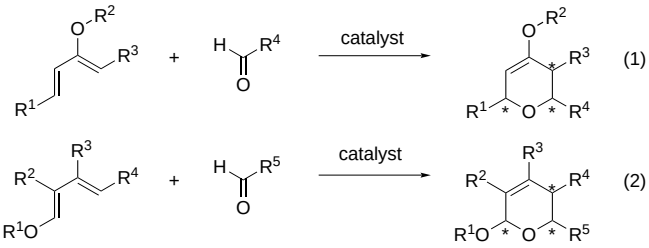
[12] Alcohol **6** was prepared by the Shapiro reaction of cyclohexanone *p*-toluenesulfonylhydrazone with *n*-nonanal in 48% yield. R. H. Shapiro, *Org. React. (N.Y.)* **1976**, *13*, 405. See also: N. E. Schore, M. J. Knudsen *J. Org. Chem*. **1997**, *52*, 569.
[13] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc*. **1980**, *102*, 5974.
[14] V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc*. **1981**, *103*, 6237.
[15] A similar system to **6** was reported to give the resolved (*R*)-alcohol efficiently by using L-(+)-DIPT under the Sharpless kinetic resolution conditions.[14] The optical purity of (*R*)-**6** was determined by Mosher analysis.
[16] Although the highly diastereoselective epoxidation of (*R*)-**6** is possible without adding chiral tartrate, we added (−)-tartrate, whose chirality matches that of (*R*)-**6**, to improve the optical purity of epoxy alcohol **8**.
[17] D. P. G. Hamon, R. A. Massy-Westropp, J. L. Newton, *Tetrahedron: Asymmetry* **1990**, *1*, 771.
[18] The protection of the diol **9** is required for the subsequent oxidation of the phenylselenide group; otherwise, the selenide **9** was reconverted to the epoxy alcohol **8** under the oxidation conditions.
[19] Starting from epoxy alcohol **7** (49% *ee*), which is obtained by the first kinetic resolution of **6** with (+)-tartrate, gave (*R*)-**2** (43% *ee*) on applying the same synthetic sequence. Therefore, we believe that no epimerization takes place at the quaternary alcohol carbon atom of **9** throughout the reactions.
[20] a) E. J. Corey, L. S. Hegedus, *J. Am. Chem. Soc*. **1969**, *91*, 4926; b) M. P. Cook, Jr., R. M. Parlman, *J. Am. Chem. Soc*. **1977**, *99*, 5225; c) L. S. Hegedus, R. J. Perry, *J. Org. Chem*. **1985**, *50*, 4955; d) J. Collin, J. L. Namy, F. Dallemer, H. B. Kagan, *J. Org. Chem*. **1991**, *56*, 3118.

Highly Enantio- and Diastereoselective Hetero-Diels–Alder Reactions Catalyzed by New Chiral Tridentate Chromium(III) Catalysts**

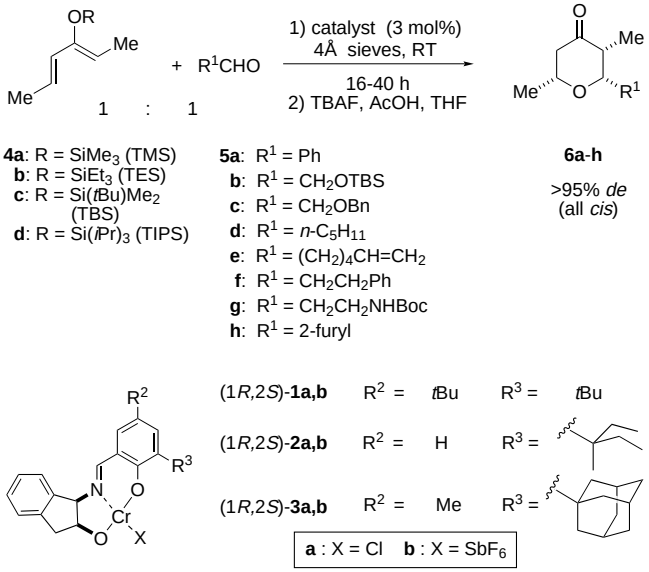
Alexander G. Dossetter, Timothy F. Jamison, and Eric N. Jacobsen*

The formal hetero-Diels–Alder reaction (HDA) between dienes and carbonyl compounds[1] has emerged as an important target for asymmetric catalysis. Successes reported in this area have involved the reaction of electron-rich dienes such as 1-methoxy-3-(trimethylsilyloxy)butadiene (Danishefsky's diene) and/or electron-deficient dienophiles such as glyoxylate derivatives.[2–4] As yet, however, there exists no effective method for asymmetric HDA reactions between less nucleophilic dienes bearing fewer than two oxygen substituents and unactivated carbonyl compounds [Eq. (1) and (2)]. This new



class of asymmetric HDA reaction would provide a direct route to enantiomerically enriched dihydropyran derivatives from simple achiral starting materials, setting up to three stereocenters in the cyclization and allowing ultimate access to tetrahydropyran derivatives with five defined stereocenters by elaboration of the resultant double bond. Herein we describe highly effective chiral catalysts for these types of HDA reactions.[5]

Evaluation of tridentate Schiff base chromium(III) complexes of the type **1a** and **1b** revealed catalysis of the HDA reaction between (2*Z*,4*E*)-triethylsilyloxy-2,4-hexadiene (**4b**) and aldehydes **5a** and **5b**, affording tetrahydropyranones **6a** and **6b** after desilylation (Scheme 1). In both cases, nearly



Scheme 1. Hetero-Diels–Alder reaction between substituted hexadienes **4** and aldehydes **5**. Bn = benzyl; Boc = *tert*-butoxycarbonyl; MS = molecular sieve; TBAF = tetrabutylammonium fluoride.

perfect selectivity for the *endo* cyclization product (all-*cis* configuration) was observed, in 80% and 57% *ee*, respectively (Table 1, entries 1 and 2).[6] Chromium(III) complexes **2a** and **2b**, bearing the larger 1-ethyl-1-methylpropyl group, retained the high diastereoselectivity exhibited by **1a** and **1b** and provided an increase in *ee*, particularly in the case of aliphatic aldehydes such as **5b** (85% *ee* with catalyst **2b**; Table 1, entry 3).

As part of this examination of the relationship of catalyst structure to reaction enantioselectivity, adamantyl-substituted chromium(III) complex **3a** was prepared from readily acces-

[*] Prof. E. N. Jacobsen, A. G. Dossetter, T. F. Jamison
Department of Chemistry and Chemical Biology
Harvard University
Cambridge, MA 02138 (USA)
Fax: (+1) 617-496-1880
E-mail: jacobsen@chemistry.harvard.edu

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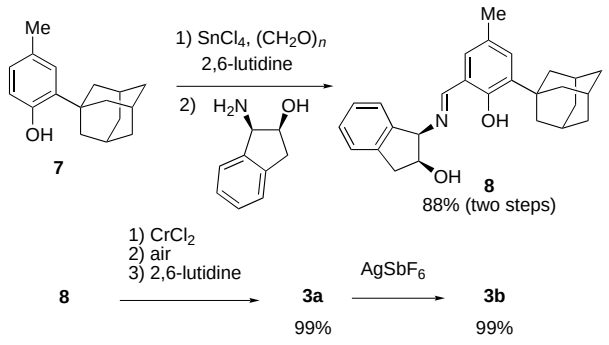
Table 1. Catalytic enantioselective hetero-Diels–Alder reactions of aldehydes and trialkylsilyloxy-substituted 2,4-hexadienes.[a]

Entry	Diene	Aldehyde	Conditions[b]	Catalyst	Yield [%][c]	ee [%][d]
1	**4b**	**5a**	A	**1b**	50	80
2	**4b**	**5b**	A	**1b**	n.d.	57
3	**4b**	**5b**	A	**2b**	n.d.	85
4	**4b**	**5b**	A	**3a**	88	98
5	**4b**	**5b**	A	**3b**	93	98
6	**4b**	**5a**	A	**3a**	n.d.	65
7	**4b**	**5a**	A	**3b**	n.d.	81
8	**4b**	**5a**	B	**3b**	72 (80)[e]	90
9	**4b**	**5b**	B	**3a**	90	99
10	**4b**	**5b**	B	**3b**	97	>99
11	**4b**	**5c**	B	**3b**	89	94
12	**4b**	**5d**	A	**3b**	85	98
13	**4b**	**5e**	A	**3b**	78	98
14	**4b**	**5f**[f]	B	**3b**	78 (84)[e]	98
15	**4b**	**5g**	B	**3b**	28 (31)[e]	96
16	**4b**	**5h**	B	**3b**	77 (86)[e]	95
17	**4a**	**5d**	A	**3b**	81	98
18	**4c**	**5d**	A	**3b**	93	96
19	**4b**	**5d**	A	**3b**	77	94

[a] Unless noted otherwise, reactions were carried out with 1:1 diene and aldehyde on a 1.0 mmol scale with 3 mol% catalyst and powdered 4 Å molecular sieves for 16–40 h as outlined in Scheme 1. [b] A: No solvent added. B: 200 μL acetone added. [c] Yields of isolated product after flash column chromatography on silica gel. In cases where nonoptimal catalyst combinations are described, yields of isolated product were not determined accurately and are therefore not reported (n.d.). [d] Enantiomeric excesses (*ee*) were determined by GC using a commercial (Cylcodex-β) column. [e] Reaction did not reach complete substrate conversion after 40 h. Numbers in parentheses correspond to substrate conversion upon work-up. [f] Two equivalents of aldehyde used.

sible components (Scheme 2). Formylation of commercially available 2-(1-adamantyl)-4-methylphenol (**7**) by standard protocols,[7] followed by Schiff base formation with *cis*-1-amino-2-indanol[8] and metal ion complexation afforded the $Cr^{III}Cl$ complex in good yield.[9] Counterion metathesis was accomplished with $AgSbF_6$ in *tert*-butyl methyl ether (TBME) to yield the corresponding hexafluoroantimonate complex **3b**.[10]

Adamantyl-substituted catalysts **3** provided a remarkable increase in enantioselectivity in HDA reactions between $TBSOCH_2CHO$ and diene **4b**. For example, the reaction of this diene and aldehyde pair yielded tetrahydropyranone **6b** in 88% yield, >95% *de* and 98% *ee* (Table 1, Entry 4). In contrast, tetrahydropyranone **6a** was obtained in only 65% *ee* in the analogous HDA reaction with benzaldehyde (**5a**) when chloride complex **3a** was employed (entry 6). While the



Scheme 2. Preparation of the chromium(III) complex **3a**.

hexafluoroantimonate catalyst **3b** proved somewhat more enantioselective (81% *ee*, entry 7),[11] no further increase was imparted by reducing the reaction temperature or by increasing the amount of catalyst used.

Up to this point, all reactions had been evaluated under solvent-free conditions, and a screen of common solvents led to the unexpected discovery that significant enhancement in enantioselectivity in the reaction with benzaldehyde could be attained by the inclusion of acetone (90% *ee*, entry 8). While the use of this solvent reduces the reaction rate slightly, the enhancement of enantioselectivity appears to be general for aliphatic and aromatic aldehydes.[12]

With these reaction parameters identified, a variety of aldehydes were screened with dienes **4a–d** (Table 1). In all reactions, the diastereoselectivity was greater than 95% in favor of the *endo* cyclization product. Aliphatic and aromatic aldehydes all underwent the HDA cycloaddition with very high enantioselectivities (entries 4, 5, 8–19), using either catalyst **3a** or **3b**. In most cases, reactions using hexafluoroantimonate catalyst **3b** were faster and more enantioselective than those in which chloride catalyst **3a** was used (data with catalyst **3a** not shown). While the use of acetone as solvent was generally beneficial, and critical in the case of aromatic aldehydes, for some substrates use of the solvent-free conditions proved satisfactory (e.g. entries 12, 13, 17–19). All of the reactions were performed at ambient temperature and required 4 Å molecular sieves for optimal results.[13] The identity of the trialkylsilyl group of the diene had only a slight effect on the *ee* and yield of the cycloaddition product (entries 11, 17–19). Unfortunately, sterically hindered aliphatic aldehydes such as isobutyraldehyde and cyclohexanecarboxaldehyde did not undergo cyclization with the diene **4b** under the prescribed conditions.

The scope of HDA reactions catalyzed by **3a** was evaluated in the context of other substituted diene derivatives (Table 2). Reaction of (2*E*)-2-triethylsilyloxy-1,3-pentadiene (**9**) with aldehyde **6b** in the presence of catalyst **3a** yielded the corresponding tetrahydropyranone **10** in 78% yield, 98% *ee*, and 98% *de* (entry 1). The isomeric pentadiene **11** afforded dihydropyranone **12** in high enantiomeric excess as well (entry 2). Reaction of **6b** with 1-methoxybutadiene (**13**) in the presence of catalyst **3a** (0.5 mol%) also proceeded cleanly and in >99% *ee* (entry 3).[14] Coupled with hydrolysis and oxidation to the corresponding lactone **15**, this method provides highly efficient access to several interesting natural product structures.[15]

While it might be assumed that a very strong Lewis acid might be required to catalyze such HDA reactions between only moderately nucleophilic dienes and simple aldehydes, no measurable complexation between catalysts **3** and the aldehydes used in this study could be detected by IR spectroscopy. Indeed, the successful use of acetone as a solvent appears inconsistent with a simple Lewis acid mechanism in these reactions. Further studies are being directed toward elucidating the mechanism of catalysis with these new complexes, as well as toward fully exploiting the synthetic potential of this cyclization reaction.

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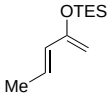
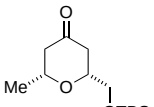
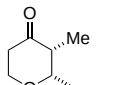
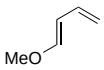
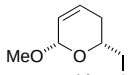
Table 2. Catalytic enantioselective hetero-Diels–Alder reactions of selected dienes and aldehydes with catalyst (1*R*,2*S*)-**3a**.[a]

Entry	Diene	Product	Conditions[a]	Yield [%][c]	ee [%][d]
1	 **9**	 **10**	B	78	98 (2*R*,6*R*)[d]
2	 **11**	 **12**	A	50	91 (2*R*,3*R*)[d]
3	 **13**	 **14**	A	91	> 99 (2*S*,6*R*)[e]

[a] All reactions were carried out as described in footnote [a, b] of Table 1. [b] The products were isolated by treatment with either TFA in CH_2Cl_2 at 0 °C or with TBAF, AcOH, THF at 0 °C followed by flash column chromatograhy on silica gel (supporting information). [c] *ee* values were determined by GLC (Cylcodex-β column). The bases for assignments of relative and absolute configuration are described in the Supporting Information. [d] > 95% *de*. [e] 97% *de*.

Keywords: asymmetric catalysis · chromium · cycloadditions · Diels–Alder reactions · heterocycles

[1] For general references on the HDA reaction, see: a) S. J. Danishefsky, *Chemtracts: Org. Chem.* **1989**, 273–297; b) S. J. Danishefsky, *Aldrichimica Acta* **1986**, *19*, 59–69; c) D. L. Boger in *Comprehensive Organic Synthesis, Vol. 5* (Eds.: B. M. Trost, I. Fleming), Pergamon, New York, **1991**, pp. 451–512; d) D. L. Boger, S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, San Diego, **1987**; d) H. Waldmann, *Synthesis*, **1994**, 535–551.

[2] For asymmetric catalytic HDA reactions involving Danishefsky's diene and its analogues, see: a) M. D. Bednarski, C. Maring, S. J. Danishefsky, *J. Am. Chem. Soc.* **1983**, *105*, 6968–6969; b) K. Maruoka, T. Itoh, T. Shirasaka, H. Yamamoto, *J. Am. Chem. Soc.* **1988**, *110*, 310–312; c) E. J. Corey, C. L. Cywin, T. D. Roper, *Tetrahedron Lett.* **1992**, *33*, 6907–6910; d) Q. Gao, T. Maruyama, M. Mouri, H. Yamamoto, *J. Org. Chem.* **1992**, *57*, 1951–1952; e) Y. Motoyama, K. Mikami, *Chem. Commun.* **1994**, 1563–1564; f) G. E. Keck, X. Y. Li, D. Krishnamurthy, *J. Org. Chem.* **1995**, *60*, 5998–5999; g) Y. Motoyama, M. Terada, K. Mikami, *Synlett* **1995**, 967–968; h) K. Mikami, O. Kotera, Y. Motoyama, H. Sakaguchi, *Synlett* **1995**, 975–977; i) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron Lett.* **1997**, *38*, 2427–2430; j) S. Matsukawa, K. Mikami, *Tetrahedron: Asymmetry* **1997**, *8*, 815–816; k) T. Hanamoto, H. Furuno, Y Sugimoto, J. Inanaga, *Synlett* **1997**, 79–80; l) S. E. Schaus, J. Brånalt, E. N. Jacobsen, *J. Org. Chem.* **1998**, *63*, 403–405; m) S. Kobayashi, H. Komiyama, T. Ishitani, *Angew. Chem.* **1998**, *110*, 1026–1028; *Angew. Chem. Int. Ed.* **1998**, *37*, 979–981; n) L.-S. Li, Y. Wu, Y.-J. Hu, L.-J. Xia, Y.-L. Wu, *Tetrahedron: Asymmetry* **1998**, *9*, 2271–2277.

[3] For asymmetric catalytic HDA reactions involving glyoxylate, pyruvate, or quinone derivatives as dienophiles, see: a) M. Terada, K. Mikami, T. Nakai, *Tetrahedron Lett.* **1991**, *32*, 935–938; b) K. Mikami, M. Terada, Y. Motoyama, T. Nakai, *Tetrahedron: Asymmetry* **1991**, *2*, 643–646; c) T. A. Engler, M. A. Letavic, M. A., F. Takusagawa, *Tetrahedron Lett.* **1992**, *33*, 6731–6734; d) K. Mikami, Y. Motoyama, M. Terada, *J. Am. Chem. Soc.* **1994**, *116*, 2812–2820; e) M. Johannsen, K. A. Jørgensen, *Tetrahedron* **1996**, *52*, 7321–7328; f) M. Johannsen, S. Yao, K. A. Jørgensen, *Chem. Commun.* **1997**, 2169–2170; g) A. Graven, M. Johannsen, K. A. Jørgensen, *Chem. Commun.* **1996**, 2373–2374; h) S. Yao, M. Johannsen, H. Audrain, R. G. Hazell, K. A. Jørgensen, *J. Am. Chem. Soc.* **1998**, *120*, 8599–8605; i) M. Johannsen, K. A. Jørgensen, X.-F. Zheng; Q.-S. Hu; L. Pu, *J. Org. Chem.* **1999**, *64*, 299–301.

[4] Examples of asymmetric catalytic inverse demand hetero-Diels–Alder reactions have been disclosed recently: a) D. A. Evans, J. S. Johnson, *J. Am. Chem. Soc.* **1998**, *120*, 4895–4896; b) J. Thorhauge, M. Johannsen, K. A. Jørgensen, *Angew. Chem.* **1998**, *110*, 2543–2546; *Angew. Chem. Int. Ed.* **1998**, *37*, 2404–2406; c) D. A. Evans, E. J. Olhava, J. S. Johnson, J. M. Janey, *Angew. Chem.* **1998**, *110*, 3554–3557; *Angew. Chem. Int. Ed.* **1998**, *37*, 3372–3375.

[5] Experimental procedures and analytical data, including *ee* analysis and determination of relative and absolute stereochemistry where appropriate are included in the Supporting Information.

[6] The previously reported tetradentate (salen)Cr^{III} complexes[2i] (salen = bis(salicylidene)ethylenediamine) provided tetrahydropyrans **6a** and **6b** in 70–82% *ee* and 24–40% *ee*, respectively, and > 95% *de*, but with significantly slower reaction rates. However, these results served as a valuable lead into this area.

[7] a) G. Casiraghi, G. Casnati, G. Puglia, G. Sartori, G. Terenghi, *J. Chem. Soc. Perkin Trans 1.* **1980**, 1862–1865; b) W. Zhang, E. N. Jacobsen, *J. Org. Chem.* **1991**, *56*, 2296–2298.

[8] Both enantiomers are available commercially (Aldrich). a) J. F. Larrow, E. Roberts, T. R. Verhoeven, K. M. Ryan, C. H. Senanayake, P. J. Reider, E. N. Jacobsen, *Organic Synth.* **1999**, *76*, 46–56; for reviews on the use of *cis*-1-amino-2-indanol in asymmetric synthesis, see: b) C. H. Senanayake, *Aldrichimica Acta* **1998**, *31*, 3–15; c) A. K. Ghosh, S. Fidanze, C. H. Senanayake, *Synthesis*, **1998**, 937–961.

[9] Analysis by low-resolution FAB mass spectrometry and IR spectroscopy indicates that **3a** exists as a mixture of oligomeric species with water molecules occupying available coordination sites (see Supporting Information).

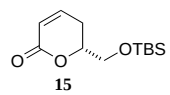
[10] See Supporting Information for details. Whereas chromium(III) chloride catalyst **3a** shows no evidence of decomposition when stored in a desiccator for several months, the hexafluoroantimonate catalyst **3b** has a shelf life of approximately two weeks under these conditions. Reactions performed by using older batches of **3b** were noticeably slower.

[11] Replacement of coordinating counterions with SbF_6^- has been shown to have significant beneficial effects in other asymmetric catalytic systems. D. A. Evans, J. A. Murry, P. von Matt, R. D. Norcross, S. J. Miller, *Angew. Chem.* **1995**, *107*, 864–866; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 798–800.

[12] Benzene, hexane, and halogenated solvents such as CH_2Cl_2 had a detrimental effect on the enantioselectivity of the reaction.

[13] For example, the reaction listed in entry 5, Table 1, when performed in the absence of 4 Å MS, gave the THP **6b** in 73% conversion and 94% *ee* after 40 h at room temperature.

[14] Use of the catalyst **3b** for this reaction resulted in polymerization of the diene. The enantioselectivity was determined chiral GC analysis of lactone **15**, prepared by PDC/AcOH oxidation of methoxyacetal **14**.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[15] For example, a) callystatin A (isolation): M. Kobayashi, K. Higuchi, N. Murakami, H. Tajima, S. Aoki, *Tetrahedron Lett.* **1997**, *38*, 2859–2862; b) (synthesis): M. T. Crimmins, B. W. King, *J. Am. Chem. Soc.* **1998**, *120*, 9084–9085; c) Fostriecin A: D. L. Boger, M. Hikota, B. M. Lewis, *J. Org. Chem.* **1997**, *62*, 1748–1753, and references therein.

  1433-7851/99/3816-2400 $ 17.50+.50/0