ORGANIC LETTERS

2002
Vol. 4, No. 5
707−709

Optically Active 1,2-Bis(1-arylhydroxymethyl) Ferrocene: A New, Efficient Chiral Ligand for Scandium-Catalyzed Asymmetric Diels–Alder Reaction

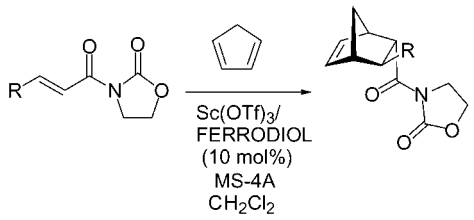
Shin-ichi Fukuzawa,* Kuniaki Fujimoto, Yoshitaka Komuro, and Hiroshi Matsuzawa

Department of Applied Chemistry, Institute of Science and Engineering, Chuo University, Kasuga, Bunkyo-ku, Tokyo 112-8551, Japan

fukuzawa@chem.chuo-u.ac.jp

Received December 4, 2001

ABSTRACT



The Sc(OTf)$_3$/FERRODIOL (2) complex was prepared at −78 °C in CH_2Cl_2 in the presence of 2,6-lutidine and MS 4A. The chiral scandium Lewis acid-catalyzed asymmetric Diels–Alder reaction of cyclopentadiene (3) with 3-acyloxazolidin-2-ones (4) effectively produced the adduct (5) in a high yield with good selectivity, i.e., *endo*/*exo* = 90:10 up to 91% ee (*endo*).

Chiral diols such as BINOL and TADDOL have been recognized as efficient bidentate ligands for Lewis acid catalysts in asymmetric synthesis, and various chiral diols have been intensively developed to date.[1] However, a certain chiral diol is not always a suitable ligand for any Lewis acid metal salt. A combination of a metal complex and a ligand is often critical for high enantioselectivity and yield in a synthetic reaction. Thus, it is important to design and prepare a new chiral diol ligand for the Lewis acid catalysts. We have been studying the stereocontrolled preparation of chiral ferrocenes and their use in asymmetric synthesis as chiral ligands/auxiliaries.[2] We now report a new ferrocenyl-based chiral diol ligand,[3] i.e., (1*R*,2*R*)-bis(arylhydroxymethyl)-ferrocene (FERRODIOL) (**3**), of which the chiral scandium complex is an effective catalyst for the enantioselective Diels−Alder reaction.[4]

FERRODIOL was easily prepared by a sequence that included the diastereoselective addition of Grignard reagent to the chiral *o*-aminoformylferrocene (**1**) leading to **2**, the

(1) (a) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (b) Maruoka, K.; Yamamoto, H. In *Asymmetric Reactions with Chiral Lewis Acid Catalysts; Catalytic Asymmetric Catalyst*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 9, pp 413−440. (c) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995.

(2) (a) Wagner, G.; Herrmann, R. In *Ferrocenes*; Togni, A., Hayashi, T., Eds.; VCH: Weinheim, 1995; Chapter 4. (b) Kagan, H. B.; Riant, O. In *Advances in Asymmetric Synthesis*;, Hassner, A., Eds.; JAI Press: London, 1997; Vol. 2, pp 189−235. (c) Kagan, H. B.; Ditter, P.; Gref, A.; Gillaneux, D.; Masson-Szymczac, A.; Rebiere, F.; Riant, O.; Samuel, O.; Tauden, S. *Pure Appl. Chem.* **1996**, *68*, 29−36. (d) Togni, A. In *Metallocene*; Togni, A., Halterman, R. L., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 2, Chapter 11. (e) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377.

(3) (a) Fukuzawa, S.; Tsuchiya, D.; Sasamoto K.; Hirano, H.; Ohtaguchi, M. *Eur. J. Org. Chem.* **2000**, 2877−2883. (c) Fukuzawa, S.; Fujimoto, K. *Synlett* **2001**, 1275. (c) Schwinl, L.; Knochel, P. *Chem. Eur. J.* **1998**, 950.

(4) (a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (b) Evans, D. A.; Johnson, J. S. In *Diels−Alder Reaction; Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfalts, A., Yamamoto, H., Eds; Springer: Berlin, 1999; Vol. III, Chapter 33.1.

10.1021/ol0171766 CCC: $22.00
Published on Web 02/09/2002

retentive displacement of the amino group by an acetoxy group, and reduction with $LiAlH_4$. Various FERRODIOL ligands (**3a**−**d**) could be obtained by changing the aryl methyl group of the amino group and the aryl Grignard reagent that adds to the formyl group. As previously reported, the methyl derivative **3e** could not be prepared by this method, but it could be prepared from the 2-trimethylsilyl-blocked formyl ferrocene.[3] (1*R*,2*R*)-**3a** and (1*S*,2*S*)-**3b**, which are enantiomers of each other, could be obtained from the starting aminoformylferrocenes (1*R*,*Sp*)-**1a** and (1*S*,*Rp*)-**1b**, respectively, via stereospecific transformation.

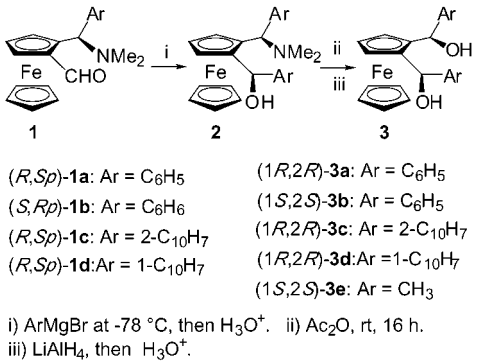
The representative Lewis acids were examined for the complex with **3**, and their catalytic efficiency in the asymmetric Diels−Alder reaction was examined.[5] The reaction was usually carried out as follows. The Lewis acid complex with **3a** was first prepared at −78 °C in CH_2Cl_2 in the presence of MS 4A[6] and 2,6-lutidine (2 equiv to **3a**). After 0.5 h aging, 3-acryloyloxazolidin-2-one (**4a**) and cyclopentadiene (**5**) were added to the solution at −78 °C, and the resulting mixture was stirred at 0 °C for 2 h. The product was isolated by PTLC, and the isomer ratio (*endo*/*exo*) and enantiomeric excess (% ee) were determined by HPLC using a chiral column (Daicel Chiralcel OD). The absolute configuration was determined by reference to the literature.[7] Table 1 summarizes the results of the reaction using a representative Lewis acid/**3a** complex as the catalyst (10 mol % to **4a**) (Scheme 1). Among the various metal salts, only $Sc(OTf)_3$ was effective for the enantioselective reaction mainly giving the *endo* adduct (**6a**) in a high yield with moderate stereoselectivity, i.e., *endo*/*exo* = 91:9, 52% ee (*R*-*endo*) (Scheme 2).[7] The reaction at −78 °C improved the enantioselectivity up to 60% ee: the extended reaction time (22 h) was required in order to obtain a satisfactory yield (Table 1, entry 2). The other Lewis acids shown in Table 1 have exhibited no enantioselectivity (<1% ee), although they catalyzed the reaction to give **6a** in good yields.

Table 1. Asymmetric Diels−Alder Reaction of **4a** with **5** Catalyzed by FERRODIOL (**3a**)/Metal Complexes[a]

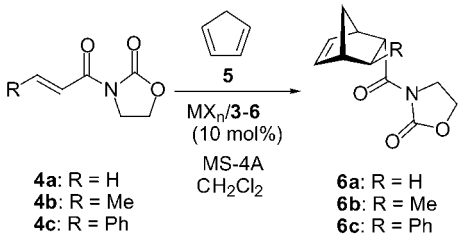
entry	metal salt	yield[b] (%)	*endo*/*exo*[c] (*endo*, config)	ee[d] (%)
1	$Sc(OTf)_3$	85	91:9	52 (*R*)
2[e]	$Sc(OTf)_3$	79	92:8	60 (*R*)
3[f]	$Sc(OTf)_3$	75	86:14	19 (*S*)
4	$Yb(OTf)_3$	51	91:9	0 (−)
5	$Sm(OTf)_3$	66	92:2	0 (−)
6	$In(OTf)_3$	52	90:10	3 (−)
7	$Cu(OTf)_2$	81	91:9	0 (−)
8	BBr_3	41	92:8	1 (−)
9[g]	Et_2AlCl	82	96:4	0 (−)
10[h]	$TiCl_2(OPr^i)_2$	94	82:18	7 (*R*)

[a] Metal salt (0.05 mmol), FERRODIOL (**3a**) (0.06 mmol), MS 4A (150 mg), 2,6-lutidine (0.12 mmol), **4a** (0.5 mmol), **5** (1.5 mmol), CH_2Cl_2 (4 mL); −78 °C, 0.5 h, then 0 °C, 2 h. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Determined by HPLC (Chiralcel OD). [e] −78 °C, 22 h. [f] Without 2,6-lutidine. [g] 0 °C, 18 h. [h] In toluene (4 mL) without 2,6-lutidine.

Scheme 1



Scheme 2



The addition of 2,6-lutidine was essential for the enantioselectivity since the reaction without the amine gave the *endo* adduct with poor enantioselectivity and the stereochemistry of the adduct as *S*-*endo*, 19% ee (entry 3). Tertiary amines other than 2,6-lutidine were examined as an additive: 2,4,6-collidine 51% ee; pyridine 19% ee; 1,2,6-trimethylpiperidine, 21% ee; 1,2,2,6,6-pentamethyl-piperidine, 10% ee; diisopropylethylamine, 16% ee. Since 2,6-lutidine was found to be the most effective additive, it was used for the Diels−Alder reaction with other dienophiles. Table 2 summarizes the reaction of 3-crotonoyl- (**4b**) and 3-cinnamoyloxazolidin-2-one (**4c**) with **5** using chiral $Sc(OTf)_3$/FERRODIOL (**3a**−**e**) complexes. The Sc/(1*R*,2*R*)-**3a** complex catalyzed the reaction of **4b** with **5** to give the (2*R*,3*S*)-*endo* adduct (**6b**) in good yields with high enantioselectivity (*endo*/*exo* = 88/12) (Table 2, entry 1). The use of **3b** as a ligand, which is an enantiomer of **3a**, gave the (2*S*,3*R*)-*endo* adduct in 91% ee (Table 2, entry 2).[8] The 2-naphthyl derivative of FERRODIOL (**3c**) is also an effective ligand for the

(5) *Lewis Acids in Organic Synthesis*, Yamamoto, H., Ed.; Wiley−VCH: Weinheim, 2000.

(6) The enantioselectivity was low in the absence of MS 4A (8% ee). (a) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340. (b) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron*, **1997**, *53*, 17015.

(7) Kobayashi et al. have reported that the $Sc(OTf)_3$/(*R*)-BINOL complex is an effective catalyst for the asymmetric Diels−Alder reaction. (a) Kobayashi, S.; Ishitani, H.; Araki, M.; Hachiya, I. *Tetrahedron Lett.* **1994**, *34*, 6325. (c) Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758.

(8) The chiral Sc/BINOL and Ti/TADDOL complexes give the *endo* adduct **6b** in 96% ee and 91% ee, respectively. See refs 6a and 7c.

Table 2. Asymmetric Diels−Alder Reaction of **4** with **5** Catalyzed by FERRODIOL (**3**−**8**)/Scandium Complexes[a]

entry	**4**	diol	yield[b] (%)	*endo*/*exo*[c]	ee[d] (%)	config (*endo*)
1	**4b**	(1*R*,2*R*)-**3a**	92	88:12	85	2*R*,3*S*
2	**4b**	(1*S*,2*S*)-**3b**	99	90:10	91	2*S*,3*R*
3	**4b**	(1*R*,2*R*)-**3c**	92	88:12	85	2*R*,3*S*
4	**4b**	(1*R*,2*R*)-**3d**	79	86:14	54	2*R*,3*S*
5	**4b**	(1*S*,2*S*)-**3e**	72	65:35	45	2*S*,3*R*
6	**4c**	(1*R*,2*R*)-**3a**	44	78:22	37	2*S*,3*S*

[a] $Sc(OTf)_3$ (0.05 mmol), FERRODIOL (**3a**−**e**) (0.06 mmol), MS 4A (150 mg), 2,6-lutidine (0.12 mmol), **4** (0.5 mmol), **5** (1.5 mmol), CH_2Cl_2 (4 mL); −78 °C, 0.5 h, then 0 °C, 18 h. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Determined by HPLC (Chiralcel OD).

scandium catalyzed Diels−Alder reaction; its complex gave **6b** in 92% yield with 85% ee (Table 2, entry 3). Mysteriously, the more sterically demanding 1-naphthyl derivative (**3d**) produced a lower enantioselectivity (Table 2, entry 4). Both 1-naphthyl groups in **3d** may be too sterically crowded to form the complex with scandium. It is reasonable that the use of the nonsterically demanding **3e** as a ligand resulted in a low enantioselectivity (Table 2, entry 5). The temperature for the preparation of the chiral scandium complex was critical to achieve a good selectivity.

When the complex was prepared at elevated temperature, i.e., 0 °C or room temperature, and the following Diels−Alder reaction of **4a** with **5** was carried out at 0 °C or even at −78 °C, the adduct was almost obtained as almost racemic (2% ee). This result may suggest that the chiral scandium complex could be formed and is stable at low temperature. The question arises as to why a high selectivity could be achieved although the asymmetric Diels−Alder reaction was actually carried out at 0 °C. The possible answer may be rationalized by chelation of the oxazolidinone with scandium, which stabilizes the scandium/FERRODIOL complex even at a higher temperature. The formation of the scandium complex with FERRODIOL could be observed by ^1H NMR measurements. The cyclopentadienyl (Cp) ring of the FERRODIOL normally appears at 4.32 ppm from TMS in CD_2Cl_2 at −70 °C. The chemical shift of the Cp ring shifted downfield to 3.89 ppm by adding $Sc(OTf)_3$. The addition of 2,6-lutidine changed the NMR spectrum pattern, but the chemical shift of the Cp ring only slightly shifted, i.e., at 3.90 ppm. The two benzylic protons also shifted from 4.8 to 5.0 ppm to 4.2−4.4 ppm as broad peaks. The methyl signal of 2,6-lutidine shifted from 2.50 to 2.40 ppm, and the pyridine ring proton also shifted from 6.90 and 7.41 ppm to 7.13 and 7.67 ppm, respectively, suggesting the presence of the coordinating 2,6-lutidine. This NMR experiment may show the formation of the chiral scandium/FERRODIOL/2,6-lutidine complex.

Though the actual reason Sc/FERRODIOL/2,6-lutidine produced a high enantioselectivity in the Diels−Alder reaction has not yet been clarified, the new Lewis acid complex, Sc/FERRODIOL/2,6-lutidine will be a promising ligand for asymmetric synthesis.

Acknowledgment. This work is financially supported by a Grant-in-Aid, No. 13650906, for Scientific Research from the Japan Society for the Promotion of Science (JSPS).

Supporting Information Available: The preparation of FERRODIOL (**3a**) and experimental details of the Diels−Alder reaction of cyclopentadiene **5** with 3-crotonoyloxazolidin-2-one **4b** catalyzed by $Sc(OTf)_3$/**3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0171766