

Enantioselective catalytic Diels–Alder reaction of ethyl 2-benzoylacrylate with chiral bis(oxazoline)– or mono(oxazoline)–magnesium complex

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The magnesium catalysed Diels–Alder reaction of 2-benzoylacrylate gave the *endo*-adduct enantioselectively with bis(oxazoline) **5** as a C₂-symmetric ligand or mono(oxazoline) **4** as a non-C₂-symmetric ligand.

A great deal of effort has been invested in enantioselective Diels–Alder reactions catalysed by chiral Lewis acids, and tremendous advances have been achieved in recent years.¹ C₂-Symmetric ligand–metal complexes have proven to be excellent catalysts, and in most cases *N*- α,β -unsaturated acyloxazolidinones have been used as two-point dienophile binding agents in these reactions.² Recently, non-C₂-symmetric phosphinoaryloxazolines have been shown to be effective ligands for Pd-catalysed asymmetric allylic substitution.³ We have reported a highly diastereoselective and *endo/exo* selective Diels–Alder reaction of (1'*R*,2'*S*,5*R*)-5-methyl-2-methyl-2-(1-phenylethyl)cyclohexyl 2-benzoylacrylate with cyclopentadiene catalysed by a Lewis acid.⁴ This suggests that an enantioselective Diels–Alder reaction should occur using ethyl 2-benzoylacrylate **1**,⁵ a two-point binding dienophile, in the presence of a chiral Lewis acid. Herein, we describe the magnesium-catalysed Diels–Alder reaction of **1**, as dienophile, with cyclopentadiene using *N*-[(1*R*)-2-chloro-1-phenylethyl]-2-ethyl-2-[(4*R*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]butyramide **4** as a non-C₂-symmetric chiral ligand and bis(oxazoline) **5** as a C₂-symmetric chiral ligand.

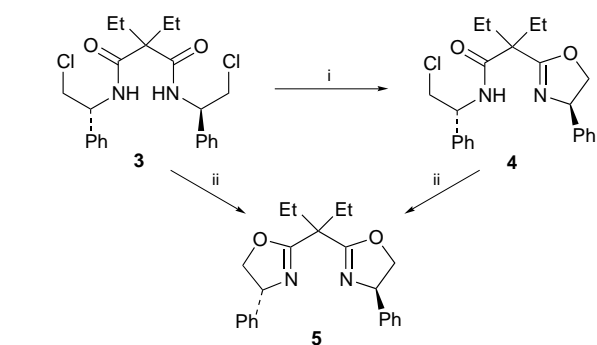
Our initial efforts were focussed on the possibility that ethyl 2-benzoylacrylate **1** should be a good two-point binding dienophile in an enantiomeric Diels–Alder reaction with cyclopentadiene by use of bis(oxazoline) **5**–magnesium complex. In the reaction with the complex prepared from **5**, MgI₂

and I₂ (co-catalyst) in CH₂Cl₂ at room temperature by Corey's procedure,^{2b} the enantioselectivity was not particularly high (Table 1, entry 1), but the selectivity was much improved with the complex prepared in refluxing MeCN (entry 2). The diastereoisomers showed one spot by TLC and could not be resolved by column or medium pressure chromatography, but the ratio was determined by ¹H NMR spectroscopy as mentioned in our previous report,⁴ and in most cases only the *endo*-isomer was obtained (Table 1).

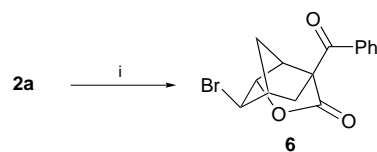
As **1** proved to be a suitable dienophile, we next examined the reaction using *N*-[(1*R*)-2-chloro-1-phenylethyl]-2-ethyl-2-[(4*R*)-4-phenyl-4,5-dihydrooxazol-2-yl]butyramide **4** as a chiral ligand. Compound **4** was synthesized by treatment of dichloride **3** with an equimolar amount of NaOH in MeOH–H₂O at 60 °C. In contrast to the fact that most of the bis(oxazoline)s used as chiral ligands are oily materials, the mono(oxazoline) **4** exists as colourless prisms (mp 127–128 °C from EtOAc) and is therefore easy to handle. The reaction with the complex prepared from **4**:MgI₂:I₂ (1:1:1) in CH₂Cl₂ at room temperature also gave poor enantioselectivity (entry 3). When the reaction was performed with the complex prepared in refluxing MeCN, the ee increased to 87% (entry 4). Interestingly, the enantioselectivities of the reactions with the complex prepared from MgI₂:**4**:I₂ (1:2:2) were almost equal or slightly higher (entries 5,6). It is well known that head or tail enrichment may occur during chromatography on achiral columns of samples containing an excess of one enantiomer.^{2i,6} We therefore collected all the Diels–Alder adducts before ¹H NMR and HPLC analyses. After separation of the *endo* adduct by preparative HPLC, if necessary, the enantioselectivities were determined by analytical HPLC.[‡] Furthermore, the ligands

Table 1 Asymmetric catalytic Diels–Alder reaction of ethyl 2-benzoylacrylate

Entry	Catalyst			Diels–Alder adduct		
	MgI ₂ (equiv.)	Ligand (equiv.)	Conditions	Yield (%)	2a:2b	%Ee of 2a
1	0.2	5 (0.2)	CH ₂ Cl ₂ , room temp., 3 h	74	97:3	69.8
2	0.2	5 (0.2)	MeCN, reflux, 1 h	81	>99:1	85.3
3	0.2	4 (0.2)	CH ₂ Cl ₂ , room temp., 3 h	76	>99:1	18.3
4	0.2	4 (0.2)	MeCN, reflux, 1 h	88	>99:1	87.0
5	0.1	4 (0.2)	MeCN, reflux, 1 h	88	>99:1	87.3
6	0.2	4 (0.4)	MeCN, reflux, 1 h	75	>99:1	88.6



Scheme 1 Reagents: i, NaOH (1 equiv.), MeOH–H₂O; ii, NaOH (excess), MeOH–H₂O



Scheme 2 Reagents: i, Br₂, CCl₄

were recovered almost quantitatively from column chromatography as the last fraction. The absolute configuration of **2a** was confirmed by treatment of **2a** with bromine in CCl_4 to give bromo-lactone **6**, whose absolute structure was determined by X-ray crystallography (Fig. 1).§

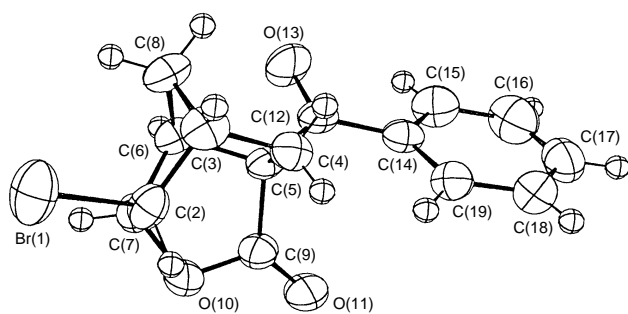


Fig. 1 ORTEP diagram of **6**

The almost perfect diastereoselectivity of the reaction can be rationalised to be due to the steric hindrance of the benzene ring situated nearly perpendicular to the ene in the fixed metal-chelated enedione as mentioned earlier.⁴ However, the reaction mechanism giving high enantioselectivity using mono(oxazoline) is unclear. An attempt to capture the complex of the Lewis acid–chiral ligand or Lewis acid–ligand–dienophile in crystal form has not been successful. Further investigations to clarify the precise structures of the catalysts formed from **4**: MgI_2 : I_2 (1:1:1 and 2:1:2) and the reaction mechanism as well as to develop other asymmetric reactions using this complex are now in progress.

Footnotes

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† General experimental procedure: a mixture of the ligand, MgI_2 and I_2 in the solvent was treated under the conditions shown in Table 1. The solvent was removed and the resulting complex was dissolved in CH_2Cl_2 (1.0 ml) and cooled at -90°C . To this solution **1** (1 mmol) in CH_2Cl_2 (1.5 ml) was added and stirred for 30 min, then cyclopentadiene (1.5 mmol) in CH_2Cl_2 (2.5 ml) was added slowly for a period of 3 h. After the reaction was completed the reaction mixture was quenched with water and washed with 5% aqueous $\text{Na}_2\text{S}_2\text{O}_3$. The organic layer was dried and evaporated. The resulting residue was subjected to column chromatography to yield the adducts.

‡ Preparative HPLC was carried out with a JASCO Megapak SIL-10 column (1.0×25 cm; eluate 5% AcOEt in hexane) and analytical HPLC with a Daisel CHIRALCEL OD column (0.46×25 cm; eluate 0.1% propan-2-ol in hexane).

§ Crystal data for **6**: $\text{C}_{15}\text{H}_{13}\text{O}_3\text{Br}$, $M = 321.16$, orthorhombic, space group $P2_12_12_1$, $a = 10.935(1)$, $b = 18.884(1)$, $c = 6.326(1)$ Å, $U = 1287.7(2)$ Å³, $Z = 4$, $D_c = 1.66$ g cm⁻³, $\mu(\text{Cu-K}\alpha) = 4.37$ mm⁻¹. Reflections were measured on a Rigaku AFC5R diffractometer in the range $4.7 < \theta < 65.1^\circ$ (Cu-K α radiation) with the ω - 2θ scan technique, 2154 reflections were used for all calculations. The structure was solved by direct methods [SHELX-86 (ref. 7)] and refined anisotropically on F^2 (SHELXL-93 (ref. 8)). All hydrogen atoms were refined for all parameters; $wR_2(F^2) = 0.0773$ with $R(F) = 0.0303$ for 225 parameters. The absolute configuration was determined Flack's χ -parameter (ref. 9) $-0.02(2)$. CCDC 182/514.

References

- 1 R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994; K. Ishihara and H. Yamamoto, in *Advances in Catalytic Processes*, ed. M. P. Doyle, JAI Press, London, 1995.
- 2 (a) E. J. Corey, N. Imai and H.-Y. Zhang, *J. Am. Chem. Soc.*, 1991, **113**, 728; (b) E. J. Corey and K. Ishihara, *Tetrahedron Lett.*, 1992, **33**, 6807; (c) D. A. Evans, S. J. Miller and T. Lectka, *J. Am. Chem. Soc.*, 1993, **115**, 6460; (d) D. A. Evans and D. M. Barnes, *Tetrahedron Lett.*, 1997, **38**, 57; (e) PS. Kobayashi and H. Ishitani, *J. Am. Chem. Soc.*, 1994, **116**, 4083; (f) K. V. Gothelf and K. A. Jørgensen, *J. Org. Chem.*, 1995, **60**, 6847; (g) C. Haase, C. Sarko and M. DiMare, *J. Org. Chem.*, 1995, **60**, 1777; (h) K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima and J. Suginori, *J. Am. Chem. Soc.*, 1989, **111**, 5340; (i) D. Seebach, R. Dahinden, R. E. Mart, A. K. Beck, D. A. Plattner, and N. M. Kühnle, *J. Org. Chem.*, 1995, **60**, 1788.
- 3 P. Matt and A. Pfaltz, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 566; P. Matt, O. Loiseleur, G. Koch and A. Pfaltz, *Tetrahedron: Asymmetry*, 1994, **5**, 573; G. Koch and A. Pfaltz, *Tetrahedron: Asymmetry*, 1996, **7**, 2213; H. Rieck and G. Helmchen, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2687.
- 4 M. Yamauchi, Y. Honda, N. Matsuki, T. Watanabe, T. Date and H. Hiramatsu, *J. Org. Chem.*, 1996, **61**, 2719.
- 5 M. Yamauchi, S. Katayama and T. Watanabe, *Synthesis*, 1982, 935.
- 6 W.-L. Tsai, K. Hermann, E. Hug, B. Rohde and A. S. Dreiding, *Helv. Chim. Acta*, 1985, **68**, 2238; P. Diter, S. Tandien, O. Samuel and H. B. Kagan, *J. Org. Chem.*, 1994, **59**, 370.
- 7 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, **46**, 467.
- 8 G. M. Sheldrick, SHELXL-93, University of Göttingen, Germany, 1993.
- 9 H. D. Flack, *Acta Crystallogr., Sect. A*, 1983, **39**, 676.

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