Highly Enantioselective Inverse-Electron-Demand Hetero-Diels–Alder Reactions of α,β-Unsaturated Aldehydes**

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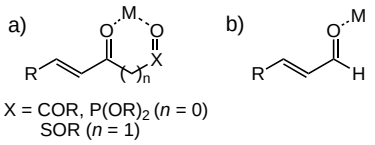
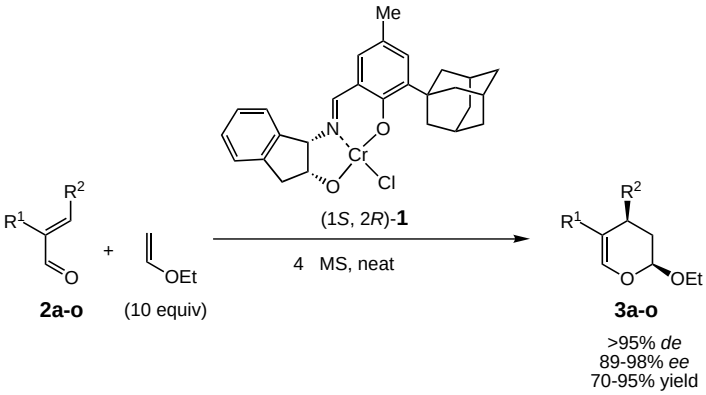
Dihydro- and tetrahydropyran derivatives are prevalent structural subunits in a variety of biologically important compounds, including carbohydrates, pheromones, iridoids, and polyether antibiotics. The inverse-electron-demand hetero-Diels–Alder (HDA) reaction of oxabutadienes with electron-rich olefins is a synthetically attractive route to such heterocycles, allowing the direct formation of dihydropyran derivatives with up to three stereogenic centers in one convergent step from simple achiral precursors.[1] Although there are numerous diastereoselective variants of the inverse-electron-demand HDA reaction known,[2] very few examples of catalytic, enantioselective versions have been identified to date.[3] The scope of reported methods is limited to oxabutadiene derivatives bearing electron-withdrawing groups such as sulfone groups,[3a] phosphonate groups,[3b] or ester groups.[3c] These ancillary groups serve both to activate the oxadiene electronically and to anchor the substrate to the catalyst by two-point binding (Scheme 1a). Chelation in this manner appears to be essential for attaining good reactivity and stereoselectivity.



Scheme 1. a) Two-point binding of oxabutadiene derivatives to a Lewis acid (M = Lewis acid); b) one-point binding of an α,β-unsaturated aldehyde to a Lewis acid.

Development of asymmetric inverse-demand HDA reactions involving simple α,β-unsaturated aldehyde substrates would expand the utility of this methodology significantly (Scheme 2).[4] This task presents a clear challenge, however, which requires effective activation and enantiofacial discrimination of the carbonyl solely through one-point binding to catalyst (Scheme 1b), while simultaneously avoiding unproductive decomposition of the sensitive oxadiene and electron-rich dienophile partners. Herein we describe the first example of a successful solution to this problem, in the highly enantioselective (Schiff base)Cr^{III}-catalyzed HDA reactions of alkyl vinyl ethers with α,β-unsaturated aldehydes.



Scheme 2. Hetero-Diels–Alder reactions catalyzed by **1**; MS = molecular sieves, *de* = diastereomeric excess.

The tridentate (Schiff base)chromium complex (**1**, see Scheme 2) has been identified as a highly diastereoselective and enantioselective catalyst in hetero-Diels–Alder (HDA) reactions between aldehydes and mono-oxygenated 1,3-diene derivatives.[5] The crucial feature of this catalyst system lies in its ability to effect activation of simple aldehydes toward pericyclic reactions with only mildly nucleophilic partners, with concomitant high enantioselectivity.[6] With an eye toward determining whether such properties might be extended to reactions of conjugated aldehydes, we evaluated the reaction of crotonaldehyde and ethyl vinyl ether as a model system for the inverse-demand HDA. The uncatalyzed HDA reaction takes place only at elevated temperatures and pressures, yielding the corresponding dihydropyran **3a** in good yields but poor *endo*/*exo* selectivity.[7] We were encouraged to find that the same reaction proceeded in the presence of 4 Å molecular sieves with 5 mol% **1**[8] in *tert*-butyl methyl ether (TBME) or CH_2Cl_2 solution at RT to provide **3a** with excellent diastereoselectivity (*endo*/*exo* > 96:4),[9] and promising enantioselectivity (72–78% *ee*; *ee* = enantiomeric excess). Unfortunately, aldehyde conversions of only approximately 20% were achieved using 1:1 molar ratios of the reactants at 1M concentration. A dramatic improvement was observed in reactions carried out under solvent-free conditions and excess ethyl vinyl ether[10] (94% *ee* and 75% isolated yield, Table 1, **2a**). Indeed, introduction of solvents (CH_2Cl_2, toluene, acetone, and *tert*-butyl methyl ether) generally resulted in significantly lower enantioselectivity in the cycloaddition (40–80% *ee*). Ethyl vinyl ether was shown to be the optimal dienophile partner. The selectivity and reactivity decreased as the steric bulk of the alkyl group was increased (Et > *n*Pr > *n*Bu ≈ *i*Bu), to the point that *tert*-butyl vinyl ether was found to be unreactive.

With these reaction parameters defined, a variety of aldehydes were examined in the inverse-electron-demand HDA reaction with ethyl vinyl ether (Table 1). A wide range of α,β-unsaturated aldehydes bearing aliphatic β substituents (**2a**–**e**) underwent cycloaddition with high enantioselectivity

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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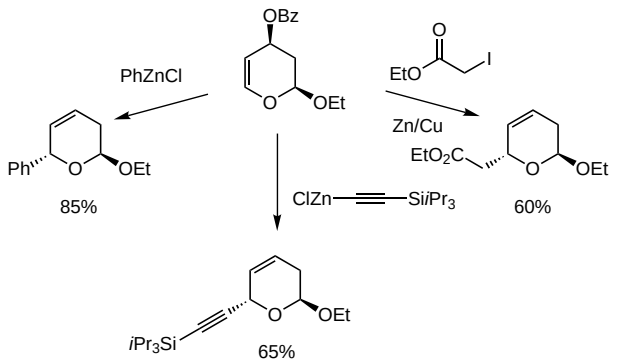
Table 1. Asymmetric inverse-electron-demand hetero-Diels–Alder reactions of α,β-unsaturated aldehydes with ethyl vinyl ether, catalyzed by **1**.[a]

Aldehyde	R^1	R^2	Catalyst loading [mol %][b]	Reaction time [h]	Yield [%][c]	*ee* [%][d]
2a	H	Me	5	24	75	94
2b	H	Et	5	48	75	94
2c	H	*i*Pr	10	48	72	94
2d	H	*n*Pr	5	48	73	94
2e	H	*n*Bu	5	48	70	95
2f	H	Ph	10	48	75	98
2g	H	4-MeO-C_6H_4	10	96	40	98
2h	H	4-NO_2-C_6H_4	10	72	90	98
2i	H	2-NO_2-C_6H_4	10	120	80	98
2j	H	CH_2OBn	5	24	90	95
2k	H	CH_2OTBS	5	24	95	92
2l	H	CO_2Et	5	24	90	95
2m	H	OBz	5	48	80	89
2n	Br	Ph	5	48	75	98
2o	Me	Me	7	96	75	92

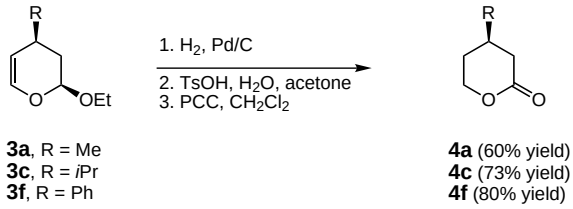
[a] Reactions were performed with aldehyde (1 mmol) and ethyl vinyl ether (10 equiv), in the presence of finely powdered 4 Å molecular sieves (150 mg). [b] Catalyst loadings refer to the amount of chromium employed, assuming the molecular structure depicted in Scheme 2. [c] Product isolation was accomplished by dilution of the reaction mixture with pentane, filtration, and distillation or column chromatography. Yields given are after isolation. [d] Enantioselectivities were determined either by HPLC or GC analysis, using commercially available chiral stationary phases. For details see the Supporting Information.

(94–95 % *ee*, 70–75 % yield). Whereas use of 5 mol % catalyst was adequate in most cases, the sterically more demanding 4-methyl-2-pentenal (**2c**) required 10 mol % of **1** to attain complete conversion within 48 h. Cinnamaldehyde derivatives (**2f–i**) underwent reactions with ethyl vinyl ether with very high enantioselectivity, and excellent diastereoselectivity. Substrates bearing functionality within R^2 (e.g. **2j–l**) were among the very best in all respects, displaying good reactivity and consistently high enantioselectivity and yields (92–95 % *ee*, 90–95 % yield). The successful application of 3-benzoylacrolein (**2m**) in the HDA reaction provides ready access to the 4-benzoyl-substituted dihydropyran derivative, a versatile intermediate poised for an assortment of useful substitution reactions (Scheme 3).[11] Finally, the promising scope of this method is illustrated further by the demonstrated tolerance for substituents at the 2-position of the aldehyde. Both 2-bromocinnamaldehyde (**2n**) and 2-methyl-2-butenal (**2o**) provided cycloadducts with high enantioselectivity.



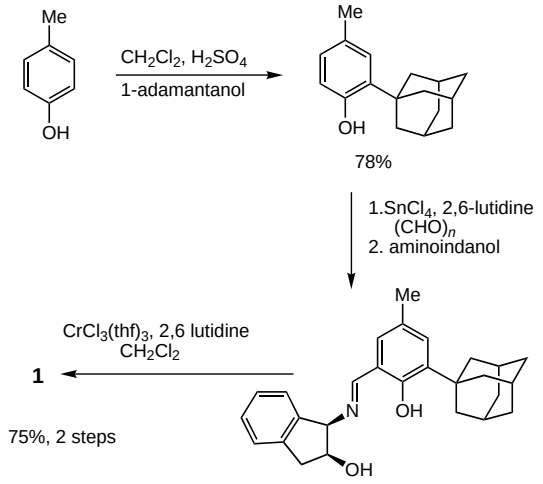
Scheme 3. Substitution reactions of the dihydropyran derivative **3m**, Bz = benzyl.

The absolute configuration of the products was established by conversion into the known 4-subtituted pyranones (Scheme 4).[12] Thus, reduction of the dihydropyrans **3a**, **3c**, and **3f** with H_2 in the presence of Pd on charcoal, followed by hydrolysis (TsOH, H_2O, acetone; Ts = tosyl) and pyridinium chlorochromate (PCC) oxidation of the resulting lactol afforded the corresponding lactones (**4**). This straightforward procedure provides a relatively concise and high-yielding (60–80 % overall) route to synthetically useful 4-substituted pyranone derivatives in an enantioenriched form.[13]



Scheme 4. Preparation of β-substituted pyranones from dihydropyrans **3a**, **3c**, and **3f**.

In an effort to render the HDA methodology as useful and accessible as possible, we have devised a new and significantly improved synthesis of catalyst **1** (Scheme 5).[14] As compared



Scheme 5. Practical synthesis of catalyst (1*R*,1*S*)-**1**.

to the procedure disclosed previously,[5] the new route avoids the use of sensitive and expensive Cr^{II} salts and can be carried out conveniently on the bench. More significant, it provides material of higher quality with respect to its chemical properties. In particular, compound **1** obtained from the new procedure requires no aging with molecular sieves to attain optimal performance, and confers 5–10 % higher enantioselectivity than does catalyst prepared by the original procedure.[15]

Insight into the basis for stereoinduction in these cycloaddition reactions will rely on a detailed understanding of the mechanism of catalysis. In this context, inspection of the crystal structure of **1** may provide a valuable starting point (Figure 1).[16] In the solid state, catalyst **1** exists as a dimeric

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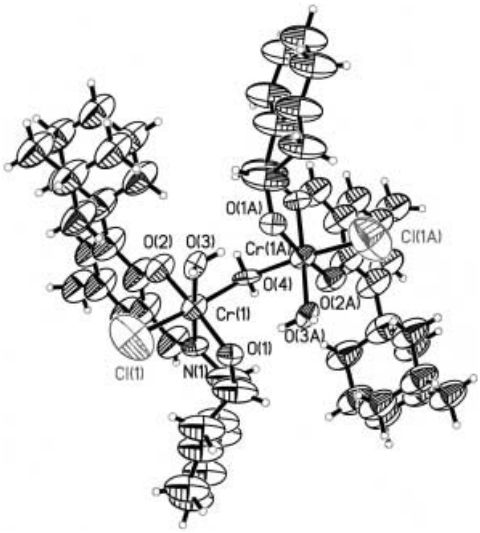

Figure 1. X-ray crystal structure of catalyst **1**; ellipsoids drawn at the 50% probability level.

structure, bridged through a single water molecule and bearing one terminal water ligand on each chromium center. On the basis of preliminary solution molecular-weight and kinetic studies,[17] it appears that this dimeric structure is maintained in the catalytic cycle. Dissociation of a terminal water molecule to open a coordination site for complexation of the aldehyde substrate is expected to be energetically difficult, and may serve to explain the crucial role of molecular sieves in these reactions.[18]

In summary, the scope of (Schiff base)Cr^{III}-catalyzed cycloaddition reactions has been expanded to inverse-demand HDA reactions of simple α,β-unsaturated aldehydes. The broad range of aldehydes utilized effectively by catalyst **1** allows access to a series of synthetically useful dihydropyran derivatives in a highly enantioenriched form. Future studies will be directed toward further extending the scope of this promising methodology in the context of more elaborate intermediates and natural product targets.

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[8] A variety of chiral tridentate (Schiff base)chromium complexes were evaluated, and complex **1** afforded the best results with regard both to enantioselectivity and reactivity.

[9] No *exo* diastereoisomer could be detected by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy.

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[14] Full experimental details are provided as Supporting Information.

[15] Improvement in catalyst performance extends to normal-demand HDA reactions as well. For example, the reaction of 1-benzyloxybutadiene with 3-(triisopropylsilyl)propynal produced cycloadduct in 89% *ee* using catalyst prepared by the original procedure, and 94% *ee* using the new catalyst. This reaction served as the starting point for the synthesis of fostriecin: D. E. Chavez, E. N. Jacobsen, *Angew. Chem.* **2001**, *113*, 3779–3782; *Angew. Chem. Int. Ed.* **2001**, *40*, 3667–3670.

[16] Details of the crystal structure analysis are provided as Supporting Information. CCDC-189470 (**1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[17] R. T. Ruck, E. N. Jacobsen, unpublished results.

[18] No cycloaddition is observed in the absence of dessicant. For a discussion on a related system, see ref [6].

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