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# Catalytic Enantioselective Diels–Alder Reaction in Ionic Liquid via a Recyclable Chiral In(III) Complex

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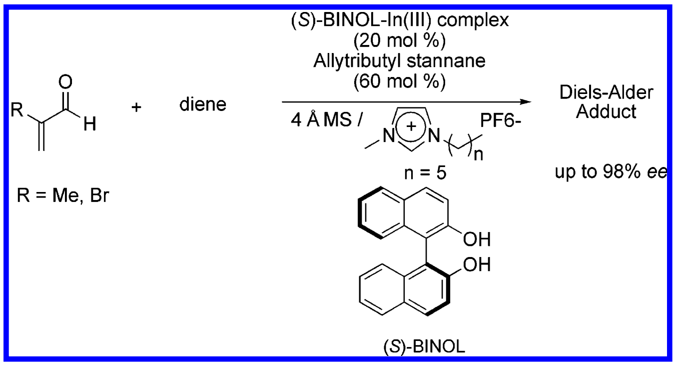
## ABSTRACT



**A recyclable, air- and moisture-stable chiral indium complex in [hmim][$PF_6^-$] ionic liquid has been developed. 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). Moreover, the chiral In(III) complex can be reused for seven successive cycles with comparable enantioselectivities and yields without loss of catalytic activity.**

The application of ionic liquids (IL) as potential “green” alternatives to conventional solvents for a wide range of organic transformations[1] has sparked an increasing interest among organic chemists. In particular, they have been demonstrated to effect large increases in reaction rates in asymmetric Diels−Alder[2,3] reactions.

To the best of our knowledge, only two asymmetric catalytic Diels−Alder reactions performed in ionic liquids have been reported.[4] However, the application of chiral

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[1] Some examples of hydrogenation using ionic liquids: (a) Chauvin, Y.; Mussman, L.; Olivier, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2698. (b) Suarez, P. A. Z.; Dullins, J. E. L.; Einloft, S.; de Souza, R. F.; Dupont, J. *Polyhedron* **1996**, *15*, 1217. (c) Monteiro, A. L.; Zinn, F. K.; de Souza, R. F.; Dupont, J. *Tetrahedron: Asymmetry* **1997**, *8*, 177. (d) Brown, R. A.; Pollet, P.; McKoon, E.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. *J. Am. Chem. Soc.* **2001**, *123*, 1254. (e) Example of enantioselective allylation in ionic liquids: McCluskey, A.; Garner, J.; Young, D. J.; Caballero, S. *Tetrahedron Lett.* **2000**, *41*, 8147.

[2] For representative examples on catalytic enantioselective Diels−Alder, see: (a) Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800. (b) Sprott, K. T.; Corey, E. J. *Org. Lett.* **2003**, *5*, 2465. (c) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388. (d) Nakano, H.; Suzuki, Y.; Kabuto, C.; Fujita, R.; Hongo, H. *J. Org. Chem.* **2002**, *67*, 5011. (e) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (f) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808. (g) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992. (h) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559.

[3] 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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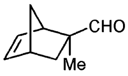
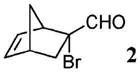
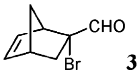
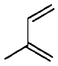
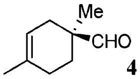
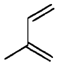
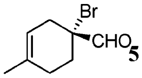
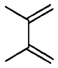
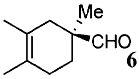
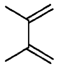
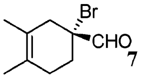
catalytic systems to the asymmetric Diels−Alder reaction in ionic liquids using a variety of dienes, in particular, open-chained dienes, has yet to be explored. In this paper, we report an efficient asymmetric Diels−Alder reaction of both cyclic and open-chained dienes to 2-methacrolein and 2-bromoacrolein catalyzed by a chiral (*S*)-BINOL−In(III) complex in [hmim][$PF_6^-$].

Recently, we have demonstrated an efficient protocol for the asymmetric Diels−Alder reaction in dichloromethane, which employs a chiral (*S*)-BINOL−In(III) as precatalyst and allyltributylstannane as activator to generate the potent Lewis acid.[5] This method has proven to be practical and convenient, furnishing a variety of cycloadducts in good yields and excellent enantioselectivities. However, the catalyst was not able to be recycled and reused.[6] In this paper, we demonstrate that the chiral BINOL−In(III) catalytic system can be extended to the asymmetric Diels−Alder reaction using ionic liquids with increased chemical yields of the cycloadducts. In addition, the chiral catalyst can be recovered and reused through a simple extraction protocol. This system in ionic liquid was also found to work using 5 mol % catalyst.

In our initial study, we carried out the catalytic enantioselective Diels−Alder reaction using a standardized protocol. The catalyst was prepared by mixing (*S*)-BINOL, 4 Å molecular sieve (MS), and $InCl_3$ in dichloromethane at room temperature. After 2 h of stirring, allyltributylstannane was added and stirred for 10 min followed by the addition of [hmim][$PF_6^-$] to the preformed catalyst. The organic solvent was removed under reduced pressure followed by subsequent addition of cyclopentadiene and 2-bromoacrolein. This preliminary study afforded the Diels−Alder adduct in a good yield of 92% and excellent enantiomeric excess of 98%. Having achieved the optimum reaction parameters for the catalytic process, we extended the asymmetric Diels−Alder reaction of a selection of cyclic and open-chained dienes to 2-methacrolein and 2-bromoacrolein. 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[a]

| entry | diene | product | condition (°C, h) | % yield[b] | % *ee*[c] |
|---|---|---|---|---|---|
| 1 |  |  **1** | rt, 20 | 89 | 98 |
| 2 |  |  **2** | rt, 20 | 92 | 98 |
| 3 |  |  **3** | 0 °C, 20 | 89 | 92[d] |
| 4 |  |  **4** | rt, 20 | 78 | 88[e] |
| 5 |  |  **5** | rt, 20 | 90 | 96[f] |
| 6 |  |  **6** | rt, 20 | 88 | 97 |
| 7 |  |  **7** | rt, 20 | 90 | 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 Supporting Information for enantiomeric excess determination. [d] Reaction carried out using 5 mol % catalyst loading. [e] Diels−Alder adduct contains ca. 23% of its regioisomer. [f] Diels−Alder adduct contains ca. 16% of its regioisomer.

The reaction of 2-methacrolein and 2-bromoacrolein with cyclopentadiene afforded both Diels−Alder adducts in 98% ee (*exo:endo* 97:3) and yields of 89 and 92%, respectively. Moreover, the Diels−Alder adduct of cyclopentadiene with 2-bromoacrolein can also be obtained with an enantiomeric excess of 92% (*exo:endo* 96:4) and a yield of 89% with as low as 5 mol % catalyst loading (entry 3). The reaction of 2-methyl-1,3-butadiene with 2-methacrolein and 2-bromoacrolein afforded the cycloadducts in 88 and 96% ee, respectively (entries 4 and 5). In addition, the cycloaddition of 2,3-dimethyl-1,3-butadiene to 2-methacrolein and 2-bromoacrolein catalyzed by the BINOL−In(III) complex also afforded both adducts with excellent enantioselectivities of 97 and 94%, respectively (entries 6 and 7). It is noteworthy that the yields obtained for the asymmetric Diels−Alder adducts in ionic liquid were significantly higher as compared to that in dichloromethane.

In conjunction with an interest in the application of this system to the synthesis of steroids, we also tested the reaction on the complex open-chain diene, 7-methoxy-4-vinyl-1,2-dihydronaphthalene (Scheme 1). The cycloadduct was obtained with an enantiomeric excess of 92% and chemical yield of 89%.

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.[5]

Next, we continued our study by exploring the recyclability of the chiral indium complex which is important from the viewpoint of cost-effectiveness. We carried out the model study by using the cycloaddition of cyclopentadiene and 2-bromoacrolein in [hmim][$PF_6^-$]. After the reaction was

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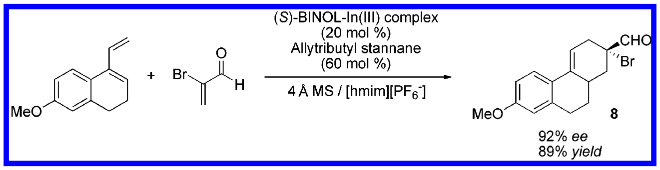
(4) Examples of asymmetric catalytic Diels−Alder reactions in ionic liquids: (a) Doherty, S.; Goodrich, P.; Hardacre, C.; Luo, H.-K.; Rooney, D.W.; Seddonab, K. R.; Styring, P. *Green Chem.* **2004**, *6*, 63. (b) Meracz, I.; Oh, T. *Tetrahedron Lett.* **2003**, *44*, 6465. Other examples of Diels−Alder reactions in ionic liquids: (c) Jaeger, D. A.; Tucker, C. E. *Tetrahedron Lett.* **1989**, *30*, 1785. (d) Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793. (e) Nobuoka, K.; Kitaoka, S.; Kunimitsu, K.; Iio, M.; Harran, T.; Wakisaka, A.; Ishikawa, Y. *J. Org. Chem.* **2005**, *70*, 10106. (f) Silvero, G.; Arevalo, M. J.; Bravo, J. L.; Avalos, M.; Jimenez, J. L.; Lopez, I. *Tetrahedron* **2005**, *61*, 7105. (g) Xiao, Y.; Malhotra, S. V. *Tetrahedron Lett.* **2004**, *45*, 8339. (h) Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. *Green Chem.* **2002**, *4*, 24. (i) Song, C. E.; Shim, W. H.; Roh, E. J.; Lee, S.-G.; Choi, J. H. *Chem. Commun.* **2001**, 1122.

(5) Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2539.

(6) Teo, Y.-C.; Goh, E. L.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 4573.

**Scheme 1**



completed, the reaction mixture was extracted with hexanes (10 mL × 5) to afford the cycloadduct. The ionic liquid residue was then azeotroped with THF to facilitate removal of solvent remnants prior to subsequent addition of the diene and dienophile in the next cycle. The results are shown in Table 2.

**Table 2.** Recyclability of (*S*)-BINOL−In(III) Complex in hmim[$PF_6^-$][a]

| no. of cycles | % yield[b] | % ee[c] |
|---|---|---|
| 1st | 92 | 98 |
| 2nd | 89 | 98 |
| 3rd | 88 | 92 |
| 4th | 89 | 90 |
| 5th | 88 | 90 |
| 6th | 86 | 90 |
| 7th | 87 | 86 |

[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. Reaction mixture was stirred at room temperature for 20 h. [b] Isolated yield. [c] Refer to Supporting Information for enantiomeric excess determination.

It was noteworthy that the chiral In(III) complex can be reused for seven successive cycles with comparable enantioselectivities and yields without loss of catalytic activity. Moreover, the extraction process was operationally simple and convenient to execute, which precludes the need for stringent anhydrous conditions. This extraction process further demonstrated the moisture-tolerance and stability of the chiral indium complex with retention of catalytic activity throughout the recyclability studies.

In conclusion, a highly catalytic In(III) complex was developed to give enantiomerically enriched Diels−Alder adducts with high enantiomeric excess in ionic liquid.[7] 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; (2) the cycloaddition of a variety of cyclic and open-chained dienes to 2-methacrolein and 2-bromoacrolein resulted in good yields and high enantioselectivities without the need to recourse to low temperatures; (3) good enantiomeric excess and yield of cyclopentadiene and 2-bromoacrolein adduct can be achieved with as low as 5 mol % catalyst loading in ionic liquid; (4) the catalyst can be recycled up to seven cycles with comparable yields and enantioselectivities; and (5) stringent anhydrous condition during workup for recycling the catalyst is not required. This contribution should provide a convenient and practical synthetic strategy for the construction of six-membered rings for complex molecules with medicinal and biological significance.

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**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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(7) **Representative procedure for enantioselective Diels−Alder reaction in ionic liquid: 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) and 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 followed by addition of 1 mL of hmim[$PF_6^-$] to the preformed catalyst. The organic solvent was removed in vacuo, and subsequent dropwise addition of 2-bromoacrolein (67.5 mg, 0.5 mmol, 1.0 equiv) and cyclopentadiene (0.10 mL, 1.5 mmol, 3.0 equiv) along side of the flask was carried out. The reaction mixture was stirred at room temperature for 20 h. The mixture was 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 (92% yield).