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Chiral Helical Lewis Acids for Asymmetric Diels–Alder Catalysts

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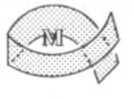
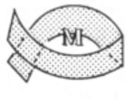
Summary: A new type of chiral helical titanium reagent has been prepared from titanium tetraisopropoxide and a chiral ligand derived from optically pure binaphthol. These reagents have been successfully utilized as an efficient chiral template for the sufficient conformational fixation of α,β-unsaturated aldehydes, thereby allowing efficient enantioface recognition of the substrates for achievement of uniformly high asymmetric induction in asymmetric Diels–Alder reaction with dienes, regardless of reaction temperature.

A variety of naturally occurring substances such as DNA, polypeptides (proteins and collagens), and starch possess a characteristic helix conformation as a second structure.[1] The spatial arrangements of these substances are beautifully fixed by effective hydrogen bond. We have been interested for some time in the possibility of utilizing this phenomenon in the design of new types of asymmetric helical metal catalysts (*P*)-1 and (*M*)-1[2] with the hope that a high level of asymmetric induction can be rationally achieved by way of an efficient enantioface recognition of prochiral substrates using a fixed helical conformation of a chiral ligand. Here, we introduce a new, chiral helical titanium reagent of type **2** as an excellent Lewis acid catalyst for asymmetric induction.

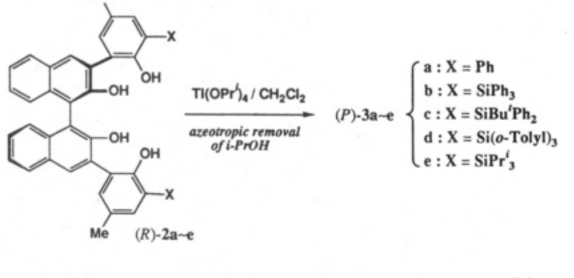


(*P*)-1

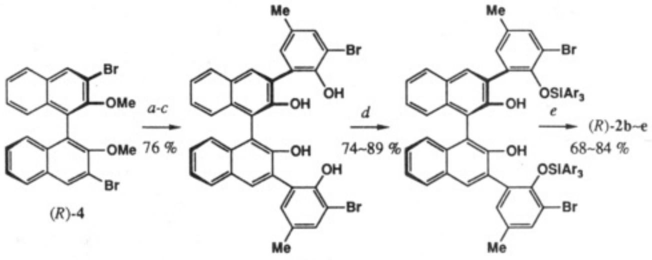


(*M*)-1

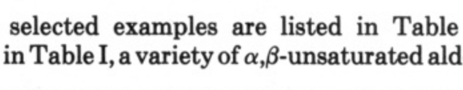
We adopted a binaphthol-derived chiral ligand of type (*R*)-**2** and transformed it into a chiral helical titanium reagent (*P*)-**3**[2] by treatment with titanium tetraisopropoxide with azeotropic removal of 2-propanol.[3] First, we prepared chiral ligand (*R*)-**2a** from (*R*)-(+)-3,3′-dibromobinaphthol dimethyl ether (*R*)-(**4**) via the Pd^0-catalyzed coupling reaction[4] of (*R*)-**4** and 2-methoxy-5-methyl-3-phenylphenylboronic acid followed by demethylation of the resulting coupling product with BBr_3. Attempted Diels–Alder reaction of cyclopentadiene with acrolein under the influence of catalytic (*P*)-**3a** (10 mol %) in CH_2Cl_2 at −40 °C for 1 h gave rise to Diels–Alder adducts (99% yield), the major *endo* isomer of which was found to possess 46% ee. Since the molecular weight of (*P*)-**3a**, found cryoscopically in benzene, corresponds closely with the value calculated for monomeric species, the low enantioselectivity is ascribed to the insufficient conformational fixation of acrolein by an unsatisfactory helix structure for the chiral titanium reagent (*P*)-**3a**. After screening of several chiral ligands of type (*R*)-**2**, we found that introduction of *o*-triarylsilyl moieties was quite effective for obtaining high enantioselectivity with chiral titanium reagents (*P*)-**3**. The chiral ligands (*R*)-**2b–e** were conveniently prepared from (*R*)-**4** as indicated in Scheme I.[5,6] Indeed, asymmetric Diels–Alder reaction of cyclopentadiene and acrolein was effected in the presence of catalytic (*P*)-**3b** (10 mol %),[7] producing the major *endo* adduct **5** ($R^1 = R^2 = H$) in 88% ee. The absolute configuration of the carbonyl α-carbon of the *endo* adduct **5** ($R^1 = R^2 = H$) was determined to be *S* by correlation to the optical rotation value of an authentic sample.[8] In addition, the minor *exo* isomer was obtained in 84% ee with the *S* configuration.



Scheme I[a]



[a] Key: (a) 2-methoxy-5-methylphenylboronic acid, $Pd(PPh_3)_4$, $Ba(OH)_2$, DME, H_2O; (b) BBr_3, CH_2Cl_2; (c) Br_2, CH_2Cl_2; (d) Ar_3SiX, imidazole, DMF; (e) *t*-BuLi, THF.



Other selected examples are listed in Table I. As revealed in Table I, a variety of α,β-unsaturated aldehydes

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(1) Recent reviews: (a) Gross, E.; Meienhofer, J. *The Peptides*; Academic Press: New York, 1981; Vol. 4. (b) Meurer, K. P.; Vogtle, F. *Top. Curr. Chem.* **1985**, *127*, 1. (c) Dickerson, R. E.; Goodsell, D. S.; Kopka, M. L.; Pjura, P. E. *J. Biomol. Struct. Dyn.* **1987**, *5*, 557.

(2) "*P*" and "*M*" denote right- and left-handed helical conformations, respectively. See: Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385.

(3) (a) Seebach, D.; Weidmann, B.; Widler, L. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Otto Salle Verlag: Frankfurt am Main, 1983; Vol. 3, p 217. (b) Seebach, D.; Behrendt, L.; Felix, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1008. (c) Schmidt, B.; Seebach, D. *Ibid.* **1991**, *30*, 1321.

(4) (a) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207. (b) Unrau, C. M.; Campbell, M. G.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2773.

(5) (*R*)-**2b**: $[\alpha]^{25}_D$ −90.5° (*c* 1.00, THF). (*R*)-**2c**: $[\alpha]^{25}_D$ +15.4° (*c* 0.50, THF). (*R*)-**2d**: $[\alpha]^{25}_D$ −23.7° (*c* 1.00, THF). $[\alpha]^{28}_D$ −20.0° (*c* 1.0, $CHCl_3$). $[\alpha]^{28}_D$ −11.9° (*c* 0.6, EtOH).

(6) Maruoka, K.; Itoh, T.; Araki, Y.; Shirasaka, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2975.

(7) The chiral titanium reagents (*P*)-**3b–d** are found to include 0.5–1 equiv of *i*-PrOH by ^1H NMR analysis.

(8) Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437.

Table I. Asymmetric Diels–Alder Reaction of α,β-Unsaturated Aldehydes and Dienes Catalyzed by Chiral Helical Lewis Acids[a]

entry	aldehyde	diene[b]	Lewis acid	conditions (°C, h)	% yield,[c] (ratio)[d]	% ee[e] (confign)[f]
1	$CH_2{=}CHCHO$	CP	(*P*)-**3b**	−78, 3.5	63 (88:12)[g]	88 (*S*)[j]
2			(*P*)-**3c**	−78, 3.5	82 (93:7)	92 (*S*)[j]
3			(*P*)-**3d**	0, 0.5	65 (78:22)[h]	88 (*S*)[j]
4				−20, 0.7	84 (81:19)[h]	92 (*S*)[j]
5				−78, 3.5	70 (85:15)[h]	96 (*S*)[j]
6				−97, 10	57 (88:12)[h]	96 (*S*)[j]
7			(*P*)-**3e**	−78, 3.5	65 (92:8)	55 (*S*)[j]
8		CH	(*P*)-**3d**	−20, 13	46 (>99:<1)	81 (*S*)[k]
9		MCH	(*P*)-**3d**	−97, 10	86 (>99:<1)	98
10	$CH_2{=}C(Me)CHO$	CP	(*P*)-**3c**	−40, 16	56 (4:96)	62 (*S*)[j]
11			(*P*)-**3d**	−78, 70	75 (1:99)	94 (*S*)[j]
12			(*P*)-**3e**	−40, 18	77 (4:96)	29 (*S*)[j]
13	$CH_3CH{=}CHCHO$	CP	(*P*)-**3b**	−20, 12	50 (78:22)	85 (*S*)[l]
14			(*P*)-**3c**	−20, 19	36 (79:21)	74 (*S*)[l]
15			(*P*)-**3d**	−40, 50	76 (70:30)[i]	95 (*S*)[l]

[a] The asymmetric Diels–Alder reaction of α,β-unsaturated aldehydes with dienes was carried out with 0.1 equiv of Lewis acid (*P*)-**3b–e** in CH_2Cl_2. [b] CP: cyclopentadiene. CH: 1,3-cyclohexadiene. MCH: 1-methoxy-1,3-cyclohexadiene. [c] Isolated yield. [d] The *endo*/*exo* ratio was determined by 200-MHz ^1H NMR and/or capillary GLC analysis. [e] The optical yield of the major isomer was established by capillary GLC analysis after conversion to the acetal of (−)-(2*R*,4*R*)-pentanediol. [f] The absolute configuration of the carbonyl α-carbon was determined by correlation to the optical rotation values of authentic samples. [g] 84% ee for the minor *exo*-(*S*)-isomer. [h] The optical yields of the minor *exo*-(*S*)-isomers follow: 84% ee at 0 °C; 90% ee at −20 °C; 93% ee at −78 and −97 °C. [i] 97% ee for the minor *exo* isomer. [j] Reference 8. [k] Determined after conversion to the corresponding alcohol: Cervinka, O.; Kriz, O. *Collect. Czech. Chem. Commun.* 1968, *33*, 2342. [l] Reference 13a.

Table II. Comparison of the Optical Purity in the Asymmetric Diels–Alder Reaction of Cyclopentadiene and α,β-Unsaturated Aldehydes with Several Chiral Lewis Acids

	% ee of major cycloadducts (config)				
		chiral (acyloxy)borane			
aldehyde	**3d**	**6**[a]	**7**[b]	**8**[c]	**9**[d]
$CH_2{=}CHCHO$	96 (*S*)	84 (*S*)	40 (*R*)		
$CH_2{=}C(Me)CHO$	94 (*S*)	96 (*S*)	92 (*S*)	35	
$CH_3CH{=}CHCHO$[e]	95 (*S*)	2		72	54

[a] Reference 11. [b] Reference 12. [c] Reference 13. [d] Reference 14. [e] *Trans* isomer.

can be utilized without difficulty. The optical yield of the cyclopentadienylacrolein *endo* adduct **5** ($R^1 = R^2 = H$) was further enhanced to 92% ee and 96% ee by switching chiral titanium reagents from (*P*)-**3b** to (*P*)-**3c** and (*P*)-**3d**, respectively (entries 2 and 5 vs 1).[9,10] In addition, the minor *exo* isomer of **5** ($R^1 = R^2 = H$) was found to have a high optical yield (93% ee with (*P*)-**3d**). However, use of bis(triisopropylsilyl)-substituted reagent (*P*)-**3e** led to the eminent loss of enantioselectivity. Using other α,β-unsaturated aldehydes and dienes in the presence of 10 mol % titanium catalyst (*P*)-**3d**, the Diels–Alder adducts were produced with a uniformly high level of enantioselectivity (81–98% ee). Such advantage was not observable previously for several effective, asymmetric Diels–Alder catalysts including chiral (acyloxy)boranes **6–9**[11-14] as shown in Table II and Figure 1. Another interesting feature is that the enantioselectivity in the present Diels–Alder reaction is not greatly influenced by the reaction temperature (entries 3–6). Such temperature effect is rather in contrast to most of the known metal-catalyzed asymmetric reactions.[15,16]

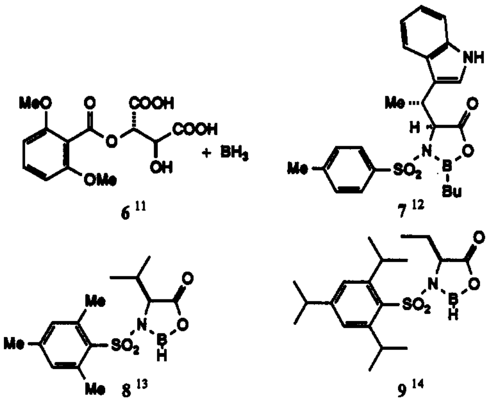

Figure 1. Asymmetric Diels–Alder catalysts.

The present titanium reagent (*P*)-**3** appears to play an important role as a reliable chiral template for the conformational fixation of α,β-unsaturated aldehydes, thereby allowing efficient enantioface recognition of the substrates for achievement of uniformly high asymmetric induction, regardless of reaction temperature. Judging from the absolute configurations of the *endo* and *exo* adducts, this reagent should cover the *re* face of carbonyl on its *anti*-coordination to the *s*-*trans* α,β-unsaturated aldehydes, and hence dienes should approach from the *si* face selectively. Further studies on the structural elucidation of the catalyst **3** and the reaction mechanism are in progress.

Supplementary Material Available: Typical experimental procedures and spectral data of products (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(9) The chiral titanium reagent (*P*)-**3** prepared in situ from $Ti(OPr^i)_4$ and (*R*)-**2** in the presence of molecular sieves (MS 4A) gave less satisfactory results in enantioselectivity. See: Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949.

(10) The chiral ligands (*R*)-**2b–d** can be recovered in >96% yields without loss of the optical purity.

(11) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481.

(12) (a) Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290. (b) Corey, E. J.; Loh, T.-P. *Ibid.* **1991**, *113*, 8966.

(13) (a) Sartor, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, 197. (b) Sartor, D.; Saffrich, J.; Helmchen, G.; Richards, C. J.; Lambert, H. *Tetrahedron: Asymmetry* **1991**, *2*, 639.

(14) Takasu, M.; Yamamoto, H. *Synlett* **1990**, 194.

(15) Reviews of metal-catalyzed asymmetric reactions: (a) Tomioka, K. *Synthesis* **1990**, 541. (b) Narasaka, K. *Ibid.* **1991**, 1.

(16) For example, the optical yields of the acetophenone reduction with BINAL-H vary 65–95% ee at temperatures ranging from 30 to −100 °C. See: Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.