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Catalytic Enantioselective Diels–Alder Reaction via a Chiral Indium(III) Complex

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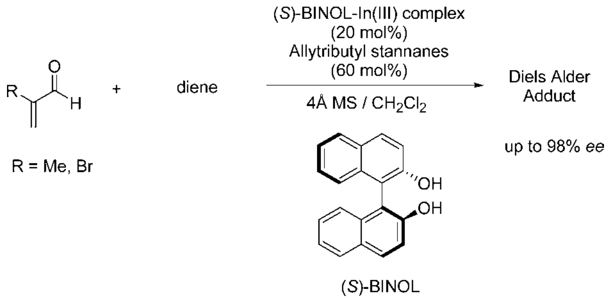
ABSTRACT



A chiral indium complex has been developed to effect high enantioselectivities in catalyzing enantioselective Diels–Alder reaction. The cycloaddition of a variety of cyclic and open-chained dienes to 2-methacrolein and 2-bromoacrolein resulted in good yields and excellent enantioselectivities (up to 98% ee).

In recent years, indium(III) complexes have gained widespread application as efficient Lewis acid catalysts for various important organic synthetic transformations.[1] The ability of some of these complexes to catalyze organic transformations in aqueous media is especially noteworthy.[2] In this paper, we described herein a new type of catalytic enantioselective Diels−Alder[3,4] which employs a chiral (*S*)-BINOL−In(III) complex[5] as precatalyst and allytributyl stannane as activator to generate a potent Lewis acid.

In our initial study, we reacted 2-bromoacrolein with cyclopentadiene in which the catalyst was prepared by stirring $InCl_3$, (*S*)-BINOL, and 4 Å molecular sieves (MS) at rt for 2 h. However, reaction using 20 mol % of this preformed catalyst at −78 °C afforded a racemic product in 32% yield. This prompted us to investigate further the catalytic species of the chiral (*S*)-BINOL−In(III) complex. We envisaged that the addition of allyltributylstannane to a prestirred solution of (*S*)-BINOL and $InCl_3$ would facilitate the transmetalation reaction to afford the formation of a chiral BINOL−In−allyl complex. This activated indium complex probably acted as the chiral Lewis acid for the enantioselective Diels−Alder reaction. Thus, when equimolar allyltributyl stannane was added to a mixture of (*S*)-BINOL−$InCl_3$ in $CDCl_3$, a new set of allylic signal was observed in the ^1H NMR spectrum with quantitative formation of tributylstannane chloride.

Optimum reaction conditions were achieved when 0.6 equiv of allyltributylstannane was added to a prestirred solution of the catalyst (20 mol %) in dichloromethane followed by subsequent dropwise addition of 2-bromoacrolein (0.5 mmol, 1.0 equiv) and cyclopentadiene (0.15 mmol, 1.5 equiv) at −40 °C. After being stirred at −40 °C for 20 h, the Diels−Alder adduct was obtained with 98% ee and 74% yield. This encouraging result demonstrated that allyltributyl stannane acted as an activator for the generation

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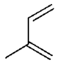
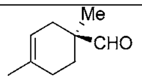
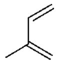
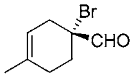
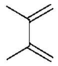
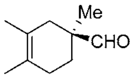
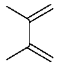
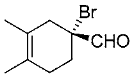
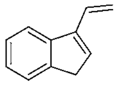
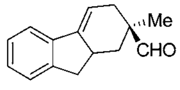
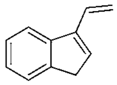
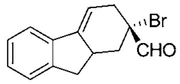
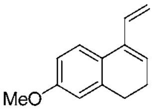
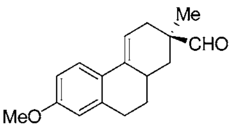
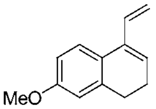
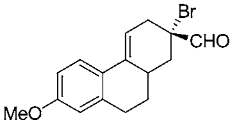
of the chiral indium(III) complex which catalyzed the Diels–Alder reaction in an enantioselective fashion.

Having achieved the optimized reaction parameters for the Diels–Alder reactions catalyzed by the chiral In(III) complex, a study was initiated to explore the reaction scope of cyclopentadiene with various dienophiles. The reaction of 2-methacrolein and 2-bromoacrolein with cyclopentadiene afforded both Diels–Alder adducts in 98% ee (*exo*/*endo* 99:1) and yields of 70% and 74%, respectively. However, no product was obtained when cyclopentadiene was reacted with methyl acrylate under the same set of conditions. Extension of the Diels–Alder reactions to open-chain dienes using 2-methacrolein and 2-bromoacrolein were investigated, and the results are shown in Table 1.

Table 1. Diels–Alder Reaction of Open-Chained 1,3-Dienes with 2-Methacrolein and 2-Bromoacrolein Catalyzed by Chiral (*S*)-BINOL–In(III) Complex in Dichloromethane[a]

diene	product	condt. (°C, h)	% yield[b]	% *ee*[c]
		RT, 20	35	90
		-20, 20	70	96
		RT, 20	63	98
		-20, 20	74	98
		-20, 20	71	98
		-20, 20	72	98
		-20, 20	75	97
		-20, 20	77	94

[a] Unless otherwise specified, the chiral indium(III) catalyst was prepared from (*S*)-BINOL (22 mol %), $InCl_3$ (20 mol %), and allyltributylstannane (60 mol %) in the presence of activated 4 Å MS. [b] Isolated yield. [c] Refer to the Supporting Information for enantiomeric excess determination.

This newly developed catalyst exhibited a broad applicability for the reactions of 2-methacrolein and 2-bromoacrolein with a variety of dienes including both cyclic and open-chain dienes, affording the respective Diels–Alder adduct with good yield and high enantioselectivities. The absolute configurations of the Diels–Alder products shown in Table 1 have been assigned by measurement of optical rotation and comparison with known substances.[31]

The stereochemical course of the Diels–Alder reactions catalyzed by the chiral (*S*)-BINOL–In(III) complex can be envisaged through the catalyst–aldehyde pre-transition-state assembly depicted in Figure 1. In assembly **1**, the aromatic rings of the (*S*)-BINOL effectively screen the *re* face of the complexed *s-trans*-α-*β*-enal from attack by the diene component. As such, this facilitated the addition of the diene to

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(4) For more examples, see: (a) Evans, D. A.; Miller, S. C.; Thomas; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559. (b) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3372. (c) Loh, T.-P.; Wang, R.-B, Sim, K. Y. *Tetrahedron Lett.* **1996**, *37*, 2989. (d) Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem*. **1994**, *59*, 3758. (e) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561. (f) Ishihara, K.; Gao, Q.-Z.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 6917. (g) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460. (h) Corey, E. J.; Loh, T.-P.; Toper, T. D.; Azinioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290. (i) Corey, E, J,; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. (j) Narasaka, K.; Tanaka, H.; Kanai, F. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 387. (k) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem*. **1989**, *54*, 1481. (l) Narasaka, K.; Inoue, M.; Yamada, T.; Sugimori, J.; Iwasawa, N. *Chem. Lett.* **1987**, *12*, 2409. (m) Narasaka, K, Inoue, M.; Yamada, T. *Chem. Lett*. **1986**, *11*, 1967.

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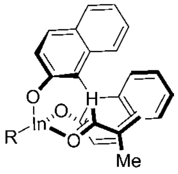

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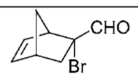
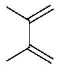
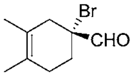
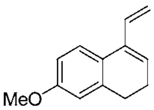
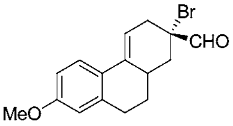
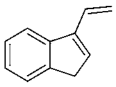
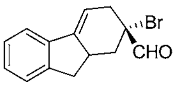
Figure 1. Pre-transition-state assembly of catalyst and dienophile.

the *si* face of the α-*β*-double bond leading to the enantiomers shown in Table 1.

Next, we proceeded to examine the possibility of realizing the catalytic enantioselective Diels−Alder reaction in aqueous media. As a preliminary study, we reacted 2-bromoacrolein with cyclopentadiene and found that the water-tolerant chiral indium complex was able to catalyze the reaction resulting in a conversion yield of 64% and an enantiomeric excess of 94%. In this experiment, the aqueous media reaction was carried out by adding water to a stirred solution of the preformed catalyst (excluding 4 Å MS) prior to the addition of the dienophile and diene. On the contrary, no product was obtained when water was added before the formation of the active catalytic indium species. These results suggested that the sequence of water addition was critical for the chiral indium complex to function in aqueous media. The scope for the reaction of 2-bromoacrolein with various dienes was investigated with the results shown in Table 2.

Table 2. Diels−Alder Reaction of 2-Bromoacrolein with Various Dienes Catalyzed by Chiral (*S*)-BINOL−In(III) Complex in Aqueous Media[a]

diene	product	condt. (°C, h)	% yield[b]	% *ee*[c]
		-20, 20	64 (98:2)	94
		RT, 20	70	80
		-20, 20	61	94
		RT, 20 -20, 20	72 68	66 66

[a] Unless otherwise specified, the chiral indium(III) catalyst was prepared from (*S*)-BINOL (22mol %), $InCl_3$ (20 mol %), and allyltributylstannane (60 mol %). [b] Isolated yield. [c] Refer to the Supporting Information for enantiomeric excess determination.

In conclusion, we have developed the first chiral indium complex for catalytic asymmetric Diels−Alder reaction by designing the novel catalyst containing $InCl_3$, (*S*)-BINOL, and allyltributylstannane.[6] The main features of this reaction are as follows: (1) the procedure is operationally simple and the catalyst can be easily prepared from commercially available chemicals at ambient temperature; (2) the cycloaddition of a wide variety of cyclic and open-chained dienes to 2-methacrolein and 2-bromoacrolein resulted in good yields and high enantioselectivities; and (3) preliminary studies have also shown that this reaction can be carried out in aqueous media. This contribution should provide a new synthetic strategy for the construction of six-membered rings for complex molecules with medicinal and biological significance. Continuing investigations in this laboratory will attempt to elucidate the identity of the BINOL−In(III) species and further expand the scope of the process.

Acknowledgment. We thank the Nanyang Technological University and National University of Singapore for their generous financial support. Y.-C.T. is grateful to the Institute of Chemical and Engineering Sciences Ltd. (ICES) for a doctorate scholarship.

Supporting Information Available: Experimental details, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) **Representative Procedure for Enantioselective Diels−Alder Reaction: Preparation of (1*R*,2*R*,4*R*)-2-Bromobicyclo[2.2.1]hept-5-ene-2-carbaldehyde.** To an oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added $InCl_3$ (22 mg, 0.1 mmol, 0.2 equiv). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL × 2) prior to the addition of 1.5 mL of dichloromethane. (*S*)-BINOL (31 mg, 0.11 mmol, 0.22 equiv), 4 Å molecular sieves (15 mg) were added, and the mixture was stirred under nitrogen at room temperature for 2 h. Allyltributylstannane (0.093 mL, 0.3 mmol, 0.6 equiv) was added to the resulting mixture and stirred for 10 min to afford a white suspension. The preformed catalyst was then cooled to −40 °C for 15 min. 2-Bromoacrolein (67.5 mg, 0.5 mmol, 1.0 equiv) and cyclopentadiene (0.10 mL, 1.5 mmol, 3.0 equiv, added dropwise alongside of the flask) were added successively and the reaction mixture stirred at −40 °C for 20 h. The mixture was then quenched by addition of 5 mL of saturated $NaHCO_3$ and extracted with ether (10 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residual crude product was purified via silica gel chromatography to afford the Diels−Alder adduct as a colorless solid (74% yield).