[10] Ginsburg, D. *Tetrahedron* **1983**, *39*, 2095.

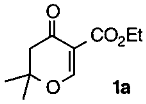
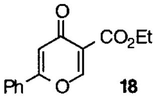
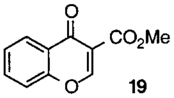
[11] The use of Lewis acid to catalyze the Diels−Alder reactions of electron-deficient olefin dienophiles with electron-rich dienes remains largely unexplored, presumably due to the considerable reactivity of these dienes under thermal conditions as well as their lability to many Lewis acids.

[12] Rubottom, G. M. Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319.

levels of diastereoselectivity.[2] In light of our results with the dihydropyrones **1**, we were interested to see the effect of Lewis acid catalysis on the outcome of these processes. As such, the reactions of the pyrone derivatives **18** and **19** with (*tert*-butyldimethylsilyl)oxy Danishefsky's diene **4**[14] were explored under both thermal and Lewis acid catalyzed conditions (Table 2).

Table 2. Diels−Alder Reaction of Pyrone Derivatives



dienophile	Δ^a		$\mathrm{ZnCl_2}^b$	
	yield[c]	endo:exo[d]	yield[c]	endo:exo[d]
 **1a**	93%	4 : 1	85%	8 : 1
 **18**	90%	1.3 : 1	71%	5 : 1
 **19**	90%	2.3 : 1	61%	8 : 1

[a] Toluene, 110 °C. [b] THF, 0 °C, 2 h. [c] Isolated yields. [d] Ratios were obtained by ^{1}H NMR of the crude reaction mixtures. Stereochemical assignments are based on published data.[2]

Under thermal conditions (110 °C, 6 h), cycloaddition of the pyrone **18** proceeded in 90% yield to give a 1.3:1 mixture of endo and exo adducts.[15] Diels−Alder reaction of the benzopyrone **19** was somewhat more selective, providing a 2.3:1 mixture of cycloadducts in 93% yield.

Though in neither of these cases did the level of selectivity approach that observed in like reactions with the dihydropyrone **1a**, we were pleased to find that here too Lewis acid catalysis had a significant effect on the stereochemical outcome of these reactions. Thus, in the presence of $\mathrm{ZnCl_2}$, the Diels−Alder reaction of pyrone **17** with diene **4** provides a 5:1 mixture of diastereomers, while in the reaction of the benzopyrone **18** the resulting cycloadducts are isolated in a ratio of 8:1. In each of these examples, the endo isomer[4] predominates.

In conclusion, we have demonstrated that the dihydropyrone Diels−Alder reaction proceeds with useful levels of diastereoselectivity, which can be exploited for the synthesis of more complex systems. Though the factors that govern diastereoselectivity in these reactions remain to be fully elucidated, for the majority of cases studied, endo selectivity, whereby approach of the diene is governed by the C4 ketone, predominates under both thermal and Lewis acid catalyzed conditions. In addition, we have demonstrated that Lewis acid catalysis can be used effectively to enhance the diastereoselectivity of Diels−Alder reactions of both pyrone and benzopyrone dienophiles with activated dienes. Further studies aimed at the application of these findings to the synthesis of complex molecules are currently underway.

Acknowledgment. Support from the National Science Foundation (CHE-9700141) is gratefully acknowledged. We thank Mr. Xiuchun Gao for conducting Diels−Alder reactions of diene **8** with dihydropyrone **1a**.

Supporting Information Available: General experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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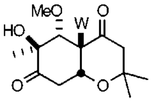
(13) That compounds **16** and **16a** are ketone and hemiketal forms of the same isomer is supported by the formation of a 1:1 mixture of diastereomers (**16**:**17**) when the oxidation is run in hexanes. Compound **17** can be cleanly separated from the mixture of **16** and **16a**.



17

(14) Use of the TBDMS derivative of Danishefsky's diene facilitates isolation of the cycloadducts. Selectivities are comparable to those reported previously using the parent diene (TMS ether). An exception is noted in ref 15.

(15) The thermal Diels−Alder reactions of both *tert*-butyl and benzyl ester derivatives **18** with Danishefsky's diene are reported to occur with complete endo diastereoselectivity, though the cycloadducts are recovered in only 52% and 53% yields, respectively: Groundwater, P. W.; Hibbs, D. E.; Hursthouse, M. B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 163.