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COMMUNICATIONS

Published on Web 05/07/2002

Design and Development of Highly Effective Lewis Acid Catalysts for Enantioselective Diels−Alder Reactions

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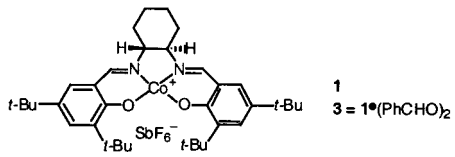
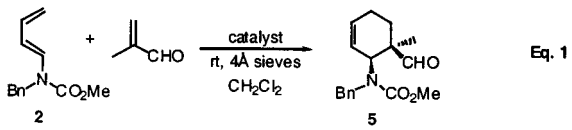
Received March 4, 2002

The development of effective methods for the synthesis of chiral compounds in high enantiomeric purity is of pressing current importance.[1] In the pharmaceutical area, for example, single enantiomer drugs constitute an important and growing segment of the total market.[2] Ideally, asymmetric synthesis methods must be effective and practical. They must afford the desired products in high yields and high enantiomeric purities, and be atom-economic—hence catalytic—and environmentally benign.[3,4] Among the transformations that are reliably used for the synthesis of complex molecules, the Diels−Alder (DA) reaction is perhaps the most powerful, allowing the stereocontrolled construction of six-membered ring compounds, with up to four embedded chiral centers.[5] Given its prominent position, there has been an intense search for catalysts that would selectively produce only one of the DA adduct enantiomers.[6] Of the many catalysts identified to date, the vast majority are used at the 5−20 mol % level, with respect to the amount of the reactants.[7] We report here the design and development of catalysts that are not only exceptionally effective (catalyst loadings down to 0.05 mol %) but are also used at room temperature, under an air atmosphere, using a minimum amount of solvent.

We recently reported the use of Jacobsen's chiral Cr(III)−salen catalyst[8] for promoting the DA reaction between α-substituted acroleins and 1-carbamate-3-siloxybutadienes[9] to give cycloadducts in excellent yield (>90%) and up to 97% ee.[10] To uncover catalysts capable of even faster turnover, the salen complexes of other metals were prepared and their activity examined. This search revealed that Co(III)−salen, **1**, was remarkably effective for catalyzing the reaction between carbamate-substituted diene **2** and methacrolein. This reaction was complete after 2 h at room temperature with 5 mol % of catalyst **1** and afforded the product in high ee (95%).[11]





Eq. 1

Critical insight on the activation of the carbonyl group by the catalyst was obtained from the X-ray structure of a complex (**3**) that crystallized from an ethanol−water solution of **1** and 2.0 equiv of benzaldehyde (Figure 1). The crystal structure showed two benzaldehyde molecules coordinated in the axial positions of the C_2-symmetric octahedral complex.[12] The edge view of the complex (Figure 1b) not only illustrates the remarkably flat topography of the salen scaffold, save for a small zigzag step,[13] but also reveals the nonperpendicular coordination of the two carbonyl groups. Given their structural similarities, the activation of methacrolein by **1** is likely to parallel the coordination observed for benzaldehyde. The enantioselection obtained from the cycloaddition can be explained by considering preferential approach of the diene from the "open" quadrants of the dienophile−catalyst complex, those that form an obtuse angle rather than an acute angle (i.e., from the top right or bottom left in Figure 1b).[14]

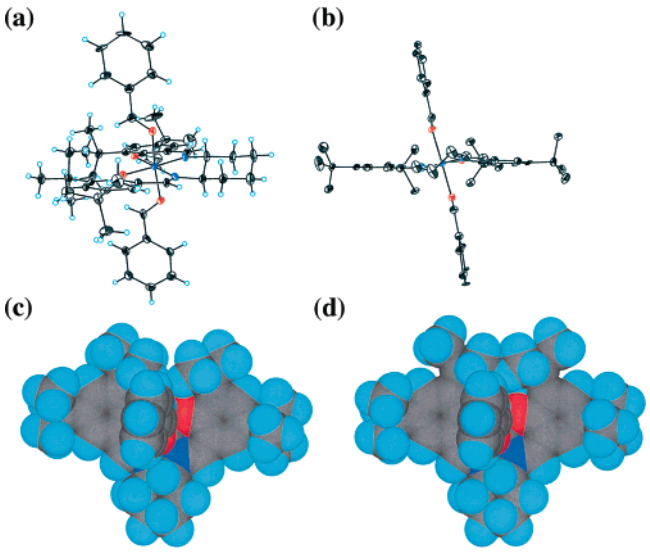


Figure 1. X-ray crystal structure of (1*R*,2*R*)-salen−Co(III)-SbF_6•2PhCHO complex **3**. For clarity, SbF_6 is not shown. (a) Side view. (b) Edge view (H's not shown). (c) Space-filling representation of top-view of **3**. (d) Representation generated by replacing the two bay-region *tert*-butyl groups of the structure of **3** with $SiMe_3$ groups.

The space-filling model of **3** (Figure 1c) shows the two bay-region *t*-Bu groups in close proximity. The steric congestion from larger groups at these positions, we hypothesized, might force the two aromatic rings out of near-parallel arrangement, and thereby accentuate the subtle helical chirality in the scaffold. With that objective in mind, we prepared the corresponding *o*-silyl substituted salen complexes, **4a,b (eq 2)**. The longer C−Si bonds would position the two bay-region substituents to well within van der Waals radii of one other (Figure 1d).

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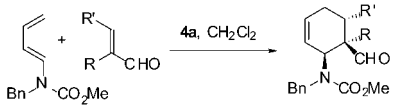
10.1021/ja026088t CCC: $22.00

Table 1. DA Reactions between Diene **2** and Methacrolein Catalyzed by Silylsalen−Co(III) Complexes **4a,b**

entry	catalyst	loading	time (h)	yield[b] (%)	ee[c] (%)
1[a]	4a	4	1	98	98
2[a]	4a	4	2	100	97
3	4a	1	3	96	98
4	4a	0.1	18	98	98
5	4a	0.05	3 d	93	98
6[a]	4b	0.1	20	100	98

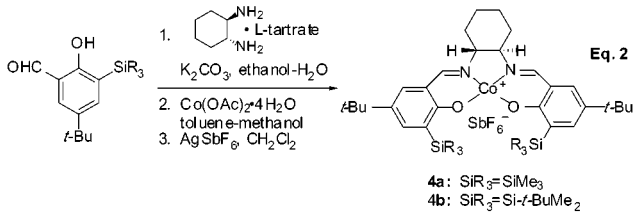
[a] 4 Å molecular sieves used (see ref 16). [b] Isolated yields. [c] ee's determined by Mosher ester NMR analysis of the corresponding alcohols. See Supporting Information for details.

Table 2. Reactions between **2** and Various Acroleins Catalyzed by **4a**



entry	R =	R′ =	4a loading	time (h)	yield[c] (%)	ee[d] (%)
1	Me	H	0.1	16	98	98
2	Et	H	0.1	30	93	>97
3	$TBSO(CH_2)_2$	H	0.5	18	100	>97
4	$-(CH_2)_4-$		2.0	3 d	78	>95
5[a]	H	H	0.1	18	100	85
6[b]	H	H	2	40	90	>97

[a] Reaction performed at 0 °C. [b] Reaction performed at −78 °C. [c] Isolated yields. [d] ee's determined through Mosher esters. See Supporting Information.



The *o*-silyl substituted complexes (**4**) were readily prepared from the corresponding salicylaldehydes and 1,2-diaminocyclohexane, as shown.[15] These silyl-substituted Co(III) complexes are the most effective catalysts reported to date for an enantioselective DA reaction (Table 1). With 4 mol % of catalyst **4a**, the cycloaddition of 1-carbamate butadiene (**2a**) and methacrolein was complete in less than an hour and afforded the product in excellent yield and ee (Table 1, entry 1). Comparable yields and ee's were obtained using lower catalyst loadings. The result in entry 4 is from a reaction carried out on a 5.0 mmol scale (1.08 g) using 4.3 mg of catalyst **4a**. The reaction went to completion overnight, and removal of the volatiles gave the expected product, which was pure by NMR. Significantly, the reaction is effectively catalyzed with just 0.05 mol % of catalyst **4a** (entry 5), which represents the lowest catalyst/substrate ratio for a DA reaction.[7] Simple concentration of the reaction mixture followed by trituration to remove the remaining reactants afforded pure cycloadduct in high yield and excellent ee. The catalyst possessing the sterically more demanding *tert*-butyldimethyl group (**4b**) was comparable in effectiveness to the TMS catalyst (**4a**) (entry 6).

Silyl catalyst **4a** efficiently catalyzes the DA reactions of other acroleins (Table 2). It is noteworthy that even the DA reaction of acrolein is effectively catalyzed by **4a** (entries 5 and 6). The reaction of **2** and acrolein using 0.1 mol % of **4a** at 0 °C afforded the cycloadduct in quantitative yield, with excellent endo selectivity (>50/1) and good enantioselectivity. Furthermore, the enantioselectivity improved considerably, to 97%, when the reaction was performed at −78 °C (entry 6).

In summary, we have developed highly effective Co(III)−salen complexes for the enantioselective catalysis of Diels−Alder reactions. A rational framework for understanding the observed enantioselectivities for the DA reactions was provided by the X-ray crystal structure of a complex between catalyst **1** and benzaldehyde. This structural information provided the basis for the design of silyl-substituted catalysts, which proved exceptionally effective for DA reactions. Importantly, the reactions are conveniently carried out at room temperature, under an air atmosphere, and with minimal solvent, conditions that are desirable for industrial applications. The high turnovers observed with these Co(III) complexes may have implications for other Lewis acid-catalyzed processes.

Acknowledgment. This work was supported by the National Institutes of Health. Financial support from Abbott Laboratories (Graduate Fellowship to Y.H.) and Merck Research Laboratories are gratefully acknowledged. We thank Dr. Ian M. Steele for the X-ray structure determination.

Supporting Information Available: General experimental procedures and spectroscopic data of new cycloadducts (PDF). X-ray crystallographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The absolute stereochemistry of the ethacrolein cycloadduct (Table 2, entry 2) was determined from the X-ray structure of the Mosher ester of the corresponding alcohol. The stereochemistry of **5** is assigned by analogy.
(12) For X-ray structures of other salen complexes see: (a) Pospisil, P. J.; Carsten, D. H.; Jacobsen, E. N. *Chem. Eur. J.* **1996**, *2*. 974. (b) Leung, W.; Chan, E. Y. Y.; Chow, E. K. F.; Williams, I. D.; Peng, S. *J. Chem. Soc., Dalton Trans.* **1996**, 1229. (c) Bernardo, K.; Leppard, S.; Robert, A.; Commenges, G.; Dahan, F.; Meunier, B. *Inorg. Chem.* **1996**, *35*, 387. (d) Hashihayata, T.; Punniyamuthy, T.; Irie, R.; Katsuki, T.; Akita, M.; Moro-oka, Y. *Tetrahedron* **1999**, *55*, 14599.
(13) A Cu−salen also shows similar structural features. See ref 12c.
(14) Assuming Cr−salen complexes coordinate similarly to complex **1**, this model explains the observed enantioselectivities in our Diels−Alder work (ref 10) and in the hetero Diels−Alder work of Jacobsen (ref 8c).
(15) Please see Supporting Information.
(16) Molecular sieves do not significantly accelerate the reactions.

JA026088T