DOI: 10.1002/adsc.200505105

Rhodium-BisbenzodioxanPhos Complex-Catalyzed Homogeneous Enantioselective Pauson–Khand-Type Cyclization in Alcoholic Solvents

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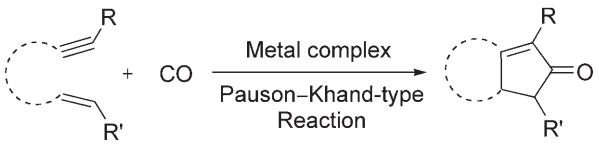
Received: March 11, 2005; Accepted: June 13, 2005

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: The chiral atropisomeric diphosphane ligand (*S*)-BisbenzodioxanPhos was found to be highly effective in the co-operative processeses of aldehyde decarbonylation and cascaded enantioselective Pauson–Khand-type reactions. Various 1,6-enynes were transformed to the corresponding bicyclic cyclopentenones in good yields and enantiomeric excesses (up to 96% ee). The attractive feature of this new Rh-catalyzed homogeneous dual catalysis system is that the reaction can be performed in alcoholic solution.

Keywords: asymmetric synthesis; cyclization; homogeneous catalysis; Pauson–Khand-type reaction; phosphane ligands; rhodium

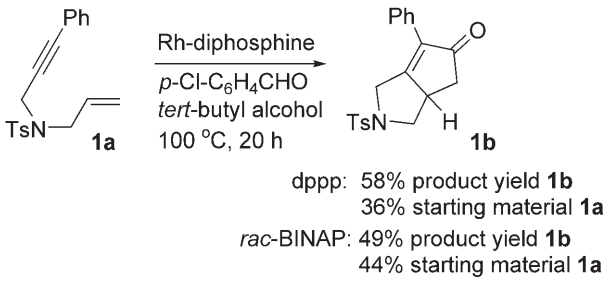
The stoichiometric cobalt-mediated [2+2+1]cyclization of an alkyne, alkene and carbon monoxide was initially developed by Pauson and Khand in early 1970s.[1] This transition metal-mediated/catalyzed metathesis represented one of the most powerful protocols for the preparation of pharmaceutically attractive cyclopentenones (Scheme 1).[2,3]



Scheme 1.

Recently, significant improvements of this cyclization has been achieved in the catalytic Pauson–Khand-type reaction (PKR);[4] the enantioselective versions of this reaction catalyzed by Co,[5] Ti,[6] Rh[7] and Ir complexes[8] are of high interest. Although major improvements have been achieved, the use of highly toxic gaseous carbon monoxide signifies a drawback to these procedures. A scientifically interesting alternative to this reaction is to use a non-toxic source of "carbon monoxide". Hence, the catalytic decarbonylation[9] of carbonyl compounds (e.g., aldehydes) as the CO surrogate is an attractive protocol for this reaction.[10,11] This alternative, which was elegantly described by two independent research groups (Kakiuchi/Morimoto[10d] and Shibata[11a]) recently, offers us a convenient "carbon monoxide" reagent for asymmetric carbonylation reactions. The desirable feature for an attractive chemical reaction is the operational simplicity, particularly under solvent-less reaction conditions or with the aid of a relatively non-toxic solvent medium.[12] Recently, Shibata and co-workers used aldehyde as both CO source as well as the solvent medium in asymmetric PKR with good ees.[11] However, no successful *homogeneous* catalytic asymmetric PKR systems that enable the use of relatively less toxic alcoholic solvents have been reported yet. Herein, we report an efficient homogeneous dual catalysis under alcoholic solvent medium. This interesting system utilized the same chiral Rh-BisbenzodioxanPhos complex for both catalytic decarbonylation of the aldehyde and the cascade asymmetric Pauson–Khand-type cyclization at the same time.

The feasibility of the Rh-catalyzed decarbonylation of aldehydes under alcoholic solvents was examined in our initial studies. The reaction of enyne **1a** and *p*-chloro-



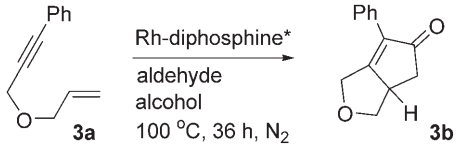
Scheme 2.

benzaldehyde in the presence of catalytic amounts of $[Rh(COD)Cl]_2$ and dppp (or *rac*-BINAP)[13] in *tert*-butyl alcohol at 100 °C for 20 hours afforded the desired cyclopentenone **1b** in 58% yield according to GC analysis, along with 36% of unreacted **1a** (Scheme 2).

These promising preliminary results showed the potential of catalytic decarbonylation in alcoholic medium. Our aim was not only focused on decarbonylation and carbonylative cyclization, but also targeted on the enantioselective version of this dual catalysis. For this reason, chiral diphosphane ligands were tested while oxygen-tethered enyne **3a** was chosen as the prototypical substrate for further optimization of other reaction parameters (Table 1).

The axially chiral (*S*)-BINAP ligand gave moderate yield and enantioselectivity of the PKR product (Table 1, entry 1). In contrast, (*S*)-BisbenzodioxanPhos, which was reported by us[14] and later independently reported by Genêt and co-workers,[15] was found to be superior in this cascade dual catalysis (catalytic decarbonylation and asymmetric PKR) (Table 1, entry 1 *vs.* 2). Presumably, the unique dihedral angle and bite angle of BisbenzodioxanPhos (and its metal complex) played an important role in this reaction.[16] In addition, we found that (*S*)-BisbenzodioxanPhos provided a better solubility in alcoholic medium in comparison to BINAP. This additional factor likely contributed to the better result in the homogeneous catalytic reaction. Branched alcoholic solvents gave higher yields of the product and *tert*-amyl alcohol was found to be the best choice of solvent (Table 1, entries 2–4). Unpurified bench grade (4-L bottle) *tert*-amyl alcohol solvent gave the same good results as those obtained from using a purified solvent. In order to increase the efficiency of the newly developed Rh-BisbenzodioxanPhos system, we examined different aldehydes as the CO surrogates. The electrochemical nature of aromatic aldehydes was found to be responsible for both CO-transfer catalysis and asymmetric carbonylative cyclization (Table 1, entries 3, 5 and 6). Electron-poor *p*-chlorobenzaldehyde provided the CO moiety more effectively than the electron-rich *p*-methoxybenzaldehyde. α,β-Unsaturated aldehydes gave the best results in terms of both yield and enantioselectivity (Table 1, entry 8). Although the decarbonylation of aliphatic aldehydes was observed, the efficiency was inferior to that found in aromatic aldehydes (Ta-

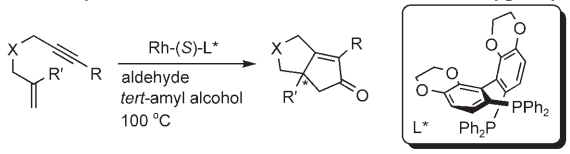
Table 1. Effects of ligand, solvent and aldehyde in enantioselective Pauson–Khand-type reaction in alcoholic medium.[a]

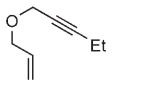
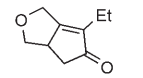
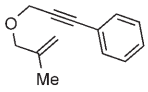
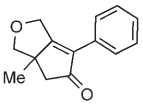
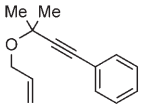
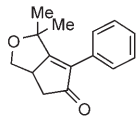
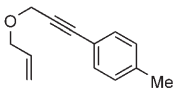
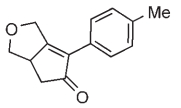
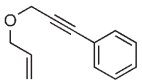
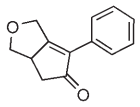
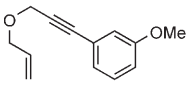
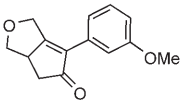
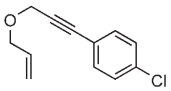
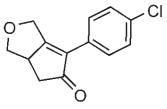
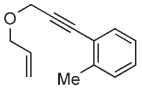
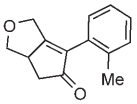


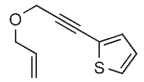
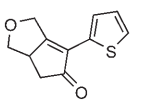
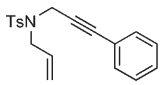
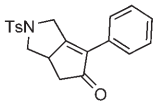
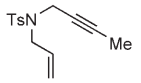
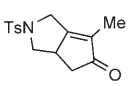
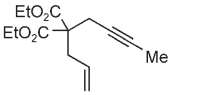
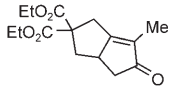
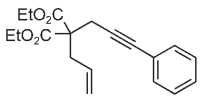
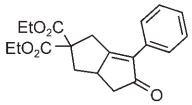
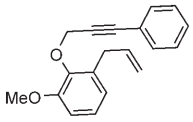
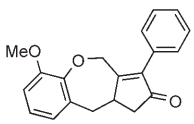
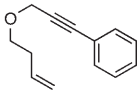
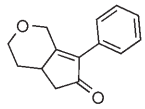
Entry	Ligand	Aldehyde	Solvent	Yield [%][b]	ee[c]
1	(*S*)-BINAP	benzaldehyde	*tert*-butyl alcohol	22	67
2	(*S*)-BisbenzodioxanPhos	benzaldehyde	*tert*-butyl alcohol	58	81
3	(*S*)-BisbenzodioxanPhos	benzaldehyde	*tert*-amyl alcohol	70	86
4	(*S*)-BisbenzodioxanPhos	benzaldehyde	*n*-butyl alcohol	44	79
5	(*S*)-BisbenzodioxanPhos	*p*-MeO-benzaldehyde	*tert*-amyl alcohol	12	33
6	(*S*)-BisbenzodioxanPhos	*p*-Cl-benzaldehyde	*tert*-amyl alcohol	72	80
7	(*S*)-BisbenzodioxanPhos	*n*-nonyl aldehyde	*tert*-amyl alcohol	39	77
8	(*S*)-BisbenzodioxanPhos	cinnamaldehyde	*tert*-amyl alcohol	81	85
9	(*S*)-BINAP	cinnamaldehyde	*tert*-amyl alcohol	49	73
10	(*S*)-tol-BINAP	cinnamaldehyde	*tert*-amyl alcohol	66	78
11[d]	(*S*)-P-Phos	cinnamaldehyde	*tert*-amyl alcohol	79	84
12[e]	(*R*,*R*)-Et-DuPhos	cinnamaldehyde	*tert*-amyl alcohol	5	n.d.

[a] Reaction conditions: $[Rh(COD)Cl]_2$ (3 mol %), ligand (6 mol %), enyne (0.3 mmol), aldehyde (0.45 mmol) and magnetic stirrer-bar were charged to a screw-capped vial at room temperature. Unpurified solvent (0.2 mL, 1.5 M, prior bubbled with nitrogen for 2 min) was added under nitrogen and the reaction mixture was stirred at 100 °C for 36 hours.
[b] Yield of isolated product.
[c] Average of two runs from chiral HPLC analysis using Daicel Chiralcel® AD-H columns (0.46 cm × 25 cm).
[d] (*S*)-P-Phos: (*S*)-2,2′,6,6′-tetramethoxy-4,4′-bis(diphenylphosphano)-3,3′-bipyridine.
[e] (*R*,*R*)-Et-DuPhos: (−)-1,2-bis((2*R*,5*R*)-2,5-diethylphospholano)benzene.

Table 2. Rh-BisbenzodioxanPhos-catalyzed enantioselective Pauson–Khand-type cyclizations in *tert*-amyl alcohol.[a]



Entry	Substrate	Product	Yield [%][b]	ee [%][c]
1			61	96
2			69	91
3			78	91
4			83	89
5			81	85
6			79	70
7			72	49
8			78	84

Entry	Substrate	Product	Yield [%][b]	ee [%][c]
9			trace	n.d.
10			94	80
11			97	88
12			90	77
13			91	69
14			trace	n.d.
15			trace	n.d.

[a] Reaction conditions: [Rh(COD)Cl]$_2$ (3 mol %), (*S*)-BisbenzodioxanPhos (6 mol %), enyne (0.3 mmol), cinnamaldehyde (0.45 mmol) and magnetic stirrer-bar were charged to a screw-capped vial at room temperature. Unpurified *tert*-amyl alcohol (0.2 mL, 1.5 M, prior bubbled with nitrogen for 2 min) was added under N_2 and the reaction mixture was stirred at 100 °C for 36 h.

[b] Yield of isolated product.

[c] Determined by chiral HPLC analysis using Daicel Chiralcel® AD-H, AS-H, OD-H columns (0.46 cm × 25 cm).

ble 1, entry 7). The effectiveness of some commercially available chiral ligands was also studied. (*S*)-BisbenzodioxanPhos was found to be the ligand of choice from our preliminary results (Table 1, entries 8–12).

To further probe the effectiveness of the Rh-BisbenzodioxanPhos system, we examined various oxygen-tethered 1,6-enynes for the enantioselective PKR (Table 2). Alkyl-substituted alkynes gave excellent enantioselectivities (96% ee) of the corresponding products (Table 2, entry 1). The enyne with a 1,1-disubstituted alkene reacted smoothly to give the chiral quaternary carbon center bicyclic cyclopentenone in high enantioselectivity (Table 2, entry 2). Various new aromatic enynes, which possessed different electronic properties, were prepared and subjected to carbonylative cyclizations (Table 2, entries 3–8). Interestingly, the electronic influence of the substrate was found to be responsible for the enantioselectivity of the product. The electron-donating aromatic enynes gave higher enantioselectivity of the product while enynes with electron-withdrawing substituents afforded relatively lower ees of the bicyclic cyclopentenones (Table 2, entries 3–7). A sterically hindered *ortho*-substituted enyne also gave a high ee value of the corresponding cycloadduct (Table 2, entry 8). The transformation of the heterocyclic thiophenyl-substituted enyne to the corresponding cyclopente-

none was found to be unsuccessful (Table 2, entry 9), probably due to the coordination of the thiophene moiety to the metal center which rendered the metal complex coordinatively saturated.

These reaction conditions were also used to explore other nitrogen- and carbon-tethered enynes (Table 2, entries 10–13). Excellent isolated yields were obtained and high ee values were observed either in N- or C-tethered substrates with alkyl substitution (instead of a phenyl group) (Table 2, entries 10–13).

In summary, we have developed an interesting homogeneous system for the efficient decarbonylation and cascaded asymmetric Pauson–Khand-type cyclizations in a relatively non-toxic alcoholic medium. In the presence of the axially chiral (*S*)-BisbenzodioxanPhos ligand, O-, N- and C-tethered cyclopentenones were obtained with good to excellent ees in this cooperative dual catalysis. Interestingly, the electronic influence of the substrate was found to be responsible for the enantioselectivity of the product.

Experimental Section

General Procedures for Asymmetric Pauson–Khand-type Cyclization of Various Enynes

$[Rh(COD)Cl]_2$ (4.4 mg, 9.0 μmol), (*S*)-BisBenzodioxanPhos (11.5 mg, 18.0 μmol), aldehyde (0.45 mmol, 1.5 equivs. with respected to enyne) and Teflon-coated magnetic stirrer bar (3 mm × 10 mm) were charged to a Teflon-lined screw-capped vial on the bench-top at room temperature with continuous stirring. The enyne (0.3 mmol) was then added. These vials were evacuated and backfilled with nitrogen (3 cycles), followed by the addition of unpurified *tert*-amyl alcohol (0.2 mL, 1.5 M, from bench grade 4-L bottle, prior bubbled with nitrogen for 2 min). The reaction mixtures were magnetically stirred in a preheated 100 °C (±3 °C) oil bath for 36 hours (reaction times were unoptimized for each substrate). The vials were allowed to reach room temperature. Diethyl ether or ethyl acetate (~2 mL) was added. The crude reaction mixtures were directly purified by column chromatography on silica gel using hexane/ethyl acetate mixture as the eluent to afford the chiral bicyclic cyclopentenones. The enantiomeric excess of the products were determined by chiral HPLC analysis using Chiralcel® columns.

See Supporting Information for the preparation of enyne substrates, detailed characterization data and chiral HPLC conditions for the optically active cyclopentenones.

Acknowledgements

We thank the University Grants Committee Areas of Excellence Scheme in Hong Kong (Project No. AoE/P-10/01) and The Hong Kong Polytechnic University Area of Strategic Development Fund for financial support of this study. We thank Miss Yi Sha Cheng for her initial preparation of some enyne substrate precursors.

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