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Catalytic asymmetric carbonylative silylcarbocyclization of enynes

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Abstract—Rh-, Co- or Ir-promoted cyclization of 1,6-enynes in the presence of a hydrosilane and carbon monoxide leads to the selective formation of functionalized cyclic compounds. Various chiral phosphine type ligands have been used in order to obtain enantiomerically enriched carbocycles. The asymmetric process proceeded with modest enantioselectivities.

1. Introduction

Functionalized carbocycles are advanced building blocks for the preparation of medicinal intermediates and more generally the synthesis of biologically active compounds.[1] Among the various processes available to synthesize such cyclic derivatives, carbocyclization of enynes[2,3] catalyzed by transition metals appears to be an efficient and elegant method. In addition, the insertion of carbon monoxide during the cyclization process allows the formation of even more functionalized carbocycles. A well-known example of carbonylative carbocyclization is the intramolecular Pauson–Khand reaction[4] catalyzed by a large number of transition metals.[4,5] Functionalized carbocycles have also been obtained through cyclization in the presence of a reducing agent such as an hydrosilane,[3,6] which allows to generate a silyl derivative available for further synthetic modifications.

On the other hand, an interesting area in this chemistry is related to an enantioselective version of such reactions. To date, catalytic asymmetric Pauson–Khand reactions are well described with almost total enantiocontrol.[7] In contrast, to the best of our knowledge, only one report deals with the asymmetric silylcarbocyclization of enynes.[8]

Surprisingly, an asymmetric version of the tandem carbonylation–silylcarbocyclization of enynes has not been reported so far. The chiral product resulting from such a transformation is a silylated carbocycle bearing an aldehyde function. Thus, we sought to develop an asymmetric procedure for such a reaction. Here, we wish to present our results of the study of these reactions and we were especially interested in the asymmetric carbonylation/silylation/carbocyclization of 1,6-enynes to form chiral silyl (formylmethyl)cyclopentane compounds.

2. Results and discussion

After a few attempts with different 1,6-enynes like ethers and diethyl malonate derivatives, we focused on the reaction of 4,4-bis(carbethoxy)hept-6-en-1-yne **1**. Compound **1** is easily accessible from commercial allylmalonate. Compared to the other enynes studied, only a few by-products are produced during the catalytic process (see below).[9] The catalytic silylcarbocyclization of **1** carried out in the presence of dimethylphenylsilane and carbon monoxide yields a mixture of two major derivatives resulting from the silylcarbocyclization reaction [4,4-bis(carbethoxy)-1-dimethylphenylsilylmethylidene-2-methylcyclopentane **2a**] and from the carbonylative silylcarbocyclization reaction [4,4-bis(carbethoxy)-1-dimethylphenylsilylmethylidene-2-(formylmethyl)cyclopentane **2b**] (Scheme 1). As mentioned above, only a small quantity of side products is produced (<5%).

From an experimental standpoint,[10] the catalyst was generated in situ prior to the carbocyclization process

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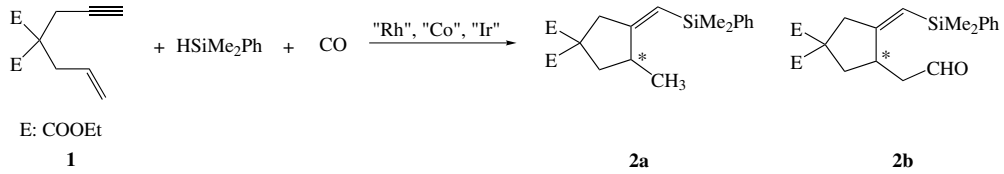


Scheme 1.

through reaction of the metallic precursor with the reducing agent and the selected ligand in the solvent used for the catalysis. After 2 h, the enyne was added followed by carbon monoxide. The catalytic reaction was performed in the conditions mentioned in the tables. Analyses of the crude reaction mixture were done by GC prior to the isolation of compound **2b** by silica gel chromatography.

We first explored several achiral catalytic systems (with and without triphenylphosphite) in order to find a way to form selectively the carbonylated derivative **2b**. The results are summarized in Table 1. The catalysts obtained by using either $Rh(acac)(CO)_2$ or $Rh_4(CO)_{12}$ in the absence or in the presence of triphenylphosphite, as reported by Ojima et al.[3] have been studied first (entries 1–8). The catalyst obtained from the cluster $Rh_4(CO)_{12}$ was much more active than that generated from the mononuclear precursor $Rh(acac)(CO)_2$. Indeed, a total conversion was obtained after 30 min in the presence of $Rh_4(CO)_{12}$ but only after 15 h for $Rh(acac)(CO)_2$. Nonetheless, the major product formed was always the noncarbonylated species **2a** in the case of the cluster $Rh_4(CO)_{12}$ whatever the CO pressure. Indeed, very high chemoselectivities were obtained with the latter (entries 5–7) even under 20 bar of CO. These results are different from those reported by Ojima on very similar systems.[3] This has been attributed to the higher substrate concentration involved in our case.[3]

While using the precatalyst $Rh(acac)(CO)_2$, the yield into derivative **2b** increased with the CO pressure, as expected (entries 1–4). A selective formation of **2b** was even obtained in the presence of triphenylphosphite (entry 4). A Rh-based cationic catalyst has also been employed (entries 9–10). At atmospheric pressure of carbon monoxide, the process was not selective. Actually, a large amount of two unidentified products was formed in such conditions (37%) (entry 9). Interestingly, under a CO pressure of 20 bar, the carbonyl compound **2b** was the major product formed. No side products were detected in such conditions but the activity of the catalyst remained quite low (entry 10).

We have also applied catalysts based on cobalt (entry 11) and iridium (entries 12–15). Such metals have been used with success in the Pauson–Khand reaction,[11] in [4 + 2] cycloaddition of dieneynes[12] and in the carbonylative alkyne–alkyne coupling.[13] In the case of dicobaltoctacarbonyl, even if the reaction is not complete after 18 h, a good chemoselectivity (90%) into the carbonyl product **2b** is reached. To our knowledge however, iridium catalysts have not been applied so far in the carbonylative silylcarbocyclization of enynes. As reported above with rhodium catalysts, under a CO pressure of 1 bar, **2a** was formed selectively in the presence of $[IrCl(COD)]_2$ with nonetheless a lower efficiency than with rhodium based catalysts (entries 12 and 14). While increasing the CO pressure to 20 bar, a greater amount of **2b** was produced, which was still accompanied with up to 50% of the noncarbonyl species **2a** (entries 13 and 15). It appears that iridium and cobalt are less suitable than rhodium for the selective preparation of **2b**.

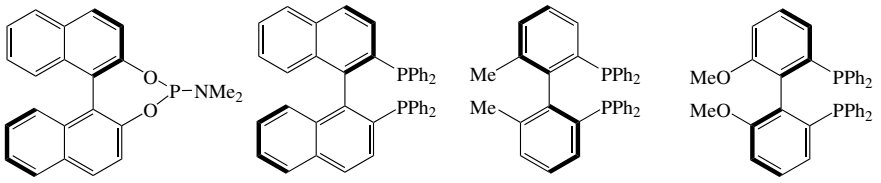
Table 1. Silylcyclization and carbonylative silylcyclization of **1**[a]

Entry	Precatalyst	Ligand	Solvent	P_{CO} (bar)	Time (h)	Conv. (%)[b]	**2a/2b**[b]
1	$Rh(acac)(CO)_2$	—	Toluene	1	15	100	1/1
2	$Rh(acac)(CO)_2$	—	Toluene	20	15	100	1/9
3	$Rh(acac)(CO)_2$	$P(OPh)_3$	Toluene	1	15	100	2/1
4	$Rh(acac)(CO)_2$	$P(OPh)_3$	Toluene	20	15	100	1/18
5	$Rh_4(CO)_{12}$	—	Hexane	1	0.5	100	1/0
6	$Rh_4(CO)_{12}$	—	Hexane	20	0.5	100	18/1
7	$Rh_4(CO)_{12}$	$P(OPh)_3$	Hexane	1	0.5	100	1/0
8	$Rh_4(CO)_{12}$	$P(OPh)_3$	Hexane	20	0.5	100	12/1
9	$[Rh(COD)]_2BF_4$	$P(OPh)_3$	DCE	1	3	98	1/31[c]
10	$[Rh(COD)]_2BF_4$	$P(OPh)_3$	DCE	20	3	85	1/6
11	$Co_2(CO)_8$	—	Toluene	20	18	80	1/9
12	$[Ir(COD)Cl]_2$	—	Toluene	1	0.5	60	1/0
13	$[Ir(COD)Cl]_2$	—	Toluene	20	18	100	1/1
14	$[Ir(COD)Cl]_2$	$P(OPh)_3$	Toluene	1	0.5	40	11/1
15	$[Ir(COD)Cl]_2$	$P(OPh)_3$	Toluene	20	18	100	1/4

[a] Reactions were carried out by using 4 mmol of substrate **1** and 4.8 mmol of $HSiMe_2Ph$ in 10 mL of the solvent at 70 °C in the presence of the catalyst and with or without ligand as mentioned in the table. Substrate/metal: 100:1. In the presence of the ligand: L/metal = 1/1.

[b] Conversion and **2a/2b** product ratio were obtained from GC analysis on a CP-Sil 5 CB capillary column.

[c] 37% of a mixture of unidentified products is observed along with the two products **2a** and **2b**.



(*R*)-MONOPHOS (*R*)-BINAP (*S*)-BIPHEMP (*R*)-MeO-BIPHEP

Scheme 2.

Table 2. Asymmetric carbonylative silylcyclization[a]

Entry	Precatalyst	Chiral auxiliary	Solvent	Time (h)	Conv. (%)[b]	**2a/2b**[b]	Ee **2b** (%)[c]
1	$Rh(acac)(CO)_2$	(*R*)-BINAP	Toluene	15	90	1/15	27
2	$Rh(acac)(CO)_2$	(*R*)-MONOPHOS	Toluene	15	95	1/10	0
3	$Rh_4(CO)_{12}$	(*R*)-BINAP	Hexane	0.5	100	1/0	—
4	$Rh_4(CO)_{12}$	(*R*)-MONOPHOS	Hexane	0.5	100	1/0	—
5	$[Rh(COD)]_2BF_4$	(*R*)-BINAP	DCE	3	80	1/10	26
6	$[Rh(COD)]_2BF_4$	(*R*)-MeO-BIPHEP	DCE	3	100	1/15	8
7	$[Rh(COD)]_2BF_4$	(*S*)-BIPHEMP	DCE	3	76[d]	1/8	6
8	$[Rh(COD)]_2BF_4$	(*R*)-MONOPHOS	DCE	3	92	1/12	22

[a] Reactions were carried out by using 4 mmol of **1** and 4.8 mmol of $HSiMe_2Ph$ in 10 mL of the mentioned solvent at 70 °C under 20 bar of CO; substrate/Rh = 100, chiral auxiliary/Rh = 1.
[b] Conversions and **2a/2b** ratios were determined by GC on CP-Sil 5 CB capillary column.
[c] Enantiomeric excesses were determined by HPLC on a Chiralpack AD column. Absolute configuration of the major enantiomer not determined.
[d] Unidentified by-products were formed in 14%.

The asymmetric carbonylative silylcarbocyclization reaction was considered next in the presence of chiral ligands associated to rhodium catalysts under 20 bar of CO. Four enantiomerically pure phosphorus type ligands have been selected, that is, (*R*)-MONOPHOS, (*R*)-BINAP, which appears to be very efficient in a large variety of asymmetric catalyses,[14] (*S*)-BIPHEMP already used in the enantioselective cyclization/hydrosilylation of 1,6-enynes,[8] and the closely related (*R*)-MeO-BIPHEP (Scheme 2). The results of the catalytic asymmetric reaction are reported in Table 2.

Associated to the chiral auxiliaries, the precatalysts $Rh(acac)(CO)_2$ and $[Rh(COD)_2]BF_4$ led to over 89% selectivities into **2b** (entries 1, 2, 5–8). Even under 20 bar of CO, compound **2a** was obtained as the sole product in the presence of the cluster $Rh_4(CO)_{12}$ (entries 3 and 4). These results are comparable to those reported above for reactions carried out in the presence of $P(OPh)_3$. On purpose, we did not check the enantiomeric excess of **2a** here, but concentrated rather on the enantioselectivity into **2b**. Thus, using (*R*)-BINAP, whatever the catalytic precursor used, an enantioselectivity of about 26% ee has been attained (entries 1 and 5). While using the monodentate (*R*)-MONOPHOS ligand, a slightly lower enantioselectivity (22% ee) was obtained (entry 8). Disappointing results were obtained while using auxiliaries bearing a biphenyl unit (entries 6 and 7). Indeed, even if the (*S*)-BIPHEMP ligand has been applied very successfully in the enantioselective cationic-rhodium assisted enyne cyclization/hydrosilylation (up to 92% ee for the transformation of the alkyne methyl substituted equivalent of **1** into the corresponding methyl substituted **2a**),[8] the chiral rhodium catalyst bearing either the (*S*)-BIPHEMP or (*R*)-MeOBIPHEP auxiliary gave very low ee's (entries 6 and 7) (6–8% ee).

3. Conclusion

In summary, we have developed the first example of asymmetric carbonylative silylcarbocyclization of an enyne. High selectivities into either noncarbonylated **2a** or carbonylated **2b** compounds could be reached according to the reaction conditions. Nevertheless, the chiral auxiliaries applied to the transformation of **1** resulted in low enantioselective formations of **2b**. As can be deduced from the literature, the enantioselectivity of the process is highly dependent upon the substituent of the alkyne residue. Further studies are under progress in order to improve the enantioselectivity into **2b**.

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9. During our initial attempts with such substrates, generally nonselective reactions occurred as deduced from GC analyses. Indeed, a multitude of signals was systematically present in the chromatograms.
10. *General procedure for the carbonylative silylcarbocyclization of* **1**: Under nitrogen, a Schlenk flask equipped with a stir bar was charged with $[Rh(COD)_2]BF_4$ (16.2 mg, 0.04 mmol) and freshly distilled dichloroethane (5 mL). Then, the silane $HSiMe_2Ph$ (0.6 mL, 4 mmol) was added via syringe followed by a solution of $P(OPh)_3$ (24.8 mg, 0.04 mmol) dissolved in dichloroethane (2 mL). The reaction mixture is stirred under nitrogen for 2 h. Substrate **1** (0.9 g, 4 mmol) was added next in solution in dichloroethane (6 mL). The resulting solution was transferred into a 50 mL double-walled autoclave via cannula. The reactor was then pressurized to 20 atm of CO and heated at 70 °C during 3 h. After cooling, the autoclave was depressurized and the solvent distilled under reduced pressure. The yellow resulting oil was analyzed by GC and the products were separated through silica gel chromatography (eluent: Petroleum ether/ethyl acetate: 95/5). Selectivities and conversions were determined by GC analysis on CP-Sil 5CB. Enantioselectivities into **2b** were determined by chiral HPLC on a Chiralpack AD column (*i*PrOH/hexane: 5:95; flow rate: 0.5 mL/min; detection UV at 254 nm; $t_R = 18.14$ and 21.58 min).
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