Iridium−Chiral Diphosphine Complex Catalyzed Highly Enantioselective Pauson-Khand-Type Reaction

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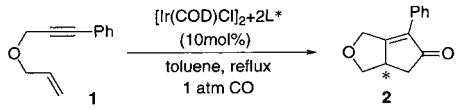
The transition metal-mediated carbonylative coupling reaction is one of the most important carbon skeleton-forming reactions, and provides cyclic compounds with a carbonyl group. Carbonylative alkene−alkyne coupling (the Pauson-Khand reaction when a cobalt carbonyl complex is used) has been extensively investigated[1] because it gives various cyclopentenones, which are useful synthetic intermediates.[2] One disadvantage of the Pauson-Khand reaction, which originally required more than a stoichiometric amount of cobalt complex, has recently been overcome: catalytic carbonylative alkene−akyne couplings have been reported with the use of Co,[3] Ti,[4] Ru,[5] and Rh[6] complexes. The development of a catalytic and enantioselective Pauson-Khand-type reaction[7,8] is now needed, since it provides a chiral five-membered-ring system. When we started the present project, however, the first and only elegant example of a catalytic enantioselective Pauson-Khand-type reaction using a chiral titanocene complex was reported by Buchwald et al.[9,10,11]

We report here that the iridium−chiral diphosphine complex catalyzes highly enantioselective intra- and intermolecular Pauson-Khand-type reactions, which provide various chiral cyclic enones in high ee (enantiomeric excess). Chiral Ir(I) catalyst is easily prepared in situ from $[Ir(COD)Cl]_2$ and tolBINAP, both of which are commercially available and air-stable, and the reaction proceeds under atmospheric pressure of carbon monoxide to give an ee of up to 98%.

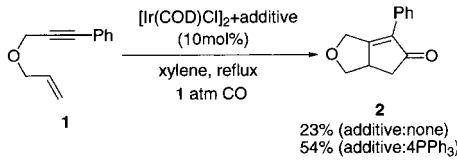
Table 1. Catalytic Enantioselective Carbonylative Coupling of **1**



entry	L*	time/h	yield/%	ee/%[a]
1	(*S*)-BINAP	12	64	86(*S*)
2	(*R*)-BINAP	12	62	88(*R*)
3	(*S*)-tolBINAP	18	83	93(*S*)
4[b]	(*S*)-tolBINAP	24	75	91(*S*)

[a] Ee was determined by HPLC using the Daicel chiral column (Chiralpak AD). Absolute configuration was determined by the comparison of specific rotation of obtained **2** with that in the literature.[9b] [b] 5 mol % of $[Ir(COD)Cl]_2$ was used.

We first examined intramolecular carbonylative alkene−alkyne coupling using 10 mol % of $[Ir(COD)Cl]_2$. Enyne **1** was readily consumed, but the reaction gave a complex mixture, and cyclopentenone **2** was isolated in low yield. On the other hand, the addition of 4 equiv. of triphenylphosphine to $[Ir(COD)Cl]_2$ dramatically improved the yield (eq 1). These results prompted us to screen chiral phosphines to realize a catalytic enantioselective Pauson-Khand-type reaction.



(1)

After examining several chiral diphosphines, we found that a binaphthyl skeleton induced high enantioselectivity (Table 1). The iridium−(*S*)-BINAP complex catalyzes carbonylative coupling to give (*S*)-**2** in 86% ee (entry 1). The use of (*R*)-BINAP certainly provides (*R*)-**2** in almost the same ee (entry 2). The tolBINAP−iridium complex is a more efficient chiral catalyst, and both the yield and ee were improved (entry 3).[12] When the amount of tolBINAP−iridium catalyst was halved, ee decreased only slightly: the ee of the resulting enone **2** was more than 90% (entry 4).[13] Other chiral diphosphines we examined showed less or no catalytic activity and enantioselectivity in this reaction ((*S*,*S*)-DIOP 53%, 17% ee(*R*); (*S*)-BDPP 23%, 22% ee(*S*); (*S*)-CHIRAPHOS 13%, <1% ee; (*S*)-Me-DUPHOS <1%, <1% ee).

Various enynes were subjected to the above optimal reaction conditions (reflux in toluene under atmospheric pressure of carbon monoxide using (*S*)-tolBINAP as a chiral ligand) (Table 2). 4-Methoxyphenyl-substituted enyne was also transformed into the corresponding bicyclic enone in good yield and high ee (entry

(1) Recent reviews of the Pauson-Khand (type) reaction: (a) Schore, N. E. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon: Oxford, 1995; Vol 12, p 703. (b) Geis, O.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **1998**, *37*, 911. (c) Jeong, N. In *Transition Metals In Organic Synthsis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 1, p 560.

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(3) (a) Jeong, N.; Hwang, S. H.; Lee, Y.; Chung, Y. K. *J. Am. Chem. Soc.* **1994**, *116*, 3159. (b) Lee, B. Y.; Chung, Y. K.; Jeong, N.; Lee, Y.; Hwang, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 8793. (c) Pagenkopf, B. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, *118*, 2285. (d) Lee, N. Y.; Chung, Y. W. *Tetrahedron Lett.* **1996**, *37*, 3145. (e) Jeong, N.; Hwang, S. H.; Lee, Y. K.; Lim, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 10549. (f) Kim, J. W.; Chung, Y. K. *Synthesis* **1998**, 142. (g) Belanger, D. B.; O'Mahony, D. J. R.; Livinghouse, T. *Tetrahedron Lett.* **1998**, *39*, 7637. (h) Belanger, D. B.; Livinghouse, T. *Tetrahedron Lett.* **1998**, *39*, 7641. (i) Sugihara, T.; Yamaguchi, M. *J. Am. Chem. Soc.* **1998**, *120*, 10782. (j) Sugihara, T.; Yamaguchi, M. *Synlett* **1998**, 1384. (k) Hayashi, M.; Hashimoto, Y.; Yamamoto, Y.; Usuki, J.; Saigo, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 631.

(4) (a) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 9450. (b) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5881.

(5) (a) Morimoto, T.; Chatani, N.; Fukumoto, Y.; Murai, S. *J. Org. Chem.* **1997**, *62*, 3762. (b) Kondo, T.; Suzuki, N.; Okada, T.; Mitsudo, T. *J. Am. Chem. Soc.* **1997**, *119*, 6187.

(6) (a) Koga, Y.; Kobayashi, T.; Narasaka, K. *Chem. Lett.* **1998**, 249. (b) Jeong, N.; Lee, S.; Sung, B. K. *Organometallics* **1998**, *17*, 3642.

(7) Stoichiometric enantioselective Pauson-Khand reactions: (a) Bladon, P.; Pauson, P. L.; Brunner, H.; Eder, R. *J. Organomet. Chem.* **1988**, *355*, 449. (b) Hay, A. M.; Kerr, W. J.; Kirk, G. G.; Milddlemiss, D. *Organometallics* **1995**, *14*, 4986. (c) Kerr, W. J.; Kirk, G. G.; Milddlemiss, D. *Synlett* **1995**, 1085.

(8) Reviews of asymmetric (including enantioselective and diastereoselective) Pauson-Khand-type reaction: (a) Ingate, S. T.; Marco-Contelles, J. *Org. Prep. Proced. Int.* **1998**, *30*, 121. (b) Buchwald, S. L.; Hicks, F. A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 491.

(9) (a) Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688. (b) Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 7026. (c) Sturla, S. J.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 5547.

(10) During the preparation of this manuscript, an asymmetric catalytic Pauson-Khand reaction was reported but ee is dependent on substituents in enynes and yield is moderate: Hiroi, K.; Watanabe, T.; Kawagishi, R.; Abe, I. *Tetrahedron Lett.* **2000**, *41*, 891.

(11) During the review process of this manuscript, a Rhodium-catalyzed enantioselective intramolecular Pauson-Khand-type reaction was reported: Jeong, N.; Sung, B. K.; Choi, Y. K. *J. Am. Chem. Soc.* **2000**, *122*, 6771.

(12) Rh(I), which is a very reactive catalyst for the Pauson-Khand-type reaction without phosphine additive (ref 6a), was used in place of Ir(I) under the same conditions ($[Rh(COD)Cl]_2$−(*S*)-tolBINAP, toluene, reflux 36h). But both yield and ee were drastitically decreased (**2** (14%, 47% ee), enyne **1** (72% recovered)).

(13) Typical experimental procedure (Table 1, Entry 4): Stirring of tolBINAP (34.3 mg, 0.051 mmol) and $[Ir(COD)Cl]_2$ (16.3 mg, 0.024 mmol) in toluene (4 mL) at 40 °C under atmospheric pressure of carbon monoxide gave a light yellow solution. After addition of a toluene solution (4 mL) of enyne **1** (83.8 mg, 0.487 mmol), the reaction mixture was refluxed for 24 h. The resulting solution was passed through a small pad of silica gel using a mixed eluent of hexane and ethyl acetate (3/1, v/v). Purification of the crude products by thin-layer chromatography of silica gel afforded pure bicyclic enone **2** (72.7 mg, 0.363 mmol, 75% yield). Ee was determined to be 91% by HPLC analysis using a chiral column.

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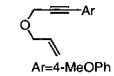
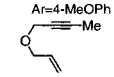
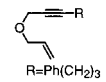
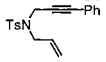
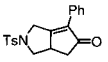
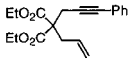
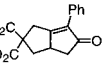
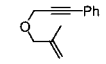
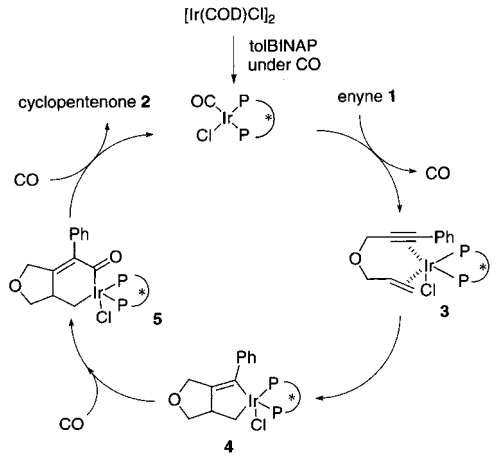
Table 2. Catalytic Enantioselective Carbonylative Coupling of Various Enynes[a]

entry	enyne	cyclopentenone	time/h	yield/%	ee/%[b]
1			20	80	96
2			20	61	98
3			48	75	97
4			20	54	90
5			24	85	95
6			36	51	88
7			72	74	84
8			24	30	88
9[c]			24	51	82

[a] Chiral catalyst: $[Ir(COD)Cl]_2$ + 2(*S*)-tolBINAP (10 mol %). The reaction was performed under atmospheric pressure of carbon monoxide in refluxed toluene, if otherwise noted. [b] Ee was determined by HPLC using Daicel chiral columns (Chiralpak AS for entries 1−3, 6 and 7, Chiralcel OD for entries 4 and 5, Chiralpak AD for enries 8 and 9. [c] The reaction was perfomed in refluxed xylene.

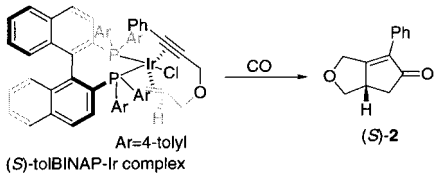
Scheme 1



1). Enynes possessing alkyl substituent on alkyne were also good substrates to give corresponding products in high ee (entries 2−4). Especially, carbonylative coupling of allyl 2-butynyl ether proceeded with almost perfect enantioselectivity (entry 2). Prolongation of the reaction time improved the yield with almost no decrease in ee (entry 3). These results imply that aromatic substituents on the alkyne are not necessary to achieve high enantioselectivity. Allylpropargyamine is also an appropriate substrate for the present enantioselective Pauson-Khand-type reaction (entry 5). The carbonylative coupling of allylpropargylmalonate took longer reaction time than that of allyl propargyl ether described above, but a high enantioselectivity was also attained (entries 6 and 7). 1,1-Disubstituted olefin is known to be a rather inactive substrate in the Pauson-Khand reaction, and a higher reaction temperature gave a better yield of a corresponding cyclopentenone possessing an asymmetric quaternary carbon (entries 8 and 9).[14]

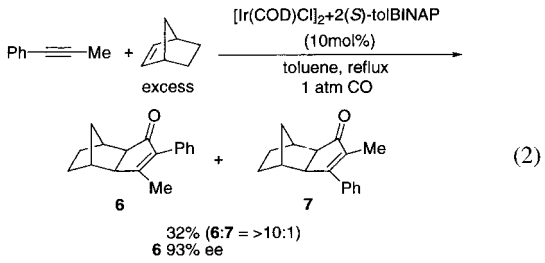
The precise mechanism of this iridium complex-catalyzed carbonylative coupling, including the structure of the actual asymmetric catalyst, is unclear; however, a plausible mechanism is depicted in Scheme 1. The selection of the enantiomeric face is determined at the formation of metallacycle **4** from **3**. Carbon monoxide is inserted between iridium and the sp^2-carbon to provide **5**.[15] Reductive elimination of iridium gives cyclopentenone **2** and regenerates the chiral iridium catalyst.

Scheme 2



Scheme 2 shows the proposed mechanism of asymmetric induction. Alkyne coordinates to iridium by placement of its substituent (phenyl for enyne **1**) at the upper side to prevent the steric hindrance to the Ar group of tolBINAP, and the alkene component is accessible from the lower side. This scheme explains the formation of bicyclic enone **2** in *S* form using (*S*)-tolBINAP.[16]

Intermolecular carbonylative coupling between 1-phenyl-1-propyne and norbornene was also examined under the same reaction conditions (eq 2). High enantioselectivity (93% ee) and



(2)

high regioselectivity (>10:1) were achieved yet in low yield.

In summary, we have developed the first iridium complex-catalyzed enantioselective Pauson-Khand-type reaction. Generally high enantioselectivity was achieved in the intra- and intermolecular carbonylative couplings to give various chiral cyclic enones. The iridium−phosphine complex has been extensively used as a (chiral) catalyst for (asymmetric) hydrogenation,[17] but has been rarely used as a catalyst for carbonylative reactions.[18] Therefore, the present results suggest a new use for the iridium−phosphine complex and provide a new and easily accessible procedure for preparing highly enantiomerically enriched cyclopentenones.

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Supporting Information Available: Listing of determination of ee by HPLC for all compounds and spectral data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Enynes possessing 1,2-disubstiuted alkene (for example, diethyl *trans*- and *cis*-1-phenyl-6-octen-1-yne-4,4-dicarboxylate) are not substrates under the same conditions. At this stage, the present asymmetric catalysis by the iridium−tolBINAP system has the same synthetic limitation as that by the titanium−EBTHI system (ref 9b).

(15) The carbonyl insertion between metal and sp^2-carbon was ascertained by characterization of the acyl metal intermediate in iron carbonyl complex-mediated carbonylative allene−alkyne coupling: Shibata, T.; Koga, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 911.

(16) In the Ir(I)−tolBINAP system, the substituent on alkyne might play one of the key roles in high enantioselectivity. In fact enynes possessing terminal alkyne (for example, *N*-allyl-*N*-(1,1-dimethyl-2-propynyl)benzylamine) were also catalyzed but in low ee (<20%). On the contrary, in the $Co_2(CO)_8$−(*S*)-BINAP system, only terminal alkynes show high enantioselectivity to give bicyclic enones in the *R* form, which is opposite the enantioface selectivity for the Ir(I)−tolBINAP system (ref 10). These results suggest that enantioselectivity is induced by the different mechanism between iridium and cobalt systems.

(17) Recent reviews of asymmetric hydrogenation of carbonyl groups and imino groups: (a) Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, p 199. (b) Blaser, H.-U.; Spindler, F. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, p 247.

(18) For the only example of the iridium-catalyzed carbonylative reaction as far as we know, see: Murakami, M.; Itami, K.; Ubukata, M.; Tsuji, I.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 4.