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Asymmetric catalytic Pauson–Khand reactions with chiral phosphine ligands: Dramatic effects of substituents in 1,6-enyne systems

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Abstract

A cobalt-catalyzed reaction of 1,6-enyne systems under a carbon monoxide atmosphere using chiral phosphine ligands provides a facile entry to optically active 2-cyclopentenone derivatives. (*S*)-BINAP was demonstrated to be the most effective in the cobalt-catalyzed cyclization of 1,6-enynes among various chiral bidentate phosphine ligands employed, affording chiral 2-cyclopentenone derivatives with high enantioselectivity. The dramatic effects of the substituents in the 1,6-enynes were observed in this asymmetric synthesis. A plausible mechanism for the asymmetric induction is proposed on the basis of the stereochemical outcome obtained.

A number of valuable methods for asymmetric synthesis have been developed so far by means of transition-metal catalysts.[1] In particular, catalytic asymmetric cyclization has received much attention for the preparation of optically active cyclic compounds.[2] Over the past decade, we have been very interested in transition-metal-catalyzed asymmetric cyclizations of unsaturated systems such as nickel- or palladium-catalyzed asymmetric rearrangements in (1,3-butadienyl)cyclopropanes,[3–5] asymmetric intramolecular metallo-type ene reactions,[6] and palladium-catalyzed intramolecular asymmetric cycloisomerizations of 1,6-enynes.[7] In the course of our research project along this line, we have explored a new catalytic asymmetric synthetic way to optically active 2-cyclopentenones. We wish to demonstrate herein the first example of the catalytic asymmetric synthesis of 2-cyclopentenone systems[8,9] using a cobalt catalyst and chiral phosphines as ligands,[10] and to reveal the dramatic effects of the substituents in the 1,6-enyne systems and bidentate phosphine ligands in the cobalt-catalyzed cyclizations.

The cobalt-catalyzed reactions of **1b** were carried out in 1,2-dimethoxyethane (DME), toluene, or 1,2-dichloroethane (DCE) at reflux except for toluene (at 80°C) for 24 h under a carbon monoxide atmosphere in the presence of $Co_2(CO)_8$ (0.2 equiv.) and a ligand (0.2 equiv.) to furnish (*R*)- or (*S*)-**2b**, depending on

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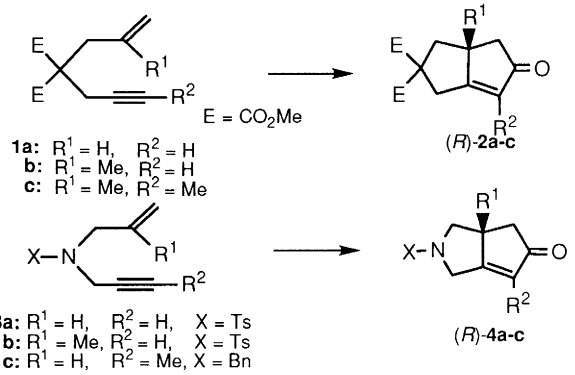
Table 1
The asymmetric Pauson–Khand reactions of **1a–c** or **3a,b** with chiral phosphine ligands[a)]

Substrate	Ligand[b)]	Solvent	Reaction time (h)	Yield (%) of **2** or **4**	e.e. (%) of **2** or **4**[c)] (Abs. Confign.)[d)]
1a	(*S*)-BINAP	DME	14	63[e)]	27 (*R*)
	(*S*)-BINAP	DME	14	53	90 (*R*)
	(*S*)-BINAP	DME	18	68[f)]	30 (*R*)
	(*S*)-BINAP	DME	20	61[g)]	68 (*R*)
	(*S*)-BINAP	DME	20	58[h)]	52 (*R*)
	(*S*)-BINAP	benzene	16	55	90 (*R*)
	(*S*)-BINAP	toluene	26	58	81 (*R*)
	(*S*)-BINAP	DCE	17	62	91 (*R*)
	(*S*)-BINAP	CH_3CN	15	74	37 (*R*)
	(*S*)-BINAP	THF	15	43	80 (*R*)
	(*R,R*)-DIOP	DME	14	76	5 (*R*)
	(*R,R*)-MOD-DIOP	DME	16	58	9 (*R*)
	(*S*)-(*R*)-BPPFOH	DME	16	77	7 (*S*)
	(*R,R*)-Me-DuPHOS	DME	26	14	44 (*S*)
1b	(*S*)-BINAP	DME	24	31	63 (*R*)
	(*S*)-BINAP	toluene	24	38	44 (*R*)
	(*S*)-BINAP	DCE	24	24	61 (*R*)
	(*R,R*)-DIOP	DME	24	54	40 (*R*)
	(*S,S*)-MOD-DIOP	DME	24	35	24 (*S*)
	(*S*)-(*R*)-BPPFA	DME	24	60	37 (*S*)
	(*S*)-(*R*)-BPPFOH	DME	24	51	46 (*S*)
	(*S*)-(*R*)-BPPFOAc	DME	24	63	23 (*S*)
1c	(*S*)-BINAP	DME	24	90	0
	(*R,R*)-DIOP	DME	24	47	31 (*R*)
3a	(*S*)-BINAP	DME	15	60	93 (*R*)
	(*S*)-BINAP	toluene	16	54	94 (*R*)
	(*S*)-BINAP	benzene	17	52	87 (*R*)
	(*S*)-BINAP	DCE	19	64	90 (*R*)
	(*S*)-BINAP	THF	19	39	78 (*R*)
3b	(*S*)-BINAP	DME	14	13	62 (*R*)
	(*R,R*)-DIOP	DME	14	69	57 (*R*)
	(*R,R*)-MOD-DIOP	DME	14	69	56 (*R*)
	(*S*)-(*R*)-PPFA	DME	13	83	10 (*R*)
	(*S*)-(*R*)-BPPFA	DME	13	67	25 (*S*)
	(*S*)-(*R*)-BPPFOH	DME	13	73	10 (*S*)
	(*S*)-(*R*)-BPPFOAc	DME	13	66	12 (*S*)

a) The cobalt-catalyzed reactions of **1a-c** or **3a,b** were carried out at reflux except for toluene (at 80°C) under carbon monooxide atmosphere in the presence of $Co_2(CO)_8$ (0.2 equiv.) and a ligand (0.2 equiv.). b) BINAP: 2,2'-Bis (diphenylphosphino)-1,1'-binaphthyl, DIOP: 4,5-Bis (diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane, MOD-DIOP: 4,5-Bis [bis (4'-methoxy-3',5'-dimethylphenyl) phosphinomethyl]-2,2-dimethyl-1,3-dioxolane, Me-DuPHOS: 1,2-Bis-2,5-dimethylphospholano) benzene, BPPFOH: 1-[1',2-Bis (diphenylphosphino) ferrocenyl] ethanol, BPPFOAc: 1-[1',2-Bis (diphenylphosphino) ferrocenyl] ethyl Acetate, BPPFA: *N,N*-Dimethyl-1-[1',2-bis (diphenylphosphino) ferrocenyl] ethylamine, PPFA: *N,N*-Dimethyl-1-[2-(diphenylphosphino) ferrocenyl] ethylamine. c) The e.e. of **2a-c** and **4a,b** was determined by the HPLC analysis with CHIRALPAK AD for **2a,c**, CHIRALCEL OD for **2b** and **4b**, and CHIRALPAK AS for **4a**. d) The absolute configuration of **2a-c** and **4a,b** deduced on the basis of the stereochemistry of analogous 2-cyclopentenones is described. e) (*S*)-BINAP (0.1equiv.) was used. f) Reacted at 65°C. g) (*S*)-BINAP (0.3 equiv.) was used. h) (*S*)-BINAP (0.4 equiv.) was used.

the chiral ligand used, with enantioselectivity as listed in Table 1. The enatiomeric excess (e.e.) of **2b** was determined by the HPLC analysis with CHIRALCEL OD. Relatively high enantioselectivity of (*R*)-**2b** was obtained by (*S*)-BINAP, as shown in Table 1, in comparison with those by other ligands employed such as (*R,R*)-DIOP, (*R,R*)-MOD-DIOP, or ferrocenyl ligands (Scheme 1).

Interestingly, the steric effects of the substituents in the enyne sites of the substrates greatly affected the degree of the asymmetric induction. A 1,6-enyne system **1a** without a methyl substituent in the enyne site provided excellent enantioselectivity in the above cobalt-catalyzed reactions with chiral phosphine ligands. The degree of asymmetric induction was greatly dependent upon the amount of the chiral ligand used. Various amounts (0.1, 0.2, 0.3, and 0.4 equiv.) of a chiral ligand ((*S*)-BINAP) were employed in the reaction of **1a**, and the use of 0.2 equiv. of (*S*)-BINAP was clearly demonstrated to be the most effective for the enantiocontrol of the asymmetric synthesis, as shown in Table 1. The use of (*S*)-BINAP (0.2



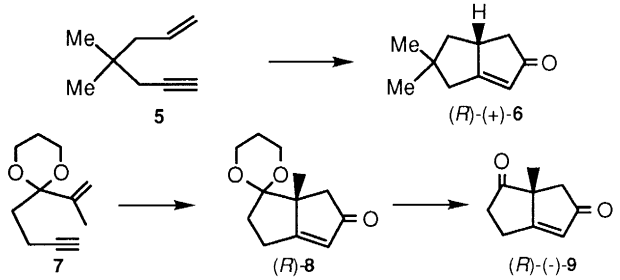
Scheme 1.

equiv.) in the cobalt-catalyzed reaction of **1a** in DME or DCE at reflux afforded (*R*)-**2a** with 90 or 91% e.e.,[11] respectively.

The substituent at the alkynyl part decreased the enantiocontrol in the cobalt-catalyzed Pauson–Khand reactions. The cobalt-catalyzed reaction of **1c** was carried out in DME at reflux for 24 h using (*S*)-BINAP as a chiral ligand, affording the product (*R*)-**2c** in high yield (90%); however, no enantioselectivity was observed. Use of (*R*,*R*)-DIOP in the above reaction gave (*R*)-**2c** with 31% e.e.

Similar enantioselectivity was obtained in the reactions of sulfonamides **3a**,**b** (X=*p*-$MeC_6H_4SO_2$). The cobalt-catalyzed reactions of **3b** were carried out in DME at reflux under the same reaction conditions as described above to give (*R*)-**4b** with 62, 57, or 56% e.e. with (*S*)-BINAP, (*R*,*R*)-DIOP, or (*R*,*R*)-MOD-DIOP, respectively. As expected, however, the reaction of **3a**, without a methyl group at the olefinic part, provided high enantioselectivity with (*S*)-BINAP, affording (*R*)-**4a** with 94% e.e.

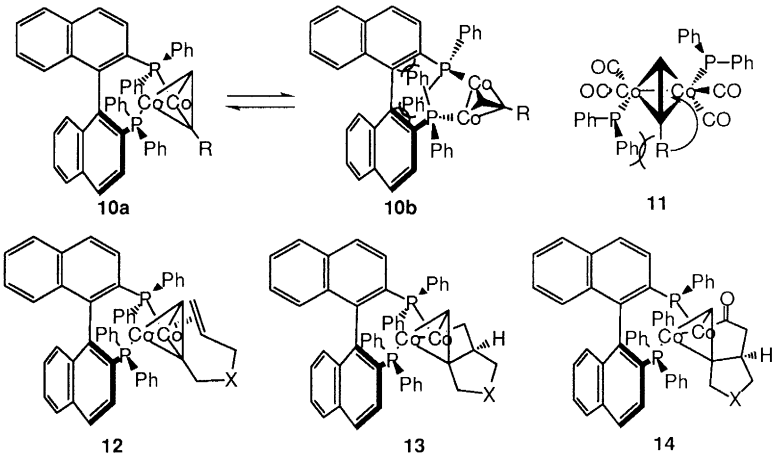
The cobalt-catalyzed reaction of **3c** (X=$PhCH_2$) using (*S*)-BINAP as a chiral ligand gave (*R*)-(+)-**4c** of known absolute configuration[9c] with 40% e.e. The cobalt-catalyzed reaction of 1,6-enyne **5** was carried out under similar reaction conditions as mentioned earlier with (*S*)-BINAP as a ligand to produce (*R*)-(+)-**6** of known absolute configuration[12] with 77% e.e. A similar reaction of **7** using (*S*)-BINAP as a ligand, followed by deketalization of (*R*)-**8** with *p*-toluenesulfonic acid–acetone, provided (*R*)-(−)-**9** of known absolute configuration (Scheme 2).[13] The absolute configuration of other products **2a**–**c** and **4a**,**b** is certainly deduced on the basis of the stereochemical results [(*R*)-(+)-**4c**, (*R*)-(+)-**6**, and (*R*)-(−)-**9**] obtained above with (*S*)-BINAP.



Scheme 2.

The mechanism of the asymmetric induction in the above reaction with chiral phosphine ligands is rationalized on the basis of the stereochemical outcome obtained as follows. The intermediary alkyne–cobalt complex coordinated by chiral bidentate phosphine (e.g. (*S*)-BINAP) would be initially formed; the bidentate phosphorus atoms would coordinate to the two different cobalt catalysts in the complex, since the coordination of the bidentate phosphorus atoms to one of the two cobalt atoms

would be unaccessible due to the steric environment around there. In the conformational equilibrium of the alkyne–cobalt complex coordinated by the bidentate phosphine of (*S*)-BINAP, a boat-like eight-membered conformer **10a** would be preferred to the corresponding chair-like conformer **10b**, since, in a view of the Dreiding model, **10b** has severe steric interference of the phenyl rings on the phosphorus atoms with the naphthyl rings of (*S*)-BINAP, as designated in **10b**. The olefinic part in the substituent R in **11** would coordinate to the sterically less crowded cobalt catalyst in the preferred **10a**, as designated in **12**, followed by reaction with the preferred cobalt–alkyne bond, insertion of carbon monooxide in **13**, and regeneration of the catalyst via **14**, affording (*R*)-**2a**–**c** and (*R*)-**4a**–**c**. It can certainly be assumed that with (*R*,*R*)-DIOP and (*R*,*R*)-MOD-DIOP as chiral ligands, a product of the same absolute configuration as that obtained with (*S*)-BINAP would be yielded on the basis of similar stereochemical consideration (Scheme 3).



Scheme 3.

Thus, the catalytic asymmetric synthesis of 2-cyclopentenone derivatives was accomplished successfully by using catalytic amounts of $Co_2(CO)_8$ and (*S*)-BINAP, providing excellent enantioselectivity.

References

1. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994.
2. Negishi, E.; Coperet, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev*. **1996**, *96*, 365.
3. Hiroi, K.; Arinaga, Y. *Tetrahedron Lett*. **1994**, *35*, 153.
4. Hiroi, K.; Arinaga, Y.; Ogino, T. *Chem. Pharm. Bull*. **1994**, *42*, 470.
5. Hiroi, K.; Yoshida, Y.; Kaneko, Y. *Tetrahedron Lett*. **1999**, *40*, 3431.
6. Hiroi, K.; Hirasawa, K. *Chem. Pharm. Bull*. **1994**, *42*, 786; *ibid*. **1994**, *42*, 1036.
7. Hiroi, K.; Nakaichi, S.; Minakata, H.; Adachi, J. to be published.
8. For asymmetric Pauson–Khand reactions, see: (a) Shore, N. E. *Chem. Rev*. **1988**, *88*, 1081; (b) Shore, N. E. *Org. React*. **1991**, *40*, 1; (c) Geis, O.; Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 911; (d) Ingate, S. T.; Marco-Contelles, J. *Org. Prep. Proced. Int*. **1998**, *30*, 121, and references cited therein.
9. For similar asymmetric synthesis with titanocene catalysts, see: (a) Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1996**, *118*, 11688; (b) *Idem, ibid*. **1999**, *121*, 7026; (c) Sturla, S. J.; Buchwald, S. L. *J. Org. Chem*. **1999**, *64*, 5547.
10. Bladon, P.; Pauson, P. L.; Brunner, H.; Eder, R. *J. Organomet. Chem*. **1988**, *355*, 449.
11. In a typical procedure: A 25 ml two-necked flask equipped with a septum inlet and a magnetic stirring bar, and containing $Co_2(CO)_8$ (22.8 mg, 0.067 mmol) and (*S*)-BINAP (41.5 mg, 0.067 mmol) was flushed with carbon monoxide, and maintained

under a positive pressure of carbon monoxide. DCE (4 ml) was added to the above flask at room temperature, and the reaction mixture was stirred at reflux for 2 h. A solution of a substrate **1a** (70 mg, 0.333 mmol) in DCE (4 ml) was added to the above solution at reflux, and the mixture was stirred at reflux for 17 h. After cooling at room temperature, the reaction mixture was filtered through a plug of silica gel with the aid of ethyl acetate, and the filtrate was concentrated in vacuo, and the crude product was purified by preparative TLC (ethyl acetate:hexane=2:3) to give **2a** (50 mg, 62% yield, 91% e.e.). The e.e. was determined by chiral HPLC (CHIRALPAK AD: 2-propanol:hexane=1:10).

12. Hua, H. *J. Am. Chem. Soc.* **1986**, *108*, 3835.
13. Brooks, D. W.; Woods, K. W. *J. Org. Chem.* **1987**, *52*, 2036.