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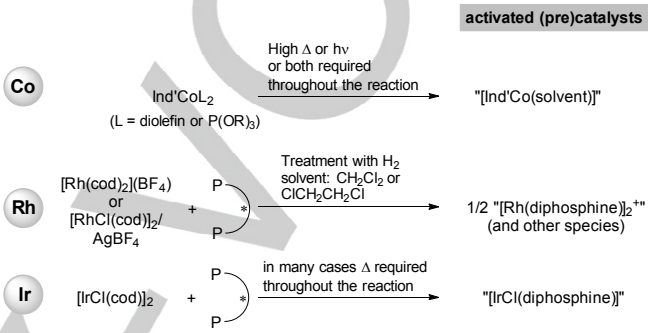
Insight into the Activation of *In Situ*-Generated Chiral Rh(I)-Catalysts and their Application in Cyclotrimerizations

Indre Thiel,[a] Moritz Horstmann,[a] Phillip Jungk,[a] Sonja Keller,[a] Fabian Fischer,[a] Hans-Joachim Drexler,[a] Detlef Heller*[a] and Marko Hapke*[a,b]

Abstract: We herein report a detailed study concerning the efficient generation of highly active chiral rhodium complexes of the general structure [Rh(diphosphine)(solvent)]$^+$ as well as their exemplary successful utilization as catalysts for cyclotrimerizations. Such solvent complexes could likewise be prepared from novel ammonia complexes of the type [Rh(diphosphine)$(NH_3)_2$]$^+$. A valuable feasible approach to generate novel chiral Rh(I)-complexes was found by *in situ* generation from Wilkinson's catalyst $RhCl(PPh_3)_3$ with chiral *P,N* ligands. The generated catalysts led to moderate to good enantioselectivities and excellent yields in cyclotrimerizations of triynes, showcasing their usefulness in the synthesis of axially chiral benzene derivatives.

Introduction

In recent years various new catalytic systems for enantioselective [2+2+2] cycloaddition reactions have been described, significantly broadening their scope of application.[1] Nevertheless, enantioselective [2+2+2] cycloadditions are still a challenging transformation, stimulating the search for novel chiral catalysts and concepts for asymmetric induction. Out of the many metals which in general catalyze this transformation, the group 9 transition metals are clearly dominating the field of the asymmetric cyclotrimerizations. However, within this group, the properties of the catalyst precursor as well as the type and efficiency of the active catalyst promoting achiral reactions may vary significantly, as earlier investigations could already demonstrate.[2] An overview of the general methods and conditions applied to generate active group 9 metal catalysts used in enantioselective [2+2+2] cycloadditions is presented in Scheme 1.



Scheme 1. General but simplified methods to obtain active chiral group 9 metal catalysts for asymmetric cyclotrimerizations (Ind' = chiral indenyl, cod = 1,5-cyclooctadiene).

The first chiral cobalt systems were derived from chiral cyclopentadienyl (Cp) or indenyl (Ind) frameworks and activation occurred by irradiation (Scheme 1, top).[3] Hapke and Heller et al reported on enantioselective Co(I)-catalyzed [2+2+2] cycloaddition reactions under photochemical conditions, where a chiral menthyl-derived indenyl-based Co(I)-complex was shown to yield enantiomerically enriched atropisomers of axially chiral 1-aryl-5,6,7,8-tetrahydroisoquinolines and biarylphosphines.[4] The implementation of phosphite ligands in this chiral indenyl-Co(I) complex led to an active catalyst without the imperative need of irradiation, which was exemplified in the synthesis of chiral pyridines from diynes/nitriles and triaryls from triynes.[5] Only very recently we reported on the first *in situ*-generated chiral Co(I)-catalyst based on *P,N* ligands, which was able to promote asymmetric cyclizations of triynes to chiral triaryls under mild conditions.[6]

Shibata et al. were the first to explore the iridium-catalyzed enantioselective [2+2+2] cycloaddition reaction in more depth. They reported on various intramolecular cyclization reactions such as e. g. the synthesis of chiral cyclohexa-1,3-dienes from enediynes,[7] atropisomeric chiral ortho-diarylbenzenes from triynes [8] or axially chiral biaryl systems from tetraynes and hexaynes.[9] Intermolecular cyclization reactions allowed the construction of axially chiral tetraaryl compounds from diynes and alkynes.[10] The active catalyst was generally assembled by combining a simple Ir(I)-precursor such as $[IrCl(cod)]_2$ and a chiral diphosphine ligand, achieving the cyclizations in good yields and high enantioselectivities (Scheme 1, bottom). However, in most cases higher reaction temperatures are required as well as structural requirements to ensure

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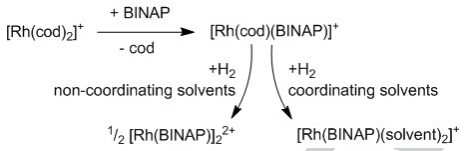
configurational stability of the chiral products against epimerization.

Rh(I)-catalyzed enantioselective [2+2+2] cycloaddition reactions are the most popular and were explored in depth especially by Tanaka et al.[11] Like in the case of the Ir(I)-systems, Rh(I)-precursors of the type $[Rh(cod)_2](BF_4)$ in combination with chiral ligands such as BINAP and Segphos were applied. The generated catalysts promoted intra- as well as intermolecular [2+2+2] cycloaddition reactions affording axially chiral phthalides[12] and biaryls[13] in high yields and high enantioselectivities. While the application of tetraynes for the synthesis of axially chiral biaryls, bipyridines and bipyridones resulted in moderate *ee* values and yields,[14] the enantioselective cycloaddition between diynes and isocyanates yielding 2-pyridones was accomplished with high enantiomeric excesses.[15] Recently, Tanaka et al. described the enantioselective synthesis of planar-chiral carbaparacyclophanes using $[Rh(cod)_2](BF_4)$ and a chiral diphosphine ligand in good yields.[16] Gandon and Aubert et al. reported on the enantioselective [2+2+2] cycloaddition of diynes and sulfonimines yielding the respective 1,2-dihydropyridines using partially the same catalytic system, although a substantial part of reactions in the study were carried out using [RhCl(1,5-hexadiene)$_2$] as metal source.[17] Further examples demonstrated the broadness of applicability of chiral *in situ*-generated rhodium catalyst systems.[18]

Depending on the metal, different protocols are applied to generate the active chiral catalyst. The efficiency of such protocols though can vary significantly, thus affecting the amount of metal effectively available for the catalytic reaction. Unique is the case of Rh(I)-catalysts prepared *in situ* from a diolefin precursor (Scheme 1, middle) and a diphosphine: generation of the catalytic active species requires displacement of 1,5-cyclooctadiene from the metal coordination sphere and this is achieved through its hydrogenation into cyclooctene or even cyclooctane. Although widely applied, this procedure may not be selective and the type of Rh(I)-species it affords can be strongly affected by the delicate role of the solvent used for the prehydrogenation reaction. In initial work on Rh-catalyzed [2+2+2] cycloadditions by Tanaka et al. the precursor $[Rh(cod)_2](BF_4)$ was reacted with the chosen diphosphine for a short period of time (usually 5 min) under argon in CH_2Cl_2, before being hydrogenated for 30 min. After removal of the solvent, the substrates for the cyclotrimerization reaction are added, usually also in a non-coordinating solvent like CH_2Cl_2.[12,19,20] A closer view on the catalyst generation process reveals details of the transformation. Combination of a diphosphine like BINAP and $[Rh(cod)]_2(BF_4)$ in a 1 : 1 ratio in CH_2Cl_2 resulted in the formation of $[Rh(cod)(BINAP)](BF_4)$.[20,21] When the latter is (pre-)hydrogenated, the arene-bridged dimer $[Rh(BINAP)]_2(BF_4)_2$ is obtained quantitatively.[22] In coordinating solvents like MeOH, THF or acetone the corresponding solvent complexes $[Rh(BINAP)(solvent)_2](BF_4)$ are formed instead (Scheme 2).



Scheme 2. Solvent-dependent (pre)catalyst generation.

The prehydrogenation activation procedure was widely adopted for cyclization reactions with BINAP also by other groups,[23] and extended to a series of other achiral and chiral diphosphines.[24] The cyclization itself was usually carried out in chlorinated alkanes (CH_2Cl_2, 1,2-dichloroethane), but examples in other solvents, e.g. chlorobenzene, were also reported.[25]

The herein described investigations aim to provide detailed information on the activation process of rhodium precatalysts and to disclose a novel synthetic route not requiring an activation step (prehydrogenation). The latter will be achieved by using the Wilkinson catalyst as a novel Rh(I)-precatalyst. Such chiral catalysts generated by both routes will be applied in asymmetric cyclotrimerization reactions. Furthermore, the optimization of the catalyst generation can minimize the amount of precious metal and ligands involved, which is a criterion for sustainable transition metal catalysis.

Results and Discussion

Synthesis of solvent complexes and studies of their catalytic activity and selectivity

Catalyst prehydrogenation and subsequent transformations like the [2+2+2] cycloadditions are generally and conveniently performed in chlorinated reaction solvents (CH_2Cl_2, ClH_2CCH_2Cl) The latter however can react with the active catalyst leading to undesired side reactions. Although typical of low-valent late transition metal complexes, oxidative addition reactions with chlorinated alkanes and arenes[26] can also occur with Rh(I)-complexes. In addition also the potential formation of two- and trinuclear Rh(I)-complexes in such media can in principle not be excluded.[27] This can be illustrated by analyzing the mixture obtained from precatalyst hydrogenation in CH_2Cl_2. Depending on the reaction conditions (especially the reaction time before hydrogenation and reaction temperature) other species, beside the desired arene-bridged dimers $[Rh(BINAP)]_2(BF_4)_2$, can be detected in significant amounts, among which $[Rh(BINAP)_2](BF_4)$ should be cited.[28] These problems do not occur in coordinating solvents like methanol. Here, the formation and subsequent splitting of the diphosphine-bridged dimeric Rh-species can be avoided entirely.

Systematic investigations into the hydrogenation of cationic Rh(I)-complexes of the type [Rh(I)(P^P)(diolefin)](anion) clearly proved that the prehydrogenation time is strongly affected by the type of diphosphine.[29] More specifically, we have focused on complexes relevant to asymmetric [2+2+2] cycloaddition

reactions in order to evaluate the time required to fully hydrogenate diolefin ligands, specifically cod,[30] and thus generate the corresponding catalytically active solvent complexes (Table 1).

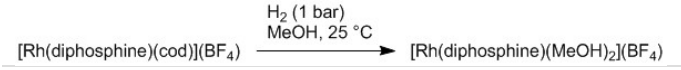


Table 1. (Pseudo) first order rate constants and required times for complete prehydrogenation (7 half-lives correspond to 99.2% cod conversion) of [Rh(P^P)(diolefin)](BF$_4$) to the corresponding solvent complex [Rh(P^P)(MeOH)$_2$](BF$_4$) in MeOH at 25.0 °C.[31]

#	Diphosphine[a]	Hydrogenation rate constant [1/min][b]	Time [min] for 99.2% of cod conversion	Ref.
1	BINAP	$2.3*10^{-1}$	21.1	[21]
2	H_8-BINAP	$8.5*10^{-1}$	5.7	this work
3	Segphos	$4.7*10^{-1}$	10.3	this work
4	DTBM-Segphos	$6.3*10^{-2}$	77.0	this work
5	Difluorphos	$1.6*10^{-1}$	30.3	this work
6	Et-Duphos	$2.8*10^{-2}$	173.3	[32]
7	Duanphos	$6.8*10^{-1}$	7.1	this work
8	Tangphos	$3.75*10^{-1}$	12.9	[34b]
9	Et-Ferrotane	$2.0*10^{-1}$	24.3	this work

[a] An overview on the investigated ligands is given in the Supporting Information. [b] The determination of the rate constants was performed under the following conditions: 0.01 mmol precatalyst, ca. 1.0 mmol cod and 15.0 mL anhydrous MeOH, normal pressure, 25.0 °C. Detailed information is given in ref. [29].

In MeOH large differences in the prehydrogenation times were observed depending on the ligand. Even diphosphines with large similarities in their structural features, e.g. BINAP vs. H_8-BINAP (Table 1, entry 1 and 2) or Segphos vs. DTBM-Segphos (Table 1, entry 3 and 4) required significantly different reaction times. This behaviour can be observed also for other solvents[29] including dichloromethane.

A more detailed discussion allows the comparison of measured (pseudo) first order rate constants for the cod hydrogenation in CH_2Cl_2 at 25.0 °C for the ligands BINAP (k'_{cod} = 0.0751 1/min) and H_8-BINAP (k'_{cod} = 0.275 1/min). Emanating from these rate constants the required prehydrogenation times for BINAP and H_8-BINAP are 65 min and 18 min, respectively. To further corroborate these findings experimentally, the stoichiometric hydrogenation of [Rh(BINAP)(cod)](BF$_4$) was stopped after 20 min reaction time, hydrogen removed by repeated freeze-thaw cycles in vacuo and the ^{31}P NMR of the solution measured (Figure 1). Because the allowed prehydrogenation time is shorter than the 7-fold half-life time, the unreacted starting complex [Rh(BINAP)(cod)](BF$_4$) should be detectable. Indeed, beside the arene-bridged dimer [Rh(BINAP)]$_2$(BF$_4$)$_2$, the NMR spectrum does show the presence of [Rh(BINAP)(cod)](BF$_4$) in 19% relative amount, which is in very good agreement with the 22.3% theoretically expected value after 20 min hydrogenation. Beside the aforementioned complexes no further organometallic Rh(I)-species could be detected, giving evidence for a very clean conversion. This was also experimentally verified for the H_8-BINAP ligand.[33]

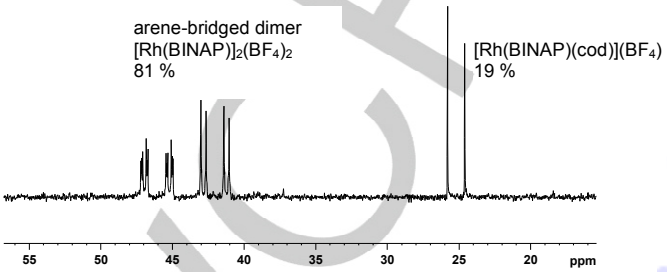
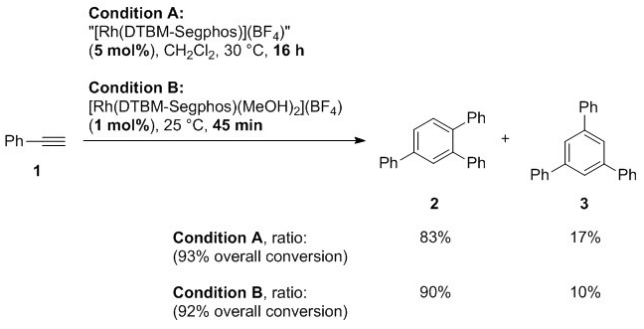


Figure 1. $^{31}P\{^1H\}$ NMR spectrum after 20 min of hydrogenation at 25.0 °C reaction of the complex [Rh(BINAP)(cod)](BF$_4$) in CH_2Cl_2.

These results hinted at a discrepancy between the common practice reported in the literature (30 min prehydrogenation time) and the observed timeframe required for a full conversion (Table 1). The reported 30 min are either too short or too long, regardless of the solvent used. In the first case only a portion of the applied Rh precatalyst is activated and can be used in the catalytic reaction, while in the latter case the prehydrogenation time is too long, possibly allowing the formation of undesired di- and trinuclear hydrides.[34,35]

Having evaluated the optimal prehydrogenation times required for each catalyst to obtain the desired solvent complexes in methanol, we set out to apply such complexes in [2+2+2] cycloaddition reactions of alkynes. Cycloaddition of phenyl acetylene (**1**) using the conventionally generated Rh-DTBM-Segphos complex as catalyst (Scheme 3) was performed as initial test reaction. The cyclization in CH_2Cl_2 at 30 °C for 16 h gave a conversion of 93% for **1** and the 1,2,4- and 1,3,5-substituted phenyl isomers **2** and **3** were obtained in a 83:17 ratio (Scheme 3, Condition A).[36]

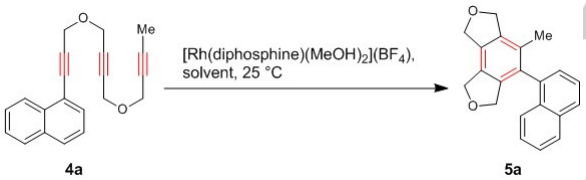


Scheme 3. Rh-catalyzed [2+2+2] cycloaddition test reaction of phenylacetylene under standard conditions for catalyst generation (**Condition A**, applying 30 min pretreatment of complex solution in CH_2Cl_2 with H_2 according to Tanaka et al.[19] and applying the complex "[Rh(DTBM-Segphos)](BF$_4$)"; **Condition B**, solution of [Rh(DTBM-Segphos)(cod)](BF$_4$) in MeOH, 77 min pretreatment with H_2, addition of substrate).

By carrying out the reaction in MeOH and raising the prehydrogenation time to 77 min to fully convert the precatalyst into the solvent complex [Rh(DTBM-Segphos)$(MeOH)_2$](BF_4) the cycloaddition was significantly accelerated requiring only 45 min at 25 °C to achieve the same conversion with lower catalyst loading (Scheme 3, Condition B). In the latter case the catalyst/substare ration can even be raised without detrimental effects for the reaction, therefore requiring even less catalyst for the reaction to occur.

Application of solvent complexes in asymmetric [2+2+2] cycloaddition reactions

The observed high reactivity of chiral Rh-diphosphine solvent complexes lead us to investigate their performance in asymmetric cyclotrimerization reactions of suitable alkyne substrates. The evaluation of their reactivity and selectivity in comparison to the conveniently applied catalytic systems would allow interesting insights into the influence of the catalyst generation step. For this purpose we chose triyne **4a** as standard cyclization substrate for the evaluation of different phosphine ligands and their solvent complexes under mild conditions. The results for selected systems are displayed in Table 2.



4a **5a**

Table 2. Evaluation of [Rh(diphosphine)$(MeOH)_2$](BF_4) complexes in intramolecular cyclotrimerization reactions.[a]

#	Ligand	Reaction solvent	*Selectivity Screening {Selectivity [%ee]}* [b]	Isolation Yield [%] (Selectivity [%ee]) [c]
1	*(R_a)*-BINAP	MeOH/THF	*2*	
2	*(R_a)*-H_8-BINAP	MeOH/THF	*2*	>98 (2)
3	*(R)*-Segphos	MeOH/THF	*6.8*	
4	*(R)*-DTBM-Segphos	MeOH/THF	*27*	
5	*(R)*-Difluorphos	MeOH/THF	*43.4*	>98 (16.9)
5a	*(R)*-Difluorphos	2,2,2-Trifluoro-ethanol	*10.4*	
5b	*(R)*-Difluorphos	Propylene carbonate	*13.5*	
5c	*(R)*-Difluorphos	THF	*31.9*	
6	*(S,S)*-Et-Duphos	MeOH/THF	*39.0*	
7	*(S_c,R_p)*-Duanphos	MeOH/THF	*30.9*	94 (27.7)
7a	*(S_c,R_p)*-Duanphos	THF/Aceton (2:1)	*18.6*	
8	*(S,S,R,R)*-Tangphos	MeOH/THF	*24.0*	
8a	*(S,S,R,R)*-Tangphos	MeOH/THF (50°C)	*20.6*	
9	*(R,R)*-Et-Ferrotane	MeOH/THF	*47.8*	69 (50.1)

[a] Experimental details and results for all investigated ligands are given in the experimental section. [b] Selectivity screening from crude reaction mixtures without isolation. [c] Isolated yields and selectivities for selected examples.

Interestingly, the commonly applied ligands BINAP and H_8-BINAP (Table 2, entry 1 and 2) only gave insignificant selectivities in the cyclization of **4a**. The best result with a selectivity of up to 50% *ee* was accomplished by Et-Ferrotane as ligand (Table 2, entry 9). Comparable selectivities were observed with Duanphos and Difluorphos (Table 2, entry 5 and 7). Raising the reaction temperature to 50 °C did not improve the selectivity, as selected experiments showed (Table 2, entry 8 and 8a). Using solvent systems other than methanol/THF lead to decreased selectivities as exemplified with Difluorphos and Duanphos (Table 2, compare entries 5, 5a-c and 7,7a). Isolated yields were obtained for several examples and are in general excellent (Table 2, entries 2, 5, 7 and 9).

Having established that [Rh($\widehat{PP}$)$(solvent)_2$](BF_4) complexes are competent for cycloaddition reactions, we wondered whether catalysts other than those containing diolefins or solvent molecules could be used to generate active species. Replacement of diolefins would allow to skip the prehydrogenation step, making the overall procedure significantly more convenient. On the other hand, solvent complexes are so reactive they can only be generated *in situ*. Rh(I)-diphosphine complexes of the type [Rh($\widehat{PP}$)$(NH_3)_2$](BF_4) may at first sight look unsuitable as catalyst precursors because of the stable coordination of ammonia to rhodium.[37,38] However, by adding a stoichiometric amount of an acid such as HBF_4 (BF_4^- is the anion in the complex anyway), ammonia should be easily displaced generating the solvent complexes, thus circumventing the need for a prehydrogenation step. In order to prove such a concept, the complexes [Rh(Duanphos)$(NH_3)_2$](BF_4) and [Rh(Et-Ferrotane)$(NH_3)_2$](BF_4) were synthesized and characterized. The molecular structures of complexes [Rh((S_c,R_p)-Duanphos)$(NH_3)_2$](BF_4) and [Rh((*R*,*R*)-Et-Ferrotane)$(NH_3)_2$](BF_4) were determined by X-ray structure analysis of suitable crystals and the molecular structure of the first mentioned complex is displayed in Figure 2.[38]

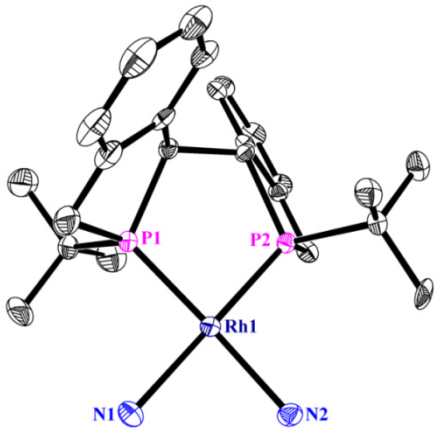
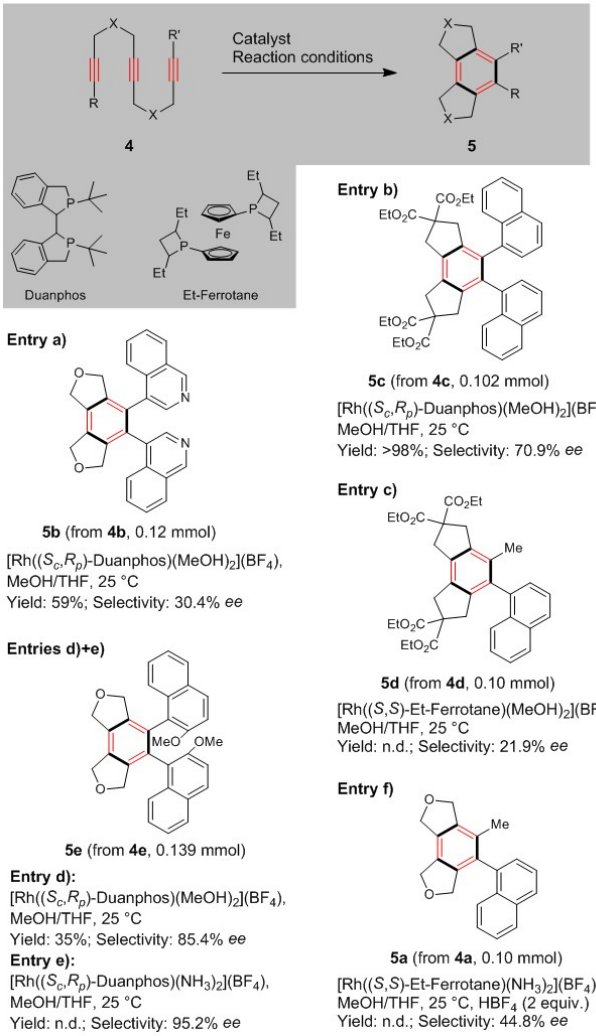


Figure 2. Molecular structure of [Rh((*S*$_c$,*R*$_p$)-Duanphos)(NH$_3$)$_2$](BF$_4$); ORTEP plot, 50% probability ellipsoids. Hydrogen atoms are omitted for clarity.

Having these complexes in hand, the solvent complexes [Rh(Duanphos)(MeOH)$_2$](BF$_4$) and [Rh(Et-Ferrotane)(MeOH)$_2$](BF$_4$) as well as the corresponding ammonia complexes were investigated regarding their activity towards triynes, which have been used in earlier Co(I)-catalyzed cyclizations (Scheme 4).[41c] The results showed that the Duanphos ligand performed superior compared to the Et-Ferrotane ligand in terms of selectivity (Scheme 4). In the cyclizations of symmetrical triynes **4c** and **4e** excellent enantioselectivities for the products **5c** and **5e** approaching 90% *ee* were obtained. For selected examples the products were isolated with yields ranging between 35 and >98%.

For the activation of the ammonia complexes (Scheme 4, entries e and f) the addition of 2 equiv. HBF$_4$ immediately leads to the quantitative formation of the corresponding solvent complexes, as could be corroborated by ^{31}P NMR analysis.[39] This novel approach to the generation of catalytic active species was tested in the cyclization of triynes **4a** and **4e**. The cyclizetion of **4e** using [Rh(Duanphos)(NH$_3$)$_2$](BF$_4$) under the above mentioned conditions gave **5e** in comparably high selectivity compared to the independently generated solvent complex (Scheme 4, compare entries d and e). Cyclization of the test substrate **4a** promoted by [Rh(Et-Ferrotane)(NH$_3$)$_2$](BF$_4$) furnished selectivities of 44.8% *ee*, which matches the result obtained with the pure solvent complex (Scheme 4, entry f). The cyclization of the structurally related malonate-bridged triynes **4c** and **4d** utilizing solvent complexes of Et-Ferrotane and Duanphos gave superior results for the latter with 71% *ee* for **5c** (Scheme 4, entries b and c), while the result for the Et-Ferrotane ligand is comparable to the solvent complex (Table 2, entry 9).



Scheme 4. [2+2+2] Cycloadditions of selected triynes catalyzed by Rh(I)-diphosphine solvent complexes and isolated Rh-diphosphine ammonia complexes as precatalysts (6 mol% loading). Identification and selectivities of crude product were determined by comparison with the known racemate.

Wilkinson catalyst RhCl(PPh$_3$)$_3$ as metal source for chiral catalysts with P,N ligands in cyclotrimerizations

The avoidance of metal-olefin complexes as precursors by using other convenient Rh(I)-precursor could open a bypass to obtain the catalyst without the hydrogenation as prerequisite step, as exemplified already by the use of ammonia complexes. Classical metal(I)-precursors for group 9 metal catalysis are MCl(PPh$_3$)$_3$ (M = Co, Rh) complexes. While the catalytic reactivity of CoCl(PPh$_3$)$_3$ has only been explored in a few cases[40] and even less for [2+2+2] cycloaddition reactions,[41] the heavier group homolog is the commercially available and widely applied Wilkinson complex RhCl(PPh$_3$)$_3$, which was quite often investigated as precatalyst in cyclotrimerization reactions.[42] Consequentially, there are a number of reports on its application in [2+2+2] cycloadditions,[43] taking place under mild conditions

and at temperatures as low as 20 °C, enabling the synthesis with sensitive substrates even in natural product synthesis.[44] Yet none of these reactions was carried out enantioselectively. Therefore our goal was to assess the potential of $RhCl(PPh_3)_3$ as Rh(I)-source in combination with a chiral ligand as *in situ* catalyst in enantioselective [2+2+2] cycloaddition reactions.

The development of general reaction conditions and screening of *in situ* generated chiral catalysts in the cyclization of test substrate **4f** led to our delight to moderate to high yields and good *ee* values between 42-87% for the triaryl **5f**. While the use of *P*,*P* ligands such as (R_a)-BINAP resulted in no significant selectivities (Table 3, entry 1), selected chiral *P*,*N* ligands such as (R_a)-QUINAP or (*R*,R_a)-*O*-PINAP afforded moderate *ee* values of 49% and 61%, respectively (Table 3, entries 2 and 7). NMR investigations corroborated the assumption of facile exchange of two PPh_3 for the *P,N* ligand at the Rh center.[45]

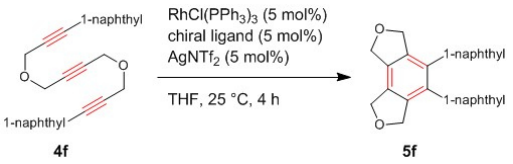


Table 3. Catalyst screening of $RhCl(PPh_3)_3$ using various chiral ligands.

#	Chiral Ligand	Yield [%]	d/l:meso[a]	*ee* [%][b]
1	(R_a)-BINAP	83	1 : 2.4	6
2	(R_a)-QUINAP	41	1 : 1.4	49
3	(R_a)-QUINAP[c]	37	1 : 1.5	42
4	(S_a)-QUINAP	48	1 : 2.3	(-)47
5	(*R*,R_a)-*N*-PINAP	88	1.3 : 1	27
6	(*R*,S_a)-*N*-PINAP	62	1.7 : 1	(-)87
7	(*R*,R_a)-*O*-PINAP	85	1.2 : 1	61
8	(*R*,S_a)-*O*-PINAP	94	1.4 : 1	(-)85
9	(*R*)-PHOX	78	1 : 1.2	(-)45

The reaction screening was performed on a 1 mmol triyne substrate scale. [a] Ratio determined by integration of peak areas in the ^{1}H NMR. [b] The *ee* values were determined by chiral HPLC. [c] 2 equiv. ligand were used.

Only (*R*,R_a)-*N*-PINAP led to mediocre 27% enantiomeric excess (Table 3, entry 5). Accordingly, the (S_a)-derivatives – namely (S_a)-QUINAP, (*R*,S_a)-*N*-PINAP and (*R*,S_a)-*O*-PINAP – led to similar or even better *ee* values of 47%, 87% and 85% respectively, while favoring the other enantiomer (Table 3, entries 4, 6 and 8). By turning to a different, phosphinooxazoline-based *P*,*N* ligand class (PHOX), which does not contain the chiral information in the backbone structure but in a group close to the nitrogen moiety, high yields and moderate *ee* values of up to 45% could be achieved (Table 3, entry 9). Application of 2 equiv. of ligand has no significant influence on the reaction outcome (Table 3, entry 2 and 3). These systems represent the first chiral Rh(I)-based catalysts generated *in situ* from $RhCl(PPh_3)_3$, avoiding the prerequisite hydrogen treatment.[11] We also tested the successfully applied *O*-PINAP ligand in related iridium-catalyzed cyclotrimerizations with triyne **4a**. However, applying $[IrCl(cod)]_2$ and (*R*,S_a)-*O*-PINAP as catalytic system at 95 °C, only 27% yield and low selectivity of 4.7% *ee* were obtained after 72 h.

Having identified $RhCl(PPh_3)_3$ and (*R*,S_a)-*O*-PINAP as the most promising *in situ* catalytic system, we ventured to investigate the substrate scope. Therefore various triynes we have synthesized previously[41c] have been cyclized yielding the respective product in moderate to good yields (Table 4).

For the firstly investigated substrates **4e**,**g** and **h** low yields of product with no or rather low selectivity were obtained (Table 4, entries 1 to 3). Symmetrically substituted triynes **4i-k** were cyclized in moderate to quantitative yields with high *ee* values of 75-85% for **5i** and **5j** respectively (Table 4, entries 4 and 5) and an only moderate *ee* for the quinoline product **5k** (Table 5, entry 6). Surprisingly, the isoquinoline-substituted triyne analogue of substrate **4k** (namely, triyne **4b**, Scheme 4) was not converted, even at elevated temperatures of up to 80 °C. The unsymmetrically substituted triynes **4l-n** gave altogether moderate yields of the corresponding benzene derivatives (**5l-n**), however, in very low enantioselectivities (Table 4, entries 8-10). We have also investigated different malonate-bridged triynes under the aforementioned reactions conditions. Higher reaction temperatures were required compared to ether-bridged triynes and basically no enantioselectivities were observed (as an example see conversion of triyne **4c**, Table 4, entry 11).[46] This trend is similar to that noticed with asymmetric cobalt-catalyzed cyclizations of triynes, where in only few cases the selective formation of arene products from malonate-bridged triynes was detected.[6]

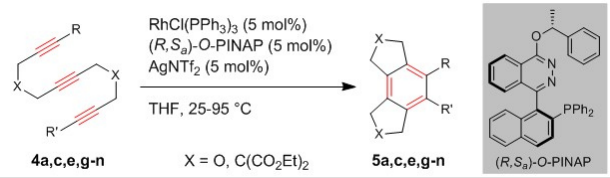
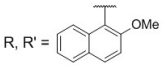
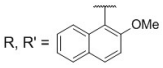
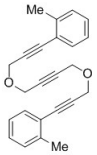
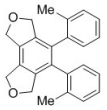
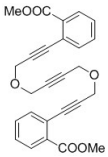
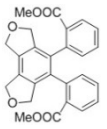
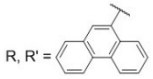
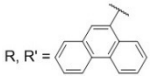
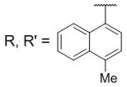
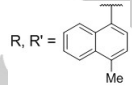
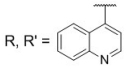
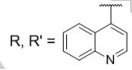
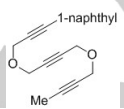
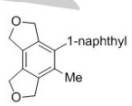
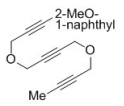
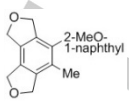
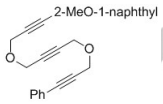
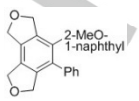
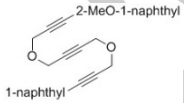
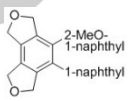
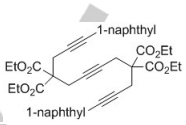
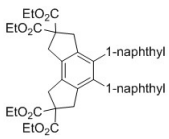
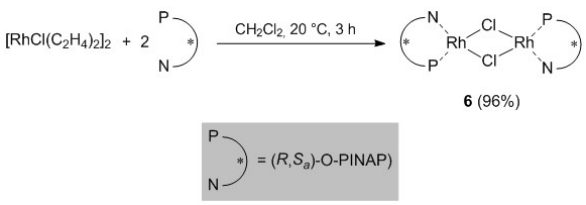


Table 4. Substrate screening with ether- and malonate-bridged triynes.

#	Substrate	**Product** (react. temp., °C; react. time, h)	**Yield** [%] (d/l:meso) **Sel.** [%*ee*][a]
1	 **4e** (X=O)	 **5e** (25 °C, 6 h)	28 (1 : 5.2) Rac
2	 **4g** (X=O)	 **5g** (40 °C, 27 h)	7 (1.1 : 1) 37
3	 **4h**	 **5h** (40 °C, 27 h)	39 (1 : 1.2) (-)6
4	 **4i** (X=O)	 **5i** (25 °C, 22 h)	75 (1 : 2.7) (-)85
5	 **4j** (X=O)	 **5j** (55 °C, 24 h)	36 (11.8 : 1) 84
6	 **4k** (X=O)	 **5k** (65 °C, 24 h)	>95 (1.3 : 1) (-)31
7	 **4a**	 **5a** (50 °C, 23 h)	40 (-)2
8	 **4l**	 **5l** (65 °C, 18 h)	51 10
9	 **4m**	 **5m** (60 °C, 24 h)	39 7
10	 **4n**	 **5n** (65 °C, 4 d)	67[b] F1: (-)7 F2: rac
11	 **4c**	 **5c** (90 °C, 3 d)	57 (1.5:1) rac

[a] Scale of the reaction was 0.125-0.5 mmol triyne substrate. The *ee* values were determined by chiral HPLC. Detailed reaction conditions and *meso*:*d/l* ratios are listed in the Supporting Information. [b] Total yield of both pair of enantiomers, which were isolated separately after column chromatography.

We have considered the simple synthesis and isolation of a dinuclear chlorido-bridged Rh(I)-complex with the (*R*,*S*$_a$)-*O*-PINAP ligand as catalyst precursor, which would circumvent the *in situ* generation from two components. Furthermore, it would possibly allow to analyze whether there is any retarding effect from the free PPh_3 released from the Wilkinson catalyst during complexation. The Rh(I)-ethylene complex was used as precursor, which easily reacted with the *O*-PINAP upon mixing in CH_2Cl_2, furnishing the dinuclear complex **6** in excellent yield (Scheme 5).



Scheme 5. Synthesis of the dinuclear chiral Rh(I)-*O*-PINAP complex **6**.

With isolated complex **6** we investigated the cyclization of triyne **4a** as test substrate in the presence of $AgNTf_2$ as described above (see Table 4 for conditions). The results indicated that

under identical conditions (50 °C, 72 h reaction time; Table 4, entry 7) only 10% yield of product **5a** with 6.6% *ee* was obtained, which is less than obtained with *in situ* catalyst. The best yield and slightly higher selectivity were obtained after heating to 50 °C for 4 h and 100 °C for 20 h, giving biaryl **5a** with 57% yield and 12% *ee*. Heating to 95 °C for 23.5 h resulted in identical selectivity and 34% yield. These experiments proved that cyclotrimerizations with complex **6** required even higher reaction temperatures to proceed, under conditions otherwise identical to those used with the catalyst generated *in situ* from *O*-PINAP ligand and $RhCl(PPh_3)_3$.

In conclusion, we have presented a detailed investigation into the quantitative formation of highly reactive chiral $[Rh(diphosphine)(solvent)_2]^+$ complexes from the corresponding cod complexes by applying appropriate prehydrogenation conditions. Furthermore we have shown that isolated ammonia complexes of the type $[Rh(diphosphine)(NH_3)_2](BF_4)$ and catalysts prepared from the Wilkinson complex $RhCl(PPh_3)_3$ and suitable P,N ligands like *O*-PINAP are competent catalyst precursors for [2+2+2] cycloaddition reactions. The following points deserve attention: a) It was shown that the time required to fully hydrogenate and thus displace the diolefin from Rh(I)-olefin complexes is strongly affected by the type of diphosphine. Therefore the prehydrogenation step required to ensure complete conversion of the starting complex into the active precatalyst should be assessed for each different catalytic system; b) catalyst generation in chlorinated solvents, although widely applied, may afford metal species other than those obtained in non-chlorinated solvents, potentially leading to undesired side products; c) Rh(I)-ammonia complexes can afford catalytic active species when treated with stoichiometric amounts of acid, thus circumventing the prehydrogenation step required by Rh(I)-olefin complexes; d) application of the Wilkinson complex $RhCl(PPh_3)_3$ as convenient Rh(I)-source avoids the necessity of prehydrogenation; here P,N ligands proved to be better ligands in cyclotrimerization reactions compared to P,P ligands.
While the cyclotrimerization of alkynes and triynes was investigated as a showcase in the presented study, the details of catalyst generation are likewise highly interesting for a range of asymmetric transformations mediated by Rh(I)-complexes, which until now applied Rh(I)-olefin complexes that had to be activated via hydrogenation. The significantly higher efficiency achieved with the catalytic systems we have presented here represents a step forward towards more sustainable syntheses.

Experimental Section

All reactions have been performed under argon using Schlenk technique. All solvents were distilled over appropriate drying reagents in an inert atmosphere or taken from a solvent purification system.

Synthesis of Rh(I)-complexes:

$[Rh((S_c,R_p)$-Duanphos)$(NH_3)_2](BF_4)$: The complex $[Rh((S_c,R_p)$-Duanphos)(cod)$](BF_4)$ (21.8 mg, 0.033 mmol) was stirred in a saturated solution of ammonia in THF (2 mL) for 1 h at room temperature. Complete conversion was confirmed by ^{31}P NMR. The bright yellow solution was layered with 6 ml heptane. Yellow crystals suitable for X-ray analysis could be obtained after one day. ^1H NMR (benzene-d_6, 400 MHz): δ = 0.78 (s, ^{t}Bu, 16H), 2.47 (s, NH_3, 6H), 3.14 (2H), 3.30 (2H), 3.68 (2H), 7.05 (8H) ppm; ^{31}P NMR (benzene-d_6, 162 MHz): δ = 120.8 ($^1J_{Rh\text{-}P}$ = 177.6 Hz) ppm; ^{15}N NMR (40.6 MHz benzene-d_6, reference is $MeNO_2$, (40.6 MHz, C_6D_6, $MeNO_2$)): δ = -398 ($^1J_{H\text{-}N}$ = 67.9 Hz) ppm.

$[Rh((R,R)$-Et-Ferrotane$)(NH_3)_2](BF_4)$: The complex $[Rh((R,R)$-Et-Ferrotane)(cod)$](BF_4)$ (23.8 mg, 0.033 mmol) was stirred in a saturated solution of ammonia in THF (2 ml) for 1 h at room temperature. Complete conversion was confirmed by ^{31}P NMR. The bright yellow solution was layered with 6 mL heptane. Yellow crystals suitable for X-ray analysis could be obtained after one day. ^1H NMR (THF-d_8, 400 MHz): δ = 0.78 (t, J = 7.1 Hz, CH_3, 6H), 1.11 (m, CH_2, 4H), 1.46 (t, J = 7.1 Hz, CH_3, 6 H), 1.80 (m, 2H), 2.04-2.49 (m, 6H), 2.5 (m, 2H), 2.61 (s, NH_3, 6H), 4.26 (bs, Cp-H, 2H), 4.41 (bs, Cp-H, 2H), 4.50 (bs, Cp-H, 2H), 4.53 (bs, Cp-H, 2H) ppm; ^{31}P NMR (THF-d_8, 162 MHz): δ = 71.6 ($^1J_{Rh\text{-}P}$ = 179.9 Hz) ppm; ^{15}N NMR (40.6 MHz, C_6D_6, $MeNO_2$): δ = -396 ($^1J_{H\text{-}N}$= 67.5 Hz) ppm.

$[RhCl\{(R,S_a)$-*O*-PINAP$\}]_2$ (6): $[RhCl(C_2H_4)]_2$) (63.0 mg, 0.162 mmol) and (R,S_a)-*O*-PINAP (184.0 mg, 0.328 mmol) were weighted into a 25 mL Schlenk tube in the glove-box and 2.8 mL CH_2Cl_2 added as solvent, resulting in the formation of a deep red solution. The solution was stirred at 20 °C for 3 h, concentrated to 1 mL in vacuo and diethyl ether (16 mL) was added. An olive green precipitate formed immediately. Solids attached to the glass wall were removed by freezing and thawing of the solution and treatment in an ultrasound bath at 30 °C for 30 min. The suspension was cooled to 0 °C and the solvent removed by a filter tube. The remaining solid was again suspended in diethyl ether (9 mL), stirred strongly and cooled to 0 °C and the solvent filtered off. This was repeated a third time with 5 mL of diethyl ether. After removal of the solvent by filtration the green powder was dried in high vacuo, yielding 201 mg (96%) product with minimal solvent residues. ^1H NMR (CD_2Cl_2, 300 MHz): δ = 0.93 (d, CH_3, J = 6.2 Hz, 6H), 5.52 (q, CH, J = 6.2 Hz, 2H), 6.75-7.00 (m, 13H), 7.05-7.15 (m, 6H), 7.23-7.35 (m, 13H), 7.35-7.45 (m, 4H), 7.48-7.58 (m, 4H), 7.63-7.73 (m, 4H), 7.94-8.00 (m, 2H), 8.00-8.11 (m, 4H) ppm; ^{31}P NMR (benzene-d_6, 162 MHz): δ = 120.8 ($^1J_{Rh\text{-}P}$ = 177.6 Hz) ppm; ^{31}P NMR (CD_2Cl_2, 121 MHz): δ = 63.3 ppm ($^1J_{Rh\text{-}P}$ = 174 Hz).

General Procedure for the preparation of the solvent complexes $[Rh(\widehat{PP})(solvent)_2](BF_4)$: The precatalyst $[Rh(\widehat{PP})(cod)](BF_4)$ (0.01 mmol) was dissolved in anhydrous MeOH (15.0 mL) and treated with hydrogen under normal pressure according to the time given in Table 1 at 25.0 °C. Afterwards the hydrogen was removed by five freeze-thaw-cycles.

Catalytic cyclotrimerization experiments:

Procedure for the cyclization of phenylacetylen: The precursor [Rh(DTBM-Segphos)(cod)](BF_4) (31 mg, 0.02 mmol) was dissolved in methanol (5 mL). The resulting solution was exposed to hydrogen for 77 min and then the hydrogen removed by five freeze-thaw-cycles. Subsequently phenylacetylene (0.2 mL, 2 mmol) was added via syringe under vigorous stirring. After 45 min the reaction mixture was quenched by exposition to air. To obtain the product composition, the samples have been analyzed by GC/MS and the individual products been identified by their fragmentation pattern.

General procedure for the cyclization of triynes with $[Rh(\widehat{PP})(solvent)_2](BF_4)$ complexes (Table 2): The precursor complex $[Rh(\widehat{PP})(cod)](BF_4)$ (0.01 mmol) was dissolved in 1 mL MeOH and stirred under hydrogen for respective time (see Table 1 and Supporting

Information) to obtain practically complete conversion into solvent complex [Rh($\widehat{PP}$)(MeOH)$_2$](BF$_4$). Afterwards the substrate (0.165 mmol) dissolved in 0.5 mL THF was added and the reaction mixture stirred for 16 h. In case of other solvent systems than MeOH, the MeOH was removed after hydrogenation and the remaining solvent complex and substrate were dissolved in the respective solvent system. Reactions in solvent mixtures like MeOH/THF result from the addition of substrate solution in THF due to better solubility to the solution of the precatalyst in MeOH. The complete screening table with all screened ligands is given in the Supporting Information.

General procedure for the cyclization of triynes with [Rh($\widehat{PP}$)(solvent)$_2$](BF$_4$) complexes (Scheme 4): The appropriate complex [Rh($\widehat{PP}$)(diolefine)](BF$_4$) (0.01 mmol) was dissolved in 1 mL MeOH and stirred under hydrogen atmosphere for respective time (Table 1 and Supporting Information) to obtain 99.2% conversion into the solvent complex [Rh($\widehat{PP}$)(MeOH)$_2$](BF$_4$). Afterwards the triyne substrate (0.165 mmol) dissolved in 0.5 mL THF was added and the reaction mixture stirred for 16 h at room temperature. The complete screening table with all screened ligands is given in the Supporting Information. In case of ammonia complexes, the solvent complexes were generated by addition of 2 equiv. HBF$_4$.

General procedure for the chiral ligands screening with Wilkinson catalyst RhCl(PPh$_3$)$_3$ in the cyclotrimerization of triyne 4f (Table 3): Triyne **4f** (1 mmol), RhCl(PPh$_3$)$_3$ (5 mol% in regard to the triyne), the respective chiral ligand (5 mol% in regard to the triyne) and AgNTf$_2$ (5 mol% in regard to the triyne) were dissolved in THF (3 mL) and the solution was stirred at room temperature for 4 h. At the end of the reaction, the solvent was removed under reduced pressure and the residue purified by column chromatography (*n*-hexane/ethyl acetate 1:1, v/v) to yield the benzene derivative **5f**. The *ee* values were determined by chiral HPLC analysis (Cellulose 2, n-heptane/isopropanol 95:5, v/v, 1 mL/min).

General procedure for the cyclization with Wilkinson catalyst RhCl(PPh$_3$)$_3$ and chiral ligands, exemplified for (*R*,*S*$_a$)-*O*-PINAP (Table 4): The triyne (0.125-0.5 mmol), RhCl(PPh$_3$)$_3$ (5 mol% with regard to the triyne), (*R*,*S*$_a$)-*O*-PINAP (5 mol% with regard to the triyne) and AgNTf$_2$ (5 mol% with regard to the triyne) were dissolved in THF/toluene (1 mL) and the solution was stirred at 25-95 °C for a specified time. At the end of the reaction, the solvent was removed under reduced pressure and the residue purified by column chromatography to yield the benzene derivative. The *ee* values were determined by HPLC analyses on chiral phases.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1531752 for [Rh(BINAP)$_2$](BF$_4$)$_2$, CCDC-1531753 for [Rh(Duanphos)(NH$_3$)$_2$](BF$_4$) and CCDC-1531754 for [Rh(Et-Ferrotane)(NH$_3$)$_2$](BF$_4$)**.** Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB21EZ, UK (fax: int. code + (1223) 336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Keywords: [2+2+2] cycloaddition • rhodium • asymmetric catalysis • triynes • diphosphine ligands

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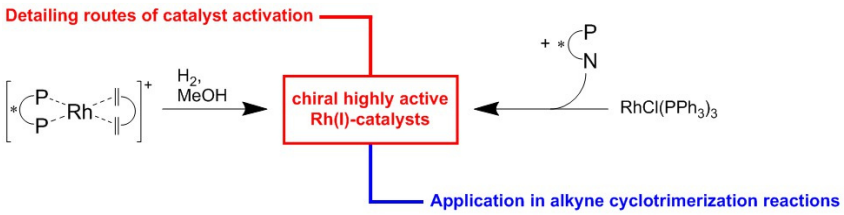
Abstract:

FULL PAPER



All roads lead to Rome, but the most frequented routes might not be the most efficient and sustainable. The detailed investigation on the generation of chiral Rh(I)-complexes from different precursors and their use exemplified in cyclotrimerizations of triynes allowed insights into the efficient generation of chiral Rh(I)-catalysts.

Indre Thiel, Moritz Horstmann, Phillip Jungk, Sonja Keller, Fabian Fischer, Hans-Joachim Drexler, Detlef Heller and Marko Hapke**

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Insight into the Activation of *In Situ*-Generated Chiral Rh(I)-Catalysts and their Application in Cyclotrimerizations