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Catalyst-Controlled Diastereoselective Hetero-Diels–Alder Reactions

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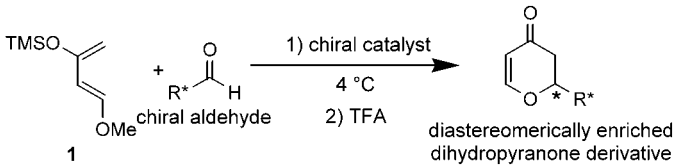
ABSTRACT



The diastereoselective hetero-Diels–Alder reaction between Danishefsky's diene and chiral aldehydes is catalyzed by chiral chromium–Schiff base complexes. High levels of catalyst control are obtained in several cases, allowing access to all four stereoisomeric products through appropriate choice of aldehyde and catalyst enantiomers.

The hetero-Diels−Alder (HDA) reaction between 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (**1**, Danishefsky's diene) and aldehydes has been the focus of extensive study and application (Scheme 1).[1] Early efforts to control stereoselectivity in these reactions focused on the use of chiral aldehydes in substrate-controlled diastereoselective reactions.[2] More recently, attention has been given to the discovery of chiral catalysts to effect enantioselective HDA reactions of **1** and related electron-rich dienes.[3] In the latter context, our research group has developed two related catalyst systems for effecting enantioselective hetero-Diels−Alder reactions.[4] The (salen)Cr(III)−BF_4 complex **2** was found to be a reactive and effective catalyst for asymmetric

Scheme 1

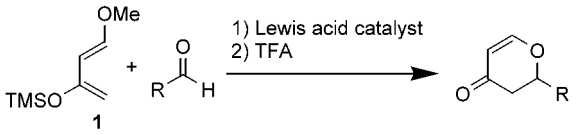


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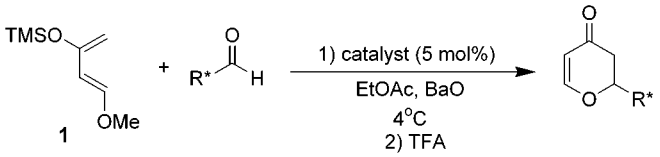
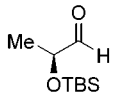
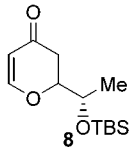
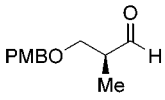
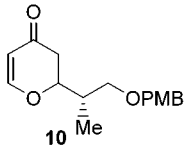
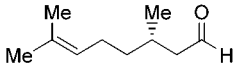
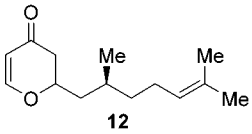
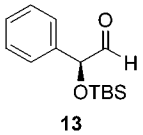
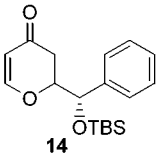
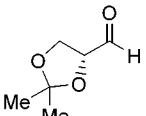
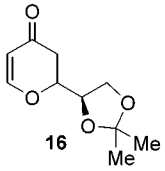
Table 1. Diastereoselective Hetero-Diels−Alder Reaction Catalyzed by Tridentate Cr(III) Catalysts[a]



hetero dienophile	product	entry	catalyst	%yield[b]	dr[c]	config of major diastereomer	%ee of major diastereomer
 **7**	 **8**	1	**5**	81	1:2.0	(2*R*,1′*S*)[e]	nd
		2	(1*R*,2*S*)-**3**	96	1:12	(2*R*,1′*S*)[e]	>99[g]
		3	(1*S*,2*R*)-**3**	97	15:1	(2*S*,1′*S*)[e]	>99[g]
 **9**	 **10**	4	**5**	50	1:1.1	(2*R*,1′*S*)[e]	nd
		5	(1*R*,2*S*)-**3**	90	1:11	(2*R*,1′*S*)[d]	>99[h]
		6	(1*S*,2*R*)-**3**	86	9.3:1	(2*S*,1′*S*)[e]	99[h]
 **11**	 **12**	7	**5**	85	1:1.3	(2*R*,2′*S*)[e]	nd
		8	(1*R*,2*S*)-**3**	98	16:1	(2*S*,2′*S*)[e]	nd
		9	(1*S*,2*R*)-**3**	99	1:11	(2*R*,2′*S*)[e]	nd
 **13**	 **14**	10	**5**	58	1.7:1	(2*R*,1′*S*)[e]	nd
		11	(1*R*,2*S*)-**3**	58	3.6:1	(2*R*,1′*S*)[e]	99[g]
		12	(1*S*,2*R*)-**3**	44	1:2.6	(2*S*,1′*S*)[e]	97[g]
 **15**	 **16**	13	**5**	68	1:4.5	(2*S*,4′*R*)[f]	>99[h]
		14	(1*R*,2*S*)-**3**	76	1:1.2	(2*S*,4′*R*)[f]	98[h]
		15	(1*S*,2*R*)-**3**	84	1:33	(2*S*,4′*R*)[f]	99[h]

[a] All reactions were run on a 1 mmol scale, with 1.2 equiv of aldehyde and 200 mg of BaO, with a 1 h prestir of catalyst and EtOAc prior to addition of aldehyde and diene. [b] Isolated yield based on diene. [c] Determined by ^{1}H NMR. [d] Relative configuration determined after PMB deprotection and cyclization to the known bicyclic acetal (ref 2b). [e] Assigned by analogy to (2*R*,1′*S*)-**10** and (2*R*,4′*R*)- and (2*S*,4′*R*)-**16**. [f] Relative configuration determined by comparison to a known compound (ref 2c). [g] Determined by chiral HPLC analysis of the TBS deprotected derivative. [h] Determined by chiral HPLC analysis.

HDA reaction between **1** and achiral aldehydes.[4a] Subsequently, the tridentate Schiff base−Cr(III) complexes **3** and **4** were identified as highly selective catalysts for enantioselective HDA reactions employing mono-oxygenated dienes (Scheme 2).[4b]

The goal of the present study was to establish the viability of chiral catalyst-controlled doubly diastereoselective HDA reactions between **1** and optically active chiral aldehydes. If successful, such a strategy would provide selective access to stereochemically elaborate dihydropyranone derivatives that are not readily accessible using substrate-controlled diastereoselective reactions or through simple enantioselective reactions of achiral substrates.[5] The first successful examples of the application of this approach are described herein.

The cycloaddition between diene **1** and lactaldehyde derivative (*S*)-**7** was investigated as a model reaction (Table

Scheme 2. HDA Catalysts

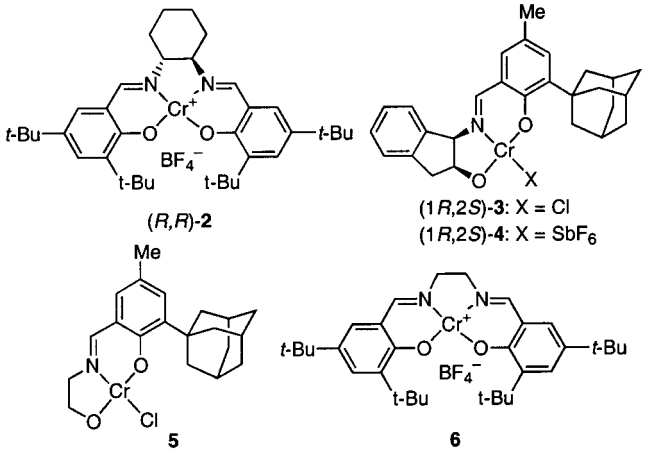
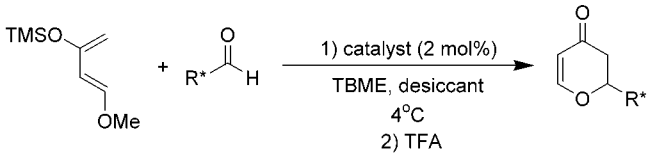
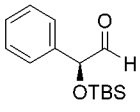
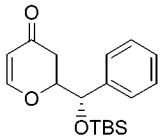
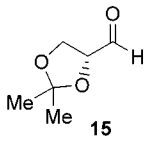
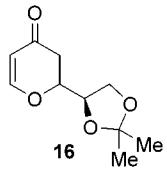


Table 2. Diastereoselective Hetero-Diels−Alder Reaction Catalyzed by (salen)Cr(III) Catalysts[a]



hetero dienophile	product	entry	catalyst	desiccant	%yield[b]	dr[c]	config of major diastereomer	%ee of major diastereomer
		1	**6**	BaO	64	1:1.1	(2*S*,1′*S*)[f]	nd
		2	(*R*,*R*)-**2**	BaO	94	4.5:1	(2*R*,1′*S*)[f]	>99[g]
		3	(*S*,*S*)-**2**	BaO	93	1:5.9	(2*S*,1′*S*)[f]	>99[g]
		4	**6**	4Å MS	56	1.1:1	(2*R*,1′*S*)[f]	nd
13	**14**	5	(*R*,*R*)-**2**	4Å MS	97	5.6:1	(2*R*,1′*S*)[f]	>99[g]
		6	(*S*,*S*)-**2**	4Å MS	97	1:9.1	(2*S*,1′*S*)[f]	>99[g]
		7	**6**	BaO	72	1:5.6	(2*S*,4′*R*)[e]	>99[h]
		8	(*R*,*R*)-**2**	BaO	81	1.4:1	(2*R*,4′*R*)[d]	>99[h]
15	**16**	9	(*S*,*S*)-**2**	BaO	82	1:32	(2*S*,4′*R*)[e]	>99[h]

[a] All reactions were run on a 1 mmol scale, with 1.2 equiv of aldehyde and 300 mg of desiccant (no prestir). [b] Isolated yield based on diene. [c] Determined by ^{1}H NMR. [d] Relative configuration determined by comparison to a known compound (ref 2b). [e] Relative configuration determined by comparison to a known compound (ref 2c). [f] Assigned by analogy to (2*R*,4′*R*)- and (2*S*,4′*R*)-**16**. [g] Determined by chiral HPLC analysis of the TBS deprotected derivative. [h] Determined by chiral HPLC analysis.

1, entries 1−3). The best results were obtained by aging ethyl acetate solutions of catalyst **3** for 1 h in the presence of a desiccant (4 Å molecular sieves or BaO[6]) prior to addition of the aldehyde and diene. Application of these optimized reaction conditions in the cycloaddition between **1** and **7** using catalysts (1*R*,2*S*)-**3** and (1*S*,2*R*)-**3** (5 mol %) provided the dihydropyranone products (2*R*,1′*S*)-**8** and (2*S*,1′*S*)-**8** in a 1:12 diastereomeric ratio (dr) (96% yield) and a 15:1 dr (97% yield), respectively (Table 1, entries 2 and 3).[7] The analogous achiral catalyst **5** provided **8** in a diastereomeric ratio of 1:2.0 (entry 1).

Other chiral aldehydes proved to be suitable as substrates for the HDA reaction. Thus, subjection of aldehyde (*S*)-**9** to reaction with **1** in the presence of **3** led to formation of the corresponding diastereomerically and enantiomerically enriched dihydropyranones in good selectivity (Table 1, entries 4−6). The same conditions were also applied to the HDA reaction of (*S*)-citronellal **11** with **1**, with good levels of catalyst control (Table 1, entries 7−9).

While the tridentate Schiff base catalyst **3** provided satisfactory results with aldehydes **7**, **9**, and **11**, it was far less effective with the more sterically congested aldehydes **13** and **15** (Table 1, entries 10−15). Thus, aldehyde (*S*)-**13** underwent HDA reaction with diene **1** under the standard conditions to provide dihydropyranone products **14** in moderate yields and diastereoselectivities (Table 1, entries 10−12). The HDA reaction of **1** with **15** catalyzed by the achiral complex **5** displayed a relatively high degree of substrate control, providing **16** with a dr of 1:4.5 (Table 1, entry 13), with the major diastereomer derived from cycloaddition on the Felkin face of **15**. The matched catalyst/substrate system in this case provided the highest level of diastereoselectivity in our study (1:33, entry 15). However, the mismatched combination failed to overcome the inherent substrate bias (Table 1, entry 14). These results are consistent with Danishefsky's previous studies, revealing that aldehyde **15** is extremely resistant to reaction at its anti-Felkin face.[8]

Fortunately, improved selectivities in cycloadditions between **1** and aldehydes **13** and **15** were achievable through use of the (salen)Cr(III)−BF_4 catalyst **2**.[4a] Reaction of

(5) To our knowledge, there has been only one report of chiral catalyst-controlled HDA reactions of chiral aldehydes (ref 3r). In this instance, only moderate diastereoselectivities were obtained (up to 1.04:1) in the substrate−catalyst mismatched case.

(6) Because BaO is much more dense than 4 Å molecular sieves, its use proved to be preferable from a practical perspective. However, in isolated cases, superior results were obtained employing 4 Å molecular sieves (e.g., with aldehyde **13**, Table 2).

(7) Representative general procedure (for complete experimental details, see Supporting Information): A solution of (1*R*,2*S*)-**3** (0.024 g, 0.05 mmol in EtOAc (200 μL)) was stirred under N_2 for 1 h in the presence of BaO (200 mg). Aldehyde **7** (0.238 g, 1.26 mmol) was added, and the mixture was cooled to 0 °C; 1-methoxy-3-[(trimethylsilyl)oxy]butadiene **1** (205 μL, 1.06 mmol) was added, and the mixture was allowed to stir at 4 °C for 22.5 h. CH_2Cl_2 (2 mL) was added, followed by a drop of TFA. The reaction mixture was allowed to warm to room temperature and stirred for 10 min. The mixture was then filtered through a plug of silica gel on Celite. The filtrate was concentrated in vacuo, and the crude residue was purified by flash chromatography (85:15 hexanes/EtOAc) to afford (2*R*,1′*S*)-**8** (0.263 g, 1.02 mmol, 96%) as a pale yellow oil.

(8) Reaction of **15** with **1** under Lewis acid catalysis by $MgBr_2$ in THF afforded the Felkin cycloadduct with only ca. 10% of the epimeric anti-Felkin product observed. See refs 2b and 2c.

aldehyde (*S*)-**13** with diene **1** catalyzed by (*R*,*R*)-**2** and (*S*,*S*)-**2** (2 mol %) in the presence of BaO afforded mixtures of dihydropyranone products (2*R*,1′*S*)-**14** and (2*S*,1′*S*)-**14** in 4.5:1 and 1:5.9 dr, respectively (Table 2, entries 2 and 3). A prestir with desiccant was not found to be beneficial with the salen catalysts. Use of 4 Å molecular sieves instead of BaO provided modest improvements in the diastereoselectivities (Table 2, entries 5 and 6) with this substrate.

Aldehyde (*R*)-**15** underwent cycloaddition with **1** in the presence of the achiral (salen)Cr(III)−BF_4 complex **6** to provide **16** with a relatively high level of substrate-induced diastereoselectivity (1:5.6), the major product being that derived from cyclocondensation on the Felkin face of **15**. The matched catalyst (*S*,*S*)-**2** reinforced the substrate bias, with (2*S*,4′*R*)-**16** obtained in high selectivity (1:32). More significant, the mismatched catalyst (*R*,*R*)-**2** provided **16** with a modest preference for reaction at the anti-Felkin face (1.4:1). Thus, it was possible to override even strong degrees of substrate bias with the chiral Diels−Alder catalysts.

In summary, catalyst-controlled doubly diastereoselective hetero-Diels−Alder reactions between diene **1** and chiral aldehydes are achievable with chromium−Schiff base catalysts **2** and **3**. This methodology provides selective access to any of the four possible stereoisomers of the dihydropyranone products by judicious use of aldehyde and catalyst enantiomers.

Acknowledgment. This work was supported by the NIH (GM-59316) and a predoctoral fellowship to G.D.J. from the National Science Foundation.

Supporting Information Available: Complete experimental procedures, analytical data, ^{1}H NMR spectra for dr determination, and chiral chromatographic analyses for ee determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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