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Tetrahedron Letters 45 (2004) 9163–9166

Tetrahedron Letters

Catalytic asymmetric Pauson–Khand-type reactions of enynes with formaldehyde in aqueous media

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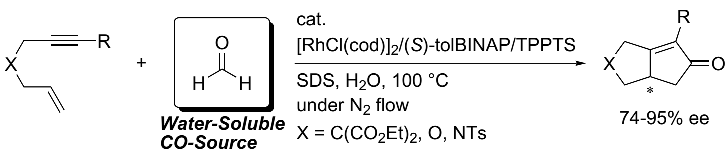
Received 17 September 2004; revised 18 October 2004; accepted 20 October 2004

Abstract—The first example of an aqueous, asymmetric, and CO gas-free Pauson–Khand-type reaction is described. Using formaldehyde as a commercially available substitute for carbon monoxide, combined use of a hydrophilic phosphine (TPPTS) and a hydrophobic, chiral phosphine (tolBINAP) enable the reaction to proceed smoothly in aqueous media, even in the absence of carbon monoxide, and stereoselectively.

The transition metal-catalyzed cyclocarbonylation of enynes with carbon monoxide, the so-called the Pauson–Khand-type reaction, has been recognized as an excellent tool for the direct construction of bicyclic cyclopentenones.[1] In the past decade, this catalytic transformation has evolved rapidly; (i) asymmetric,[2] (ii) aqueous,[3] and (iii) CO gas-free[4] variants have been successively developed. In particular, the catalytic CO gas-free methods, in which an aldehyde and a formate are used as a substitute for gaseous carbon monoxide, provide more accessibility to synthetic chemists.

Here we report on a catalytic aqueous asymmetric Pauson–Khand-type reaction of enynes using formaldehyde as a commercially available substitute for carbon monoxide.[5] This method can utilize simply the readily available chiral tolBINAP, without the need to develop any new water-soluble chiral ligand (Eq. 1). We previously reported on aqueous Pauson–Khand-type reactions of enynes with formaldehyde.[3d] The substitution of carbon monoxide by the easily handled formaldehyde (formalin), made the Pauson–Khand-type reaction experimentally accessible, from an experimental standpoint. In catalysis, the simultaneous use of a hydrophilic phosphine and a hydrophobic phosphine led to the highly efficient transformation of enynes to bicyclic cyclopentenones. According to our previous report, the first attempt at an asymmetric Pauson–Khand-type reaction of enyne **1** with formaldehyde was conducted in the presence of a catalytic amount of $[RhCl(cod)]_2$ (5 mol%), (*S*)-tolBINAP[6] (10 mol%), TPPTS (10 mol%) in aqueous media to give the carbonylated product (*S*)-**2** in 61% yield and 84% ee (Table 1, entry 1). Under otherwise similar conditions, additional chiral phosphines were examined. (*S*,*S*)-BDPP, which is characterized as a structurally analogous ligand of dppp, showed a lower catalytic activity with almost no enantioselectivity (entry 2). Similarly, no results that were



(1)

Keywords: Pauson–Khand; Asymmetric catalysis; Enynes; Formaldehyde.

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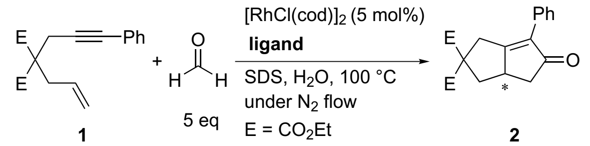
doi:10.1016/j.tetlet.2004.10.100

superior to that of (*S*)-tolBINAP were obtained for (*S*,*S*)-DIOP and (*S*,*S*)-Me-DuPHOS (entries 3 and 4). In the case of a reaction attempted using (*S*,*S*)-CHIRAPHOS, no catalytic activity was observed (entry 5). Regarding Rh-catalyzed asymmetric Pauson–Khand-type reactions already reported,[2e,g,i,l] (*S*)-tolBINAP, which has a BINAP framework, was the ligand of choice.

Table 1. Asymmetric catalytic Pauson–Khand-type reaction of enyne **1** using formaldehyde in aqueous media[a]



Entry	Ligand (mol%)	Time (h)	Yield of **2**[b] (%)	Ee[c] (%)
1	(*S*)-tolBINAP(10) TPPTS(10)	5	57	85
2	(*S*,*S*)-BDPP(10) TPPTS(10)	7	35	1
3	(*S*,*S*)-DIOP(10) TPPTS(10)	10	33	17
4	(*S*,*S*)-Me-DuPHOS(10) TPPTS(10)	10	17	6
5	(*S*,*S*)-CHIRAPHOS(10) TPPTS(10)	10	0	0
6	(*S*)-tolBINAP(10) TPPTS(5)	5	61	84
7	(*S*)-tolBINAP(10) TPPTS(15)	6	66	86
8	(*S*)-tolBINAP(10) TPPTS(20)	12	52	87
9[d]	(*S*)-tolBINAP(10) TPPTS(15)	6	70	80
10[e]		**6**	**83**	**81**

[a] Conditions: **1** (0.25 mmol), 37% formalin (0.1 ml), SDS (0.5 mmol) and H_2O (1.9 ml) at 100 °C under N_2 flow.

[b] Isolated yield. Values in parentheses are the yield of **1** recovered.

[c] Determined by HPLC analysis with chiral stationary columns.

[d] The reaction was carried out using 0.1 equiv of SOS.

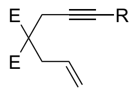
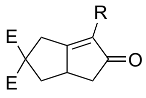
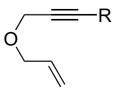
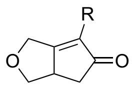
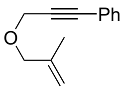
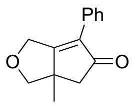
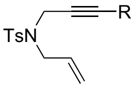
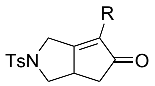
[e] The reaction was carried out using 0.5 equiv of SOS.

When (*S*)-tolBINAP was used as a chiral ligand, the reaction was not affected by the loading amount of TPPTS. While the enantiomeric excess of **2** remains virtually constant with variations in the amount of TPPTS from 5 to 20 mol%, a higher yield was observed for the combined use of 15 mol% TPPTS and 10 mol% tolBINAP (entries 6–8).

Use of SOS (sodium octadecylsulfate), in place of SDS, also allowed the reaction to proceed, resulting in an increase in the yield of **2** without any significant loss of ee (entries 9 and 10).[7] Because tolBINAP is apparently bulkier than dppp, a rhodium, a phosphine, and an enyne could be assembled more effectively in aqueous media to form an appropriate intermediate. This can be realized by adding a surfactant having a longer hydrophobic chain. An explanation for the effect of the surfactant at this point, would be speculative.[8] A more definitive answer awaits further mechanistic studies as well as the elucidation of the morphology of the reagents in the system employed here.

Some results of reactions of various enynes are shown in Table 2. Using the above conditions, most of the reactions proceeded to completion within 6 h to give the desired bicyclic cyclopentenones with high enantioselectivity. The detailed reaction conditions such as the amount of added formalin and surfactant were dependent upon the substrate. When a cationic rhodium complex $[Rh(cod)_2]BF_4$ was used as catalyst, the yield and enantioselectivity were similar to that for $[RhCl(cod)]_2$ (76% yield and 82% ee) (entry 2). Reactions of enynes in which the phenyl group in **1** is replaced by a butyl

Table 2. Asymmetric cyclocarbonylation of various enynes with formaldehyde in aqueous media[a]

Entry	Enyne	HCHO[b]	SOS	Time (h)	Product	Ee (isolated yield)[c]
1		5	0.5	6		R = Ph: 81%ee (83%)
2[d]		5	0.1	6		R = Ph: 74%ee (76%)
3		5	0.5	8		R = Bu: 87%ee (62%)
4		10	0.5	6		R = Me: 91%ee (47%)
5		5	0.5	6		R = H: — (0%)
6		20	1.0	1		R = Ph: 93%ee (61%)
7		10	2.0	3		R = Bu: 95%ee (75%)
8		10	1.0	5		94%ee (73%)
9		10	1.0	1		R = Ph: 91%ee (58%)
10		10	2.0	3		R = Bu: 92%ee (60%)

[a] Conditions: enyne (0.25 mmol), $[RhCl(cod)]_2$ (0.0125 mmol), (*S*)-tolBINAP (0.025 mmol), TPPTS (0.025 mmol), SOS and H_2O at 100 °C under N_2 flow.

[b] Formalin (37%) was used.

[c] Determined by HPLC analysis with chiral stationary columns.

[d] $[Rh(cod)_2]BF_4$ was used in place of $[RhCl(cod)]_2$.

or a methyl group also resulted in the formation of carbonylated products in high yield and ee (entries 3 and 4). An attempt to carbonylate the enyne unsubstituted at the acetylenic terminus resulted in a smooth consumption of the enyne to give a complex mixture of many unidentified products (entry 5). Substrates tethered by oxygen also gave the corresponding bicyclic cyclopentenones with high enantioselectivities (entries 6 and 7). This asymmetric method was tolerant to a substrate that contained 1,1-disubstituted olefins (entry 8). Allylpropargylamines were also carbonylated in high enantiomeric excess (entries 9 and 10). Compared with the methods using carbon monoxide, although the high enantioselectivities equal to or more than conventional ones are achieved, some decreases of the chemical yields were observed. According to Jeong's report, there is a trade-off between the chemical yield and enantioselectivity of the carbonylated product in Rh(I)-catalyzed asymmetric Pauson–Khand-type reaction of enynes with carbon monoxide; under lower pressure (less amount) of carbon monoxide, higher enantioselectivity would be obtained.[2e] The present carbonylation system should be almost equal to the reaction in which only 1 equiv of carbon monoxide is introduced.[9] Therefore, the higher level of the enantioselectivity of the product might be obtained at the cost of the chemical yield.

In conclusion, we report herein on the first aqueous, asymmetric, and CO gas-free Pauson–Khand-type reaction. The combined use of a hydrophilic phosphine (TPPTS) and a hydrophobic, chiral phosphine ((*S*)-tolBINAP) enables the reaction to proceed smoothly in aqueous media, even in the absence of carbon monoxide, and stereoselectively. In the asymmetric synthesis of bicyclic cyclopentenones, the strategy in which formaldehyde is used in aqueous media can satisfactorily replace conventional methods that use of carbon monoxide.

Acknowledgements

This work was financially supported, in part, by a Giant-in-Aid for Scientific Research (No. 15750133) and Scientific Research on Priority Area (No. 15036247, 'Reaction Control of Dynamic Complexes') form MEXT. K.F. acknowledges a JSPS Research Fellowship for Young Scientists. We also thank Ms. Yoshiko Nishikawa for assistance in obtaining HRMS spectra.

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5. Shibata et al. reported on the catalytic asymmetric Pauson–Khand-type reaction of enynes under CO gas-free conditions without any solvent (even water). They utilized more expensive cinnamaldehyde as a substitute for carbon monoxide. See Refs. 2g,i.
6. Abbreviations: tolBINAP = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl; TPPTS = triphenylphosphine-3,3′,3″-trisulfonic acid trisodium salt; (*S*,*S*)-BDPP = (2*S*,4*S*)-(−)-2,4-bis(diphenylphosphino)pentane; (*S*,*S*)-DIOP = (2*S*,3*S*)-(+)-1,4-bis(diphenylphosphino)-2,3-*O*-isopropyridene-2,3-butanediol; (*S*,*S*)-Me-DuPHOS = (+)-1,2-bis((2*S*,5*S*)-2,5-dimethylphosphino)benzene; (*S*,*S*)-CHIRAPHOS = (2*S*,3*S*)-(−)-bis(diphenylphosphino)butane; SDS = sodium dodecylsulfate; SOS = sodium octadecylsulfate.
7. *Typical procedure for the catalytic asymmetric Pauson–Khand-type reaction of enynes with formaldehyde in aqueous media (Table 1, entry 10)*: In a 5 ml two-necked flask equipped a reflux condenser were placed $[RhCl(cod)]_2$ (6.16 mg, 0.0125 mmol), (*S*)-tolBINAP (16.97 mg, 0.025 mmol), TPPTS (21.32 mg, 0.0375 mmol) and water (0.5 ml). After stirring the mixture at room temperature for 15 min, a light yellow suspension appeared. After adding SOS (46.57 mg, 0.125 mmol), formalin (0.1 ml, 1.25 mmol), enyne **1** (78.60 mg, 0.25 mmol) and water (1.4 ml) to the mixture, it was degassed, charged with N_2, and stirred at 100 °C under a stream of N_2 until **1** was consumed. The course of the reaction was monitored by TLC. Ether (10 ml) was added to the reaction mixture, and the biphasic mixture stirred for an additional 15 min. The separated aqueous layer was extracted with ether (3 × 10 ml), and the combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica-gel (eluent; hexane/AcOEt = 4/1) to give bicyclic cyclopentenone **2** (78.5 mg, 0.23 mmol) in 83% yield as a colorless oil. The ee was determined to be 81% by HPLC analysis using chiral column (Daicel Chiralpak AS: 4 × 250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane. Flow rate: 1.0 ml/min, retention time: 9 min for the major isomer and 14 min for the minor isomer). $[\alpha]_D^{24} - 17.7$ ($c = 2.10$, $CHCl_3$). The absolute configuration of (*S*)-**2** was determined by compared of the specific rotation with that in a previous report.[2e]
8. For example, the surfactant (sodium octadecylsulfate, SOS) might form an organic (hydrophobic) field, such as a micelle or an emulsion. However, we have, at present, no

direct information concerning such a formation in the presence of the other reagents at the reaction temperature (100 °C). Refer to critical micelle concentration (CMC): for $C_{12}H_{25}OSO_3Na$ (SDS), 8.1×10^{-3} M; for $C_{16}H_{33}OSO_3Na$, 0.52×10^{-3} M (at 25 °C).

9. We and Shibata's group confirmed, independently, that the CO moiety abstracted from aldehyde by the action of the rhodium complex was utilized almost directly in the carbonylation process with negligible loss as carbon monoxide gas. See Refs. 2g,i,4a.