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

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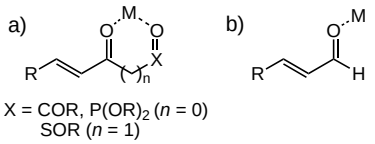
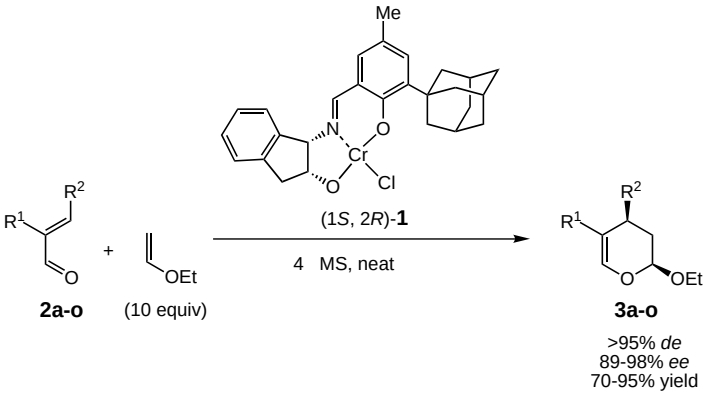
Dihydro- and tetrahydropyran derivatives are prevalent structural subunits in a variety of biologically important compounds, including carbohydrates, pheromones, iridoids, and polyether antibiotics. The inverse-electron-demand hetero-Diels–Alder (HDA) reaction of oxabutadienes with electron-rich olefins 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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[**] This work was supported by the NIH (GM-59316), with additional support from the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung (postdoctoral fellowship to K.G.), and the National Science Foundation (predoctoral fellowship to D.E.C.). We are grateful to Dr. R. Staples for carrying out the X-ray crystal structure analysis of **1**.

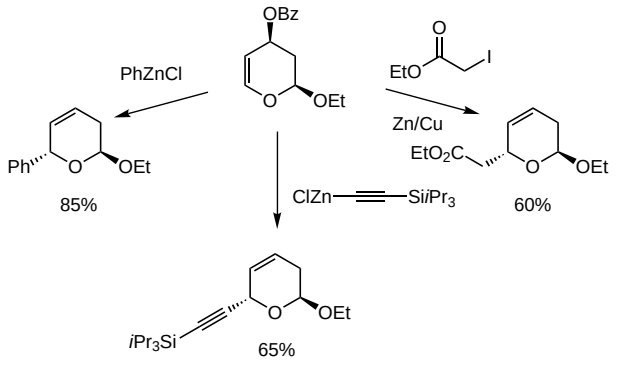
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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

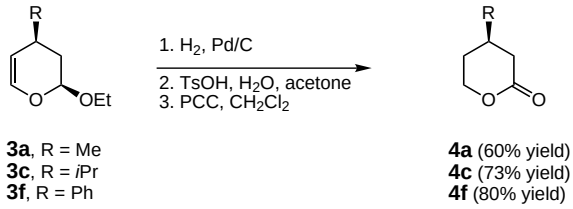
[a] Reactions were performed with aldehyde (1 mmol) and ethyl vinyl ether (10 equiv), in the presence of finely powdered 4 Å molecular sieves (150 mg). [b] Catalyst loadings refer to the amount of chromium employed, assuming the molecular structure depicted in Scheme 2. [c] Product isolation was accomplished 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.



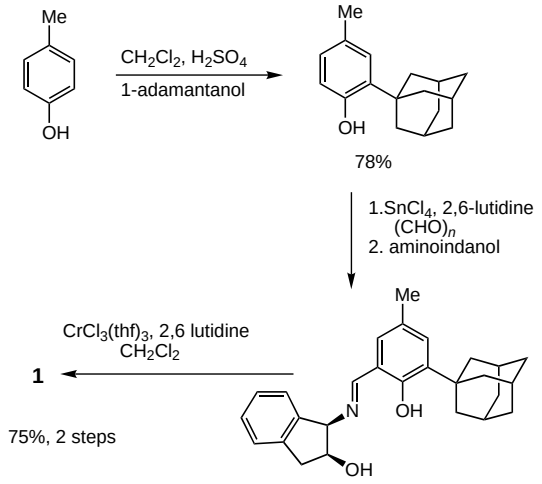
Scheme 3. Substitution reactions of the dihydropyran derivative **3m**, Bz = benzyl.

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

  0044-8249/02/11416-3186 $ 20.00+.50/0 *Angew. Chem.* **2002**, *114*, Nr. 16

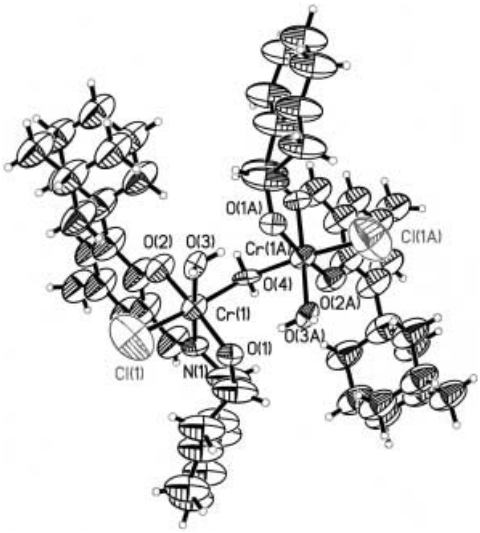


Figure 1. X-ray crystal structure of catalyst **1**; ellipsoids drawn at the 50% probability level.

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.

Received: June 11, 2002 [Z19516]

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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.

[10] The use of excess ethyl vinyl ether had a beneficial effect on conversion and prevented aldehyde self-condensation in the case of substrates with aliphatic β substituents.

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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 CB2 1EZ, 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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