Rhodium-Catalyzed Asymmetric Pauson–Khand Reaction Using Monophosphoramidite Ligand SIPHOS

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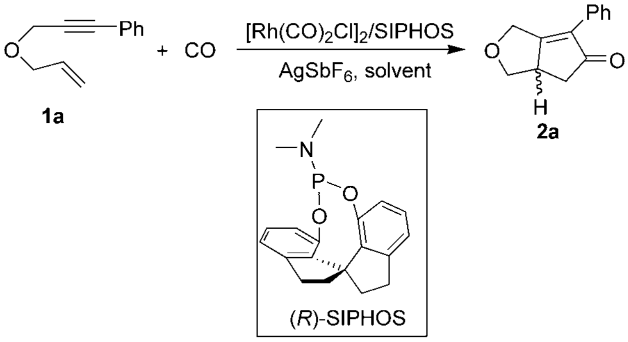
Abstract: A novel rhodium-catalyzed asymmetric intramolecular Pauson–Khand reaction using a chiral monophosphoramidite ligands is described. In this reaction, an *in situ* generated catalyst from $[Rh(CO)_2Cl]_2$, the spiro-monophosphoramidite ligand SIPHOS and $AgSbF_6$ was found to be effective for a series of 1,6-enynes, providing the co-cyclization products in good enantioselectivities (84% ee).

Keywords: asymmetric catalysis; 1,6-enynes; monophosphoramidites; Pauson–Khand reaction; P ligands; rhodium

Since its discovery in the early 1970 s,[1] the carbonylative co-cyclization of an alkyne and an alkene to a cyclopentenone, known as the Pauson–Khand reaction, has been recognized as one of the most important methodologies to synthesize cyclopentenone derivatives or cyclopentane-containing natural products.[2] Progress in recent years has shown that a catalytic asymmetric version of the Pauson–Khand reaction can be achieved by using chiral transition metal catalysts.[3] In 1996, Buchwald and Hicks reported the first example of an asymmetric Pauson–Khand reaction catalyzed by chiral titanocene complex.[4] With the chiral titanocene catalyst, (*S,S*)-(EBTHI)Ti$(CO)_2$, a variety of 1,6-enynes were converted to the corresponding cyclopentenones in high yields and high enantiomeric purities. Later, Hiroi compared different chiral bidentate phosphine ligands in the Co-catalyzed asymmetric Pauson–Khand reaction, and found that the BINAP ligands provided the highest level of enantiocontrol with moderate yields.[5] Shibata and Takagi developed a chiral iridium complex system for the intra- and intermolecular carbonylative cyclization of alkynes and alkenes to give various chiral cyclic enones.[6] In this Ir-catalytic system, the BINAP ligands were also shown to be highly enantioselective. Jeong and co-workers reported an asymmetric rhodium-catalyzed Pauson–Khand reaction using BINAP as chiral ligands to provide the cyclization products in good enantiomeric excesses.[7] However, in all of these catalytic asymmetric systems, the good enantioselectivities were only possible by using bidentate phosphorus ligands, especially the BINAP ligands.[8]

It is of practical significance that monodentate phosphorus ligands are less expensive and more readily available than most bidentate ligands. Recently, we have developed a new type of chiral spiro-monophosphoramidite ligands, SIPHOS, based on a chiral 1,1′-spirobiindane scaffold and found they were highly efficient for the Rh-catalyzed asymmetric hydrogenation of enamides and dehydroamino acid derivatives,[9] the Cu-catalyzed 1,4-addition of dialkylzincs to enones,[10] as well as the Pd-catalyzed hydrosilylation of styrenes.[11] Encouraged by the highly efficiency of SIPHOS ligands in these catalytic asymmetric reactions, we wanted to establish a new Rh-catalyzed asymmetric Pauson–Khand reaction using monophosphoramidite ligands to replace diphosphorus ligands, such as BINAP.

Towards this end, we firstly synthesized a series of 1,6-enynes linked with ether, amine, or diester units according to literature methods,[12] and selected allyl 3-phenylprop-2-ynyl ether (**1a**) as the standard substrate. The primary experiments were performed under 1 atm CO in refluxing 1,2-dichloroethane (DCE) at 90 °C. The catalyst was generated *in situ* from $[Rh(CO)_2Cl]_2$ (6 mol %



Scheme 1. Rhodium-catalyzed enantioselective Pauson–Khand reaction using (*R*)-SIPHOS.

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of Rh) and (R)-SIPHOS (13.2 mol %), and activated by $AgSbF_6$ at room temperature for 30 min. Allyl 3-phenylprop-2-ynyl ether (**1a**) was then added to co-cyclize with CO at 90 °C for 3 h, providing chiral 2-phenyl-7-oxabicyclo[3.3.0]oct-1-en-3-one (**2a**) in moderate yield (56%) with 84% ee (Table 1, entry 1). This result showed that use of monophosphoramidite ligands in the Rh-catalyzed asymmetric Pauson–Khand reaction could afford good enantioselectivity. A further investigation on the solvent effect showed that the enantioselectivity decreased when the reaction was carried out in coordinating solvents like THF, EtOAc, 1,2-dimethoxyethane (DME) and dioxane and in the aromatic solvent toluene. The effect of the ligand structure on the reaction was vital. When the alkyl groups on the nitrogen atom in the SIPHOS ligand were changed to isopropyl and 1-phenylethyl, the product **2a** was isolated in only 18% yield (13% ee) and a trace amount, respectively (entries 9, 10 and 11). This indicated that a smaller amino group was favorable for obtaining a high yield and a high enantioselectivity, which is similar to the behavior of SIPHOS ligands in the rhodium-catalyzed hydrogenation of functionalized olefins.[9b] When the ratio of ligand to Rh was reduced to 1:1, both the yield of product and the enantioselectivity of the reaction decreased (26% yield, 25% ee) (entry 8).

The Rh-catalyzed Pauson–Khand reaction of enyne **1a** was very sensitive to the reaction temperature. The optimal reaction temperature was found to be 90 °C. The reactions carried out at 85 °C or 110 °C gave cyclization products in lower yield and lower enantioselectivity (Table 2, entries 1 and 2 *vs.* entry 3). The SbF_6^- was the best choice of anion although other anions such as PF_6^-, OTf^- and BF_4^- also could be used (entries 3–6). Increasing the catalyst loading to 10 mol % accelerated the reaction rate, but slightly decreased the enantioselectivity of the reaction (entry 7). However, lowering the catalyst loading to 3 mol % reduced the reaction rate (entry 8).

At the optimal reaction conditions, a variety of 1,6-enynes were converted to the corresponding bicyclic pentenones. The results are summarized in Table 3. In the reaction of ether-linked enynes, the electronic effect of substituent on the phenyl group at the alkyne terminal was examined. It was found that the substrates with an electron-donating group had similar enantioselectivities, but lower yields (entries 2–4 *vs.* entry 1). However, the substrates with an electron-withdrawing group gave higher yields at the expense of the enantioselectivities (entries 5–7). Amine-linked and diester-linked 1,6-enynes could also serve as substrates for Pauson–Khand reaction under the same reaction conditions. The yields

Table 2. Effects of temperature, anion of catalyst and catalyst loading in the Pauson–Khand reaction of **1a**.[a]

Entry	Anion	Temp. [°C]	Time [h]	Yield [%]	ee [%]
1	SbF_6^-	85	8	47	79
2	SbF_6^-	110	3	40	68
3	SbF_6^-	90	3	56	84
4	PF_6^-	90	15	36	72
5	OTf^-	90	11	56	68
6	BF_4^-	90	15	42	74
7[b]	SbF_6^-	90	1	55	81
8[c]	SbF_6^-	90	11	42	81

[a] Reaction conditions, see Table 1.

[b] 5 mol % $[Rh(CO)_2Cl]_2$, 22 mol % (R)-SIPHOS, 20 mol % Ag^+.

[c] 1.5 mol % $[Rh(CO)_2Cl]_2$, 6.6 mol % (R)-SIPHOS, 6 mol % Ag^+.

Table 1. Effect of solvent, ligand structure and Rh-to-ligand ratio in Pauson–Khand reaction of compound **1a**.[a]

Entry	Ligand	Solvent	Temp. [°C][b]	Time [h][c]	Yield [%][d]	ee [%][e]
1	(R)-SIPHOS	DCE	90	3	56	84
2	(R)-SIPHOS	THF	90	15	56	68
3	(R)-SIPHOS	EtOAc	90	15	50	63
4	(R)-SIPHOS	DME	100	3	68	66
5	(R)-SIPHOS	Toluene	120	2.5	68	63
6	(R)-SIPHOS	Dioxane	120	8	53	56
7	(R)-SIPHOS	DCE/DME (4:1)	90	4	68	72
8[f]	(R)-SIPHOS	DCE	90	8	26	25
9	(R)-SIPHOS-Pr-*i*	DCE	90	7	18	13
10[g]	(R,S,S)-SIPHOS-PE	DCE	90	9	trace	/
11[g]	(R,R,R)-SIPHOS-PE	DCE	90	9	trace	/

[a] 3 mol % $[Rh(CO)_2Cl]_2$, 13.2 mol % (R)-SIPHOS, 12 mol % $AgSbF_6$, 1 atm CO, 6 mL solvent.

[b] Oil bath temperature.

[c] The time at which starting material was completely consumed.

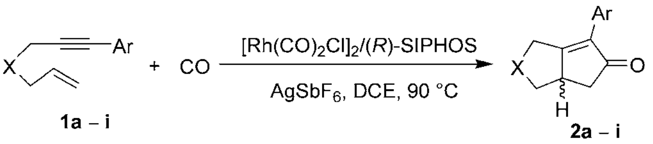
[d] Yield of product isolated by column chromatography.

[e] Determined by chiral HPLC using a Daicel Chiralpak AD-H column.

[f] 3 mol % $[Rh(CO)_2Cl]_2$, 7.2 mol % (R)-SIPHOS.

[g] Substrate was recovered.

Table 3. Asymmetric Pauson–Khand reactions of 1,6-enynes.[a]



Entry	X	Ar	Time [h]	Yield [%]	ee [%][b]
1	O	Ph (**1a**)	3	56	84 (+)
2	O	4-CH_3Ph (**1b**)	2	44	80 (+)
3	O	4-CH_3OPh (**1c**)	7.5	37	82 (+)
4	O	3,5-diCH_3Ph (**1d**)	7.5	28	81 (+)
5	O	4-CF_3Ph (**1e**)	2.5	46	77 (+)
6	O	3,5-diCF_3Ph (**1f**)	2.5	41	75 (+)
7	O	4-NO_2Ph (**1 g**)	7.5	62	56 (−)
8	TsN	Ph (**1 h**)	7.5	58	62 (+)
9	$(EtO_2C)_2C$	Ph (**1i**)	9	73	47 (−)

[a] Reaction conditions, see Table 1.

[b] Determined by HPLC using a chiral column (Daicel Chiralpak AD-H column for entries 1, 8 and 9; Chiralpak AS column for entries 2–7).

were relatively high, but the enantiomeric excesses of the products were not very good (entries 8 and 9).

In conclusion, the SIPHOS ligands were proven to be efficient for the enantioselective rhodium-catalyzed intramolecular Pauson–Khand reaction. This finding indicated that monodentate chiral phosphorus ligands, especially monophosphoramidites, have a potential application in the control of enantioselectivity in the catalytic Pauson–Khand reaction, in which only the bidentate chiral ligands were previously reported to be successful.

Experimental Section

Typical Procedure for Rhodium-Catalyzed Asymmetric Intramolecular Pauson–Khand Reaction

A mixture of $[Rh(CO)_2Cl]_2$ (2.5 mg, 6.4×10^{-3} mol) and (*R*)-SIPHOS (9.2 mg, 28.3×10^{-3} mol) in 6 mL DCE was stirred under argon at 45 °C for 4.5 h. After cooling to room temperature, the solution was transferred into a 10 mL two-necked round-bottomed flask charged with $AgSbF_6$ (9.0 mg, 26.2×10^{-3} mol) and equipped with a reflux condenser. The resultant suspension was stirred at room temperature for 30 min and the inert atmosphere was replaced by three CO/release cycles. After addition of 1,6-enyne **1a** (37 mg, 0.215 mmol), the reaction mixture was heated at 90 °C for 3 h with bubbling CO gas. After being cooled, the reaction mixture was concentrated and purified by column chromatography on silica gel eluting with petroleum ether/EtOAc (3:1) to give the product **2a** as a colorless oil; yield: 24 mg (56%). ^1H NMR(400 MHz, $CDCl_3$): $\delta=$ 7.51–7.33 (m, 5H), 4.92 (d, $J=15.6$ Hz, 1H), 4.57 (d, $J=16.4$ Hz, 1H), 4.35 (t, $J=7.2$ Hz, 1H), 3.29 (s, br, 1H), 3.21 (dd, $J=6.8$, 10.8 Hz,1H), 2.82 (dd, $J=6.0$, 18.0 Hz, 1H), 2.32 (dd, $J=2.8$, 16.8 Hz, 1H); ^{13}C NMR(100 MHz, $CDCl_3$): $\delta=$ 207.2, 177.7, 134.9, 130.8, 128.8, 128.2, 71.6, 66.5, 43.5, 40.5. The ee value of the product was determined by chiral HPLC (Daicel Chiralpak AD-H column; 25 cm × 0.46 cm, 2-propanol/hexane, 20:80, 0.9 mL/min) $t_R=9.4$ min for minor isomer and $t_R=11.4$ min for major isomer.

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