On the Enantioselective Rhodium-Catalyzed Enyne Cyclization

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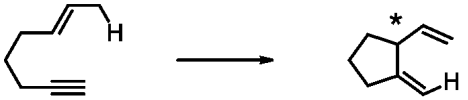
Abstract: Several chiral ligands were tested in the enantioselective rhodium-catalyzed enyne cyclization, but none gave results comparable to the BINAP ligand. Among the tested catalyst precursors the soon to be commercially available $[(COD)Rh(H_2O)_2]CF_3SO_3$ complex is an interesting alternative to the $[(COD)RhCl]_2$ because it did not need the activation with silver ions. A new stereogenic and 1,2-disubstituted double bond was formed in the product **12**, the latter was proved to have an (*E*)-configuration. A new product, the 1,3-diene **16** was observed at higher temperatures. In the presence of an (*E*)-configurated double bond in the starting material, the reaction completely failed.

Keywords: alkenes; alkynes; asymmetric catalysis; cyclization; homogeneous catalysis; rhodium

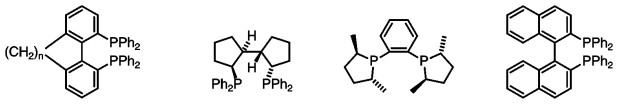
Introduction

The transition metal-catalyzed enyne cyclization, the intramolecular version of the Alder-ene-reaction,[1] has become an important tool in organic synthesis. The catalyst allows this transformation under mild conditions at moderate temperatures with substrates that, for electronic reasons, would need very high reaction temperatures in a concerted, uncatalyzed reaction. Initially, this was developed with palladium catalysts by Trost et al.[2] In the meantime, many other groups have contributed and several other metals have proven to be catalytically active for this transformation.[3] In these reactions from a planar sp^2-carbon in the starting material **1**, a tetrahedral stereogenic center is generated in the product **2**. There have been several efforts for a catalytic enantioselective version of this reaction in the past years.[4,5] While these used palladium catalysts, so far the most convincing synthetic results come from Zhang et al.'s recent and most beautiful work utilizing rhodium catalysts.[6,7,8]



1 **2**

They could achieve excellent enantioselectivities (sometimes above 99% ee) and good to excellent yields.[6,7,8] Typical ligands they used initially were Tunaphos **3**, BICPO **4** and (*R*,*R*)-Me-DuPhos **5**. In the latest publication the work focused on BINAP **6**, which delivered the best and most reliable results.[8] One general drawback was the relatively high amount of catalyst needed (in most cases 10 mol % of rhodium). Furthermore, only (*Z*)-olefins were used as substrates, certainly a significant synthetic limitation. On the other hand, in related reactions that proceed through similar intermediates, (*E*)-olefins reacted readily.[9] In preceding publications it was also mentioned that the reaction can in principle be conducted with only 0.4 mol% of catalyst[8] and that only (*Z*)-olefins react.[10]



3 **4** **5** **6**

We now wanted to test whether other ligands and catalyst precursors allow a significant reduction of the amount of catalyst and still give a good ee, and briefly readdress the question of the use of (*E*)-olefins.

Results and Discussion

First we wanted to gather some experience with the rhodium catalysts, thus we prepared the (*Z*)-enyne **11** from phenylacetylene **7** and commercially available (*Z*)-pent-2-en-1-ol **10**. Subjecting **11** to 10 mol % of $[(COD)RhCl]_2$, *rac*-BINAP and $AgSbF_6$ readily delivered the cyclization product *rac*-**12** in a satisfying 85% yield (Table 1, entry 1). Then we switched to enantio-

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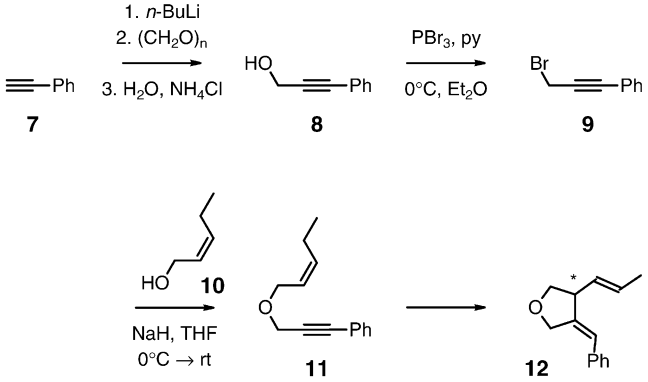
Table 1. Different precursors and ligands for the conversion of **11** to **12**.

Entry	Catalyst precursor	Ligand	Ag salt	Temp.	ee (by GC)	Isolated yield
1	$[(COD)RhCl]_2$	*rac*-BINAP	$AgSbF_6$	rt	–	85%
2	$[(COD)RhCl]_2$	(*R*)-BINAP	$AgSbF_6$	rt	>99%	69%
3	$[(COD)RhCl]_2$	dppe	$AgSbF_6$	rt	–	–[a]
4	$[(COD)RhCl]_2$	(*R*,*R*)-MeDuphos	$AgSbF_6$	rt	–	–[a]
5	$[(COD)RhCl]_2$	(*R*,*R*)-Depyphos	$AgSbF_6$	rt	–	–[a]
6	$[(COD)RhCl]_2$	TaniaPhos	$AgSbF_6$	rt	–	–[a]
7	$[(COD)RhCl]_2$	MandyPhos	$AgSbF_6$	rt	–	–[a]
8	$[((R,R)$-Depyphos$)Rh(COD)]BF_4$	–	–	rt	75%	76%
9	$[(COD)_2Rh]BF_4$	(*R*)-BINAP	–	50 °C	>99%	93%
10	$[(NBD)_2Rh]BF_4$	(*R*)-BINAP	–	50 °C	78.5%	4%
11	$[(COD)Rh(acac)]$	(*R*)-BINAP	–	80 °C	–	–[a]
12	$[(COD)Rh(H_2O)_2]CF_3SO_3$	(*R*)-BINAP	–	rt	>99%	82%
13	$[(COD)RhCl]_2$	(*R*)-BINAP	$AgBF_4$	rt	>99%	90%
14	$[(COD)RhCl]_2$	(*R*,*R*)-Depyphos	$AgBF_4$	rt	–	–[a]
15	$[(COD)RhCl]_2$	TaniaPhos	$AgBF_4$	rt	–	–[a]
16	$[(COD)RhCl]_2$	MandyPhos	$AgBF_4$	rt	–	–[a]
17	$[(COD)Rh(H_2O)_2]CF_3SO_3$	-	–	rt	–	–[a]
18	$[(COD)Rh(H_2O)_2]CF_3SO_3$	(*R*)-BINAP	–	80 °C	–	–[b]
19	$[((R,R)$-Depyphos$)Rh(COD)]BF_4$	–	$AgSbF_6$	rt	–	–[a]
20	$[(COD)RhCl]_2$	–	$AgSbF_6$	rt	–	–[a]

All reactions were conducted with 10 mol % of catalyst in DCE.
[a] Only starting material could be isolated.
[b] Formation of the 1,3-diene **16** in 16% yield.

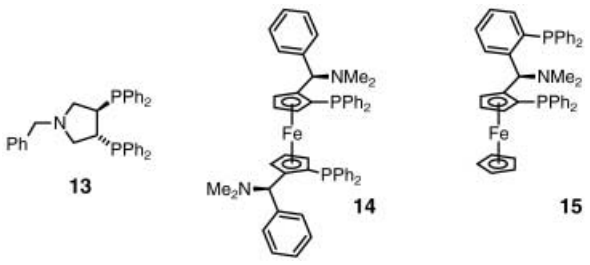
merically pure (*R*)-BINAP (entry 2) that delivered an ee of more than 99% (with the same configuration as Zhang et al.)[11] as determined by chiral GC (direct comparison with *rac*-**12**). In both products the configuration of the newly formed stereogenic double bond is (*E*) as clearly deduced from the 15.2 Hz coupling constant of the two vicinal hydrogen atoms at this 1,2-disubstituted double bond.[12]



With the ligands dppe, (*R*,*R*)-Me-Duphos **5**, (*R*,*R*)-Depyphos **13**, TaniaPhos **14** and MandyPhos **15**, no reaction was observed under the same conditions (entries 3–7).

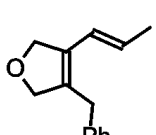
Then we switched to cationic catalyst precursors for the (*R*)-BINAP complexes which do not need the activation by silver(I). $[((R,R)$-Depyphos$)Rh(COD)]BF_4$ delivered a 76% yield and a 75% ee (entry 8). With (*R*)-BINAP and $[(COD)_2Rh]BF_4$, a 93% yield and 99% ee were observed (entry 9), while $[(NBD)_2Rh]BF_4$ (entry 10) provided a low 4% yield with a 78.5% ee, and [(COD)Rh(acac)] gave no conversion at all (entry 11). Only the new $[(COD)Rh(H_2O)_2]CF_3SO_3$[13,14] delivered an 82% yield with more than 99% ee (entry 12).

Then going back to the $[(COD)RhCl]_2$ dimer as a catalyst precursor and an activation with the easier to handle silver tetrafluoroborate instead of the extremely hygroscopic hexafluoroantimonate did not change anything: with (*R*)-BINAP again an ee higher than 99% and a 90% yield were obtained while with (*R*,*R*)-Depyphos, TaniaPhos and MandyPhos the reaction failed once more (entries 13–16).

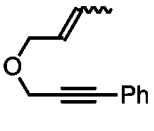


Control experiments confirmed that $[(COD)Rh(H_2O)_2]CF_3SO_3$ without a diphosphane ligand failed to convert **11** (entry 17), with (*R*)-BINAP at 80 °C a new side-product, the quite unusual 1,3-diene **16** was obtained (entry 18). The structure is easily deduced from

the NMR data, nicely showing the 1-propenyl moiety with the methyl proton resonance at 1.84 ppm and a vicinal coupling of 6.6 Hz, one vinyl proton resonance at 5.52 ppm possessing as one coupling constant the same 6.6 Hz and the last vinyl proton resonance at 6.57 ppm. The (*E*)-configuration was deduced from a coupling constant of 15.7 Hz between the two vicinal hydrogen atoms at that double bond.[15] The carbon NMR shows no more alkyne resonances, there are now two methylene group resonances at 76.6 and 78.6 ppm for the carbon atoms next to the oxygen atoms and the double bond and, most significant, one methylene group at 31.7 ppm for the benzylic-allylic methylene group. Suitable methylene resonances are also found in the proton NMR (4.52 ppm/4.59 ppm for the methylene groups between oxygen and the double bond in the heterocycle and 3.54 ppm for the benzylic-allylic methylene group).



16



17

All efforts for a significant reduction of the amount of catalyst (at least one order of magnitude) did not deliver any product even after longer reaction times. We did not try heating, as mentioned above an increase of temperature should lead to a different and achiral product.

Compared to other precursors for the catalyst, at room temperature $[(COD)Rh(H_2O)_2]CF_3SO_3$ shows only about 1/8 of the activity of the $[(COD)RhCl]_2$/$AgSbF_6$ system but is clearly the most active catalyst among the precursors that do not need an activation by a silver salt (entries 8–12). It is interesting that the rhodium-Depyphos complex is catalytically active (albeit with low enantioselectivity, entry 8), while efforts for the *in situ* generation with either $AgSbF_6$ or $AgBF_4$ were unsuccessful (entries 5 and 14). As the chloro-(1,5-cyclooctadiene)-rhodium(I) itself is inactive (entry 20), maybe the *in situ* formation of the diphosphane complex is hindered. Futhermore, the Depyphos ligand might co-ordinate more strongly to the silver ion und and thus not co-ordinate to rhodium. Evidence for this was obtained when silver ions ($AgBF_4$) were added to the rhodium-Depyphos complex; this led to an inhibition of the reaction (entry 19).

Trying to use a 3:1 mixture of the (*E*)- and the (*Z*)-isomer of the known **17** was completely unsuccessful, not even the (*Z*)-portion of the mixture reacted under several conditions in the presence of the (*R*)-BINAP ligand.

Conclusion

None of the tested ligands gave results comparable to the BINAP ligand, but the soon to be commercially available[16] $[(COD)Rh(H_2O)_2]CF_3SO_3$ complex, which does not need the activation with silver ions, is an interesting alternative to the $[(COD)RhCl]_2$ as a catalyst precursor. In the product **12** apart from the new stereogenic center also a stereogenic 1,2-disubstituted double bond is formed, the latter was proved to have an (*E*)-configuration. At higher temperatures the 1,3-diene **16** was observed as a new product. Efforts to conduct the reaction with an (*E*)-configurated double bond in the starting material were unsuccessful.

Experimental Section

3-Phenyl-2-propyn-1-ol (8)

The substance was prepared by a general procedure for related substances given in ref.[17] Under a nitrogen atmosphere 10.0 mL (9.30 g, 91.1 mmol) phenylacetylene (**7**) in 80.0 mL of absolute THF were cooled to −78 °C. Then 56.9 mL *n*-BuLi (91.1 mmol, 1.6 M in hexanes) were added dropwise. The solution was allowed to warm to 0 °C and then 3.60 g (120 mmol) paraformaldehyde are added. After the solution had warmed to room temperature it finally was heated to 45 °C for 90 minutes. After cooling to room temperature, the reaction mixture was poured into a solution of 25 g ammonium chloride in 250 mL of water. After separation of the phases the aqueous phase was extracted with ether five times, dried over $MgSO_4$, filtered and the solvent removed under vacuum. A subsequent column chromatography furnished **8** as a yellow oil; yield: 10.7 g (81.0 mmol, 90%). The spectroscopic data were in accordance with the literature.[17] R_f (PE:EE, 2:1) = 0.30; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.69 (t, *J* = 6.2 Hz, 1H), 4.50 (d, *J* = 6.1 Hz, 2H), 7.30–7.34 (m, 3H), 7.42–7.46 (m, 2H).

3-Phenyl-2-propynyl Bromide (9)

The substance was prepared by a procedure from ref.[19] 4.84 g (36.7 mmol) **8** in 40 mL of absolute ether were cooled to 0 °C. Then 0.5 mL pyridine and 1.40 mL (3.98 g, 14.7 mmol) PBr_3 were added and stirring was continued for 4 hours at 0 °C. Then the mixture was poured into $NaHCO_3$ solution, extracted with ether three times and dried over Na_2SO_4. After filtration and removal of the solvent under vacuum **9** was obtained as a yellow oil; yield: 4.14 g (21.2 mmol, 58%). R_f (PE:Et_2O, 50:1) = 0.43; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.17 (s, 2H), 7.28–7.46 (m, 5H).

(2*Z*)-(3-Pent-2-enyloxy-prop-1-ynyl)benzene (11)

The substance was prepared by a combination of two procedures.[20,21] 82.0 μL (699 mg, 812 μmol) *cis*-2-penten-1-ol (**10**) in THF were cooled to 0 °C. Then 19.4 mg (81.0 μmol) NaH were added. When no more gas was evolved, 158 mg

(810 μmol) 3-phenyl-2-propyn-1-yl bromide (**9**) in THF were added. Stirring was continued at 0 °C for one hour, then the solution was allowed to warm to room temperature, washed with water and the aqueous phase extracted with ether three times. The combined organic phases were dried over $MgSO_4$, filtered and the solvent removed under vacuum. Column chromatography on silica gel afforded **11** as a pale yellow oil; yield: 76.3 mg (381 μmol, 47%). R_f (PE : Et_2O, 50 : 1) = 0.20; IR (neat): $\tilde{\nu}$ = 2964 cm, 2933, 2236, 1072, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.00 (t, *J* = 7.6 Hz, 3H), 2.14 (ddq, *J* = 7.5 Hz, 7.5 Hz, 1.5 Hz, 2H), 4.20 (d, *J* = 6.75 Hz, 2H), 4.37 (s, 2H), 5.53 (dtt, *J* = 11.0, 6.75, 1.5 Hz, 1H), 5.66 (dtt, *J* = 11.0 Hz, 7.37 Hz, 1.4 Hz, 1H), 7.29 – 7.36 (m, 3H), 7.43 – 7.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.3 (q), 21.0 (t), 58.0 (t), 65.4 (t), 85.4 (s), 86.2 (s), 122.8 (s), 123.2 (d), 124. 9 (d), 128.7 (d, 2C), 132.1 (d, 2C), 136.9 (d); MS [EI (+), 70 eV]: *m/z* (%) = 200 (0.13) [M^+], 129 (35), 115 (100); anal. calcd. for $C_{14}H_{16}O$ (200.28): C 83.83, H 7.58; found: C 82.10, H 7.90.

General Procedure for Rhodium-Catalyzed Reactions

The enyne was placed in a Schlenk tube, 2.0 mL solvent (DCE, DCM or C_6D_6) were added and the solution was degassed by freeze-thaw cycles. Depending on the precursor, now two different procedures were used:

Procedure A: The rhodium cation was prepared *in situ* by the addition of a silver salt at room temperature.

Procedure B: A diphosphane ligand was either already coordinated to rhodium or becomes attached by ligand exchange at 50 °C or 80 °C.

Gas chromatography (GC): the determination of the enantiomeric excess (ee) was done with chiral GC by comparison with the racemic sample in the GC facility of the Institut für Organische Chemie at the Universität Stuttgart on an instrument from Firma Mega/Split with a chiral column Bondex u n β; carrier gas H_2, 0.4 bar; temperature program: 100 °C/70 min isotherm/1 °C per minute up to 120 °C / then up to 200 °C.

Retention times for the racemic sample of **12**: enantiomer 1 : 86.03 minutes; enantiomer 2 : 87.35 minutes.

3-Benzylidene-4-propenyltetrahydrofuran (12)

40.0 mg (200 μmol) of the **11** and 2.0 mL dichloroethane were degassed in a Schlenk tube. Then 5.0 mg (10 μmol) $[(COD)RhCl]_2$ and 12.5 mg (201 μmol) (*R*)-BINAP were added. After stirring for one minute $AgSbF_6$ was added. The reaction was monitored by TLC. Column chromatography (PE : EE : DCM, 30 : 1 : 1) furnished **12** as a yellow oil; yield: 27.5 mg (140 μmol, 69%, >99% ee). R_f (PE : EE : DCM, 30 : 1 : 1) = 0.23; IR (neat): $\tilde{\nu}$ = 2938, 1473, 1375, 1061, 893, 632 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.78 (dd, *J* = 6.5 Hz, 1.6 Hz, 3H), 3.43 – 3.51 (m, 2H), 4.08 (dd with the same coupling constant, thus pseudo-t, *J* = 7.1 Hz, 7.1 Hz, 1H), 4.61 (dt, *J* = 14.4 Hz, 2.2 Hz, 1H), 4.75 (d, *J* = 14.4 Hz, 1H), 5.35 (ddq, *J* = 15.2 Hz, 8.2 Hz, 1.6 Hz, 1H), 5.67 (dq, *J* = 15.2 Hz, 6.5 Hz, 1H), 6.25 – 6.26 (m, 1H), 7.15 – 7.35 (m, 3H), 7.35 – 7.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.0 (q), 49.7 (d), 70.3 (t), 72.6 (t), 121.6 (d), 126.6 (d), 127.9 (d, 2C), 128.5 (d, 2C), 128.8 (d), 129.2 (d), 137.3 (s), 144.5 (s); MS [EI (+), 70 eV]: *m/z* (%) = 200 (7) [M^+], 105 (94), 77 (72); anal. calcd. for $C_{14}H_{16}O$ (200.28): C 83.96, H 8.05; found: C 81.38, H 7.89.

3-Benzyl-4-propenyl-2,5-dihydrofuran (16)

40.0 mg (200 μmol) of the enyne **11** in 2.0 mL DCE were degassed in a Schlenk tube. Then 7.9 mg (199 μmol, 10 mol %) $[(COD)Rh(H_2O)_2]CF_3SO_3$ and 12.5 mg (201 μmol) (*R*)-BINAP were added and the mixture was heated to 80 °C for 16 hours. Column chromatography (PE:DCM; 1 : 1) furnished **16** as a yellow oil; yield: 6.5 mg (32 μmol, 16%). R_f (PE:DCM; 1 : 1) = 0.14; IR (film): $\tilde{\nu}$ = 3026, 2912, 2840, 1455, 1168, 1064, 757, 700, 533 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.84 (d, *J* = 6.6 Hz, 3H), 3.54 (s, 2H), 4.52 – 4.54 (m, 2H), 4.79 – 4.81 (m, 2H), 5.52 (ddt, *J* = 15.7 Hz, 6.6 Hz, 1.0 Hz, 1H), 6.57 (d, *J* = 15.7 Hz, 1H), 7.14 – 7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.2 (q), 31.7 (t), 76.6 (t), 78.6 (t), 122.2 (d), 126.3 (d), 128.3 (d), 128.7 (d, 2C), 128.9 (d, 2C), 131.4 (s), 132.4 (s), 139.0 (s); MS [EI (+), 70 eV]: *m/z* (%) = 200 (23) [M^+], 109 (89), 84 (97); HRMS [EI (+), 70 eV]: calcd. for $C_{14}H_{16}O$: 200.1201; found: 200.1201.

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[11] The absolute configuration is still unknown; in analogy to Zhang et al.[8] (*R*)-BINAP delivered the (–)-product.
[12] Zhang et al. reported that both double bonds of the product possess the (*E*)-configuration.[7] They based their assignment on unpublished NOE data. In principle

this is indeed needed for the exocyclic double bond, but might be ambiguous for the other double bond since the hydrogen atoms involved also show a scalar coupling. Here the vicinal coupling constant between the two hydrogen atoms on the double bond is probably the most direct way to retrieve this information.
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